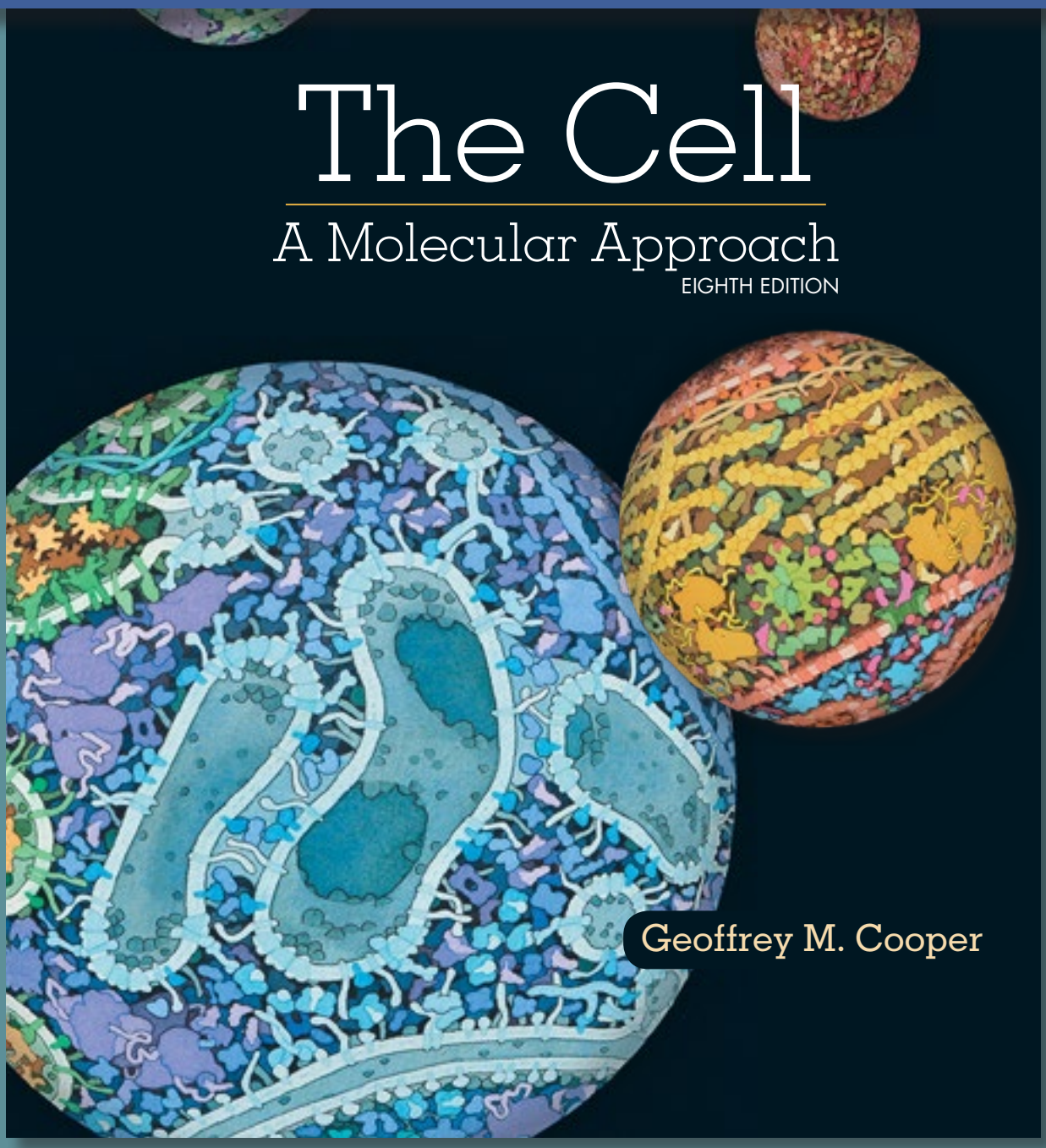
Instructor's Manual and Active Learning Guide

for



Instructor's Manual and Active Learning Guide

for

The Cell

A Molecular Approach

EIGHTH EDITION

Geoffrey M. Cooper

Active Learning Exercises by Robert R. Wise

With an introduction to active learning by Carly N. Jordan

SINAUER ASSOCIATES

NEW YORK OXFORD
OXFORD UNIVERSITY PRESS

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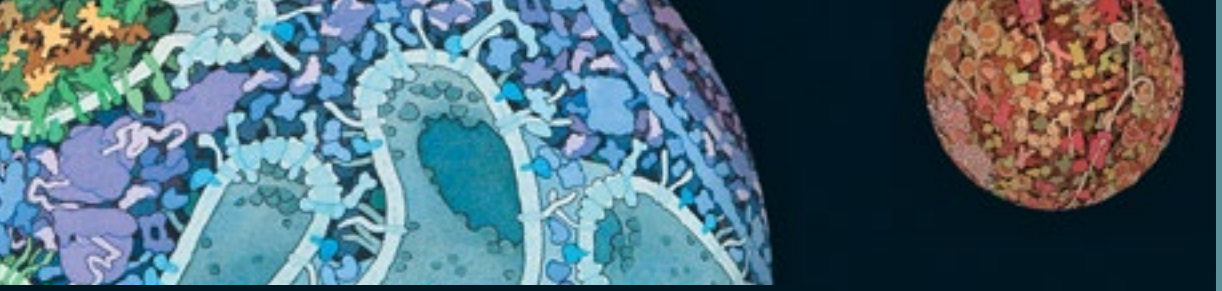
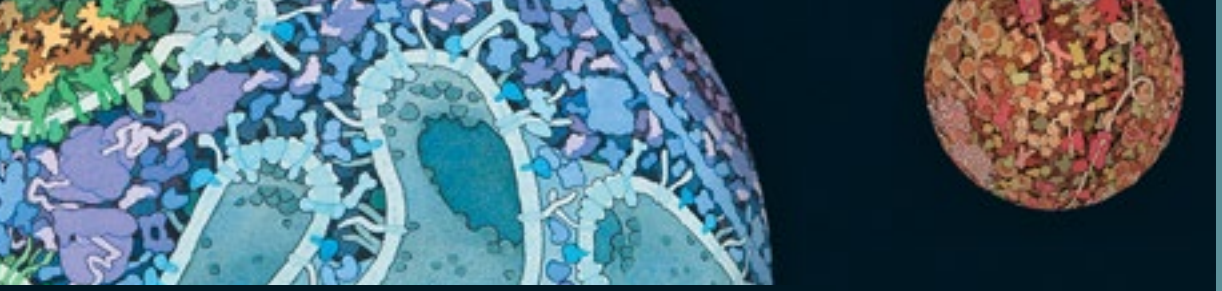
Instructor's Manual and Active Learning Guide
To accompany
The Cell: A Molecular Approach, Eighth Edition

Address editorial correspondence to:
Sinauer Associates, an imprint of Oxford University Press, 23 Plumtree Road,
Sunderland, MA 01375 U.S.A.



Instructor's Manual: **Contents**



Instructor's Manual: **Instructor and Student Resources**

The Cell: A Molecular Approach, Eighth Edition, by Geoffrey M. Cooper is the only one-semester intro cell biology text that is built around a specific set of learning objectives. These learning objectives provide a foundation for the numerous resources offered with the book. To help you navigate the course and get the most from these materials, this Instructor's Manual includes an overview of instructor and student resources, a brief introduction to active learning, and a chapter-by-chapter guide to relevant media components, active learning exercises, and clicker questions for use in the classroom.

The following materials have been prepared specifically to accompany *The Cell: A Molecular Approach*, Eighth Edition.

For Instructors:

Ancillary Resource Center oup.com/uk/cooper8e

Instructor's Manual and Active Learning Guide This chapter-by-chapter playbook shows instructors how to create a dynamic learning environment with in-class exercises, clicker questions, and links to relevant media, animations, testing, and self-quizzing, aligned with the new in-text learning objectives, wherever appropriate.

PowerPoint Resources All of the textbook's figures and tables are provided as JPEG and PowerPoint files for easy inclusion in presentations and other course documents. Artwork has been reformatted and optimized for exceptional image quality when projected in class.

Test Bank, in Microsoft Word format The Test Bank includes more than 1,300 multiple-choice, fill-in-the-blank, true/false, and short-answer questions covering the full range of content in every chapter, including all chapter quiz questions.

Computerized Test Bank The entire test bank is provided in Blackboard's Diploma software. Diploma makes it easy to assemble quizzes and exams from any combination of publisher-provided and instructor-created questions. In addition, quizzes and exams can be exported to many different course management systems, such as Blackboard and Moodle.

For Students:

Companion Website oup.com/uk/cooper8e

The Companion Website to accompany *The Cell* provides students with a wide range of study and review materials and rich multimedia resources. The site is available free of charge (no access code required) and includes the following resources:

Videos A collection of online videos (referenced throughout the book) to help students visualize complex cellular and molecular structures and processes

Animations Narrated animations of key concepts and processes

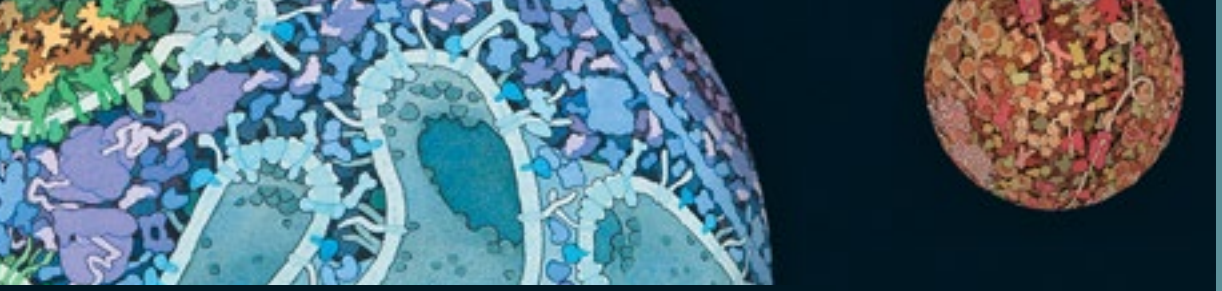
Micrographs Interactive micrographs illustrating cellular structure

Flashcards A great way for students to learn the key terminology introduced in each chapter

Chapter outlines and reviews An overview of each chapter's content, with questions

Web Links A set of links to websites and online resources relevant to each chapter

Glossary A complete online version of the book's glossary



Engaging Students through Active Learning

The term "active learning" encompasses many types of teaching methods that encourage students to be active participants in the classroom. It is often discussed in contrast to traditional lecture-based courses, in which students are more passive listeners. Research has demonstrated that students in active learning courses show greater learning gains and increased interest and engagement with the subject (see Appendix A).

The goal of active learning is to engage students in critical thinking and communication during class, which usually means moving at least some of the work of knowledge acquisition out of the classroom through assigned readings, recorded lectures, video tutorials, and/or pre-class assessments. This frees up classroom time for students to apply that knowledge, extend it, evaluate it, and discuss it with peers. Group work is typically a large component of active learning classes, and students team up to take on challenging problems and assignments in class with the support of instructors, who guide their progress. The types of activities used in class are wide-ranging and draw from many other popular teaching methods, such as problem-based learning, team-based learning, peer instruction, and case study teaching. However, simply asking questions, assigning worksheets, initiating discussions, or writing in class are all also part of active learning.

The Active Learning Guide that follows this introduction provides student-centered exercises that are directly related to the text in *The Cell*, Eighth Edition. It offers chapter-by-chapter materials to help instructors create a dynamic learning environment in the classroom, including in-class exercises, clicker questions, and links to relevant media, animations, tests, and quizzes.

Appendices at the end of this manual provide additional materials related to active learning. Appendix A is an overview of the science behind active learning initiatives and the value of employing active learning in the classroom. Appendix B describes some popular active learning techniques, such as backward course design and "flipping the classroom." If you're curious about active learning but not prepared to engage fully from the start, you'll find support here for easing into the active learning model. Appendix C presents an overview of Bloom's Taxonomy that will guide you in the administration of the Test Banks and can even help you create course content that best engages students.

Preparing your Lessons

After you have spent some time thinking about your course as a whole, you can begin to prepare for each class period. Your preparation can vary, from planning a few minutes of activities for one class period to choosing an entire semester's worth of assignments.

Preparing for an active learning class is very different from preparing a lecture. Instead of crafting a narrative that you will deliver to your students, you will create (or find) challenges to present to them. For most instructors, there is no need to design an activity

from scratch for every class period—there are many great repositories for curriculum, including *The Cell,* Eighth Edition instructor resources.

Most active learning methods involve some amount of small group interaction. If you are going to include frequent activities, you may want to spend some time organizing student groups. This can be done as needed ("work with the students around you for this activity"), but for very large classes, careful planning can simplify assignment collection and the grading of student work. One method, described in the book *Pathways to Scientific Teaching* (Ebert-May and Hodder, 2008), is to use folders to organize individual and group work. Each student is assigned his or her own folder, which doubles as a name card in a large lecture hall, and group members' folders are stored together in a hanging file folder with a group ID. All of the folders are brought to class each day, either in a file box or, for especially large classes, a rolling file cart. Instructors (or teaching assistants) place handouts for the day into the folders before class, and one member of each group picks up the folder on the way in. Students place completed work in the folder and return it to the box or cart on the way out. This method keeps student work organized and makes paper exchange in a large classroom much easier.

Since some of the activities you will encounter have handouts, also remember to build a few minutes into your schedule for printing, or give students enough notice to have them print handouts and bring them to class. Lessons can include activities for students to complete before class, or you may choose to assign the reading and quizzes before covering a topic in class. With all strategies, it is important to convey due dates clearly.

Setting the Tone

As in any course, setting expectations is fundamental to a successful semester, and this is especially key for active learning courses. Many students are used to lecture courses and may be fearful of the course material. During the first few meetings, working to set the tone for the course in an active learning environment can help them overcome this hurdle.

On day one or before, let the students know what the course structure will be. If you plan to incorporate active learning regularly, let them know that your lectures will be peppered with activity breaks and discussion. Most students won't have any problem with this approach and, in fact, will welcome the lecture break and find it energizing. If you intend to teach using the flipped-classroom method, you will need to work harder to get students happily engaged in the course. Addressing student motivation, concerns, and questions on the first day of class will help everyone engage more readily.

Getting students to buy into your teaching methods is key to reducing student complaints, and one great way to do that is to begin by asking them to establish their own goals for the course.

- Start by asking them to brainstorm a list of three things they hope to gain from the course. You can do this ahead of time online, or give them a few minutes to think in class on the first day.
- Gather their responses and share them with the class. You are likely to receive a fairly predictable set of answers: specific content that students are interested in, essential science skills (laboratory techniques, data analysis), and some broad, transferable skills (communication, critical thinking, problem solving).

- Help the students see how these learning goals fall into two basic categories—knowledge acquisition and skill-building. If you are doing this in person, you can ask one student to draw a star next to each item that represents knowledge acquisition, as a visual representation of the balance of goals they have provided.
- Discuss the timing of the course—how many hours you have together in class each week, and how many hours they should expect to work on their own outside of class. You may also choose to show them the list of topics that you intend to cover during the semester. Emphasize that the list they have created is excellent and also a bit daunting, but you'll work together toward a successful outcome.
- Discuss which goals students think they can best achieve on their own, outside of class, and with you and their peers. Without fail, students will come to the conclusion that they can probably learn basic content on their own but that the skill-building goals will be more easily achieved by working with others. Tell them that you have thoughtfully designed the course structure to facilitate their development in the skills they wish to grow. You will spend your precious class time working on things like problem solving, communication, and data analysis—and you will leave the task of information acquisition to them to work on outside of class.

This activity can be conducted with a whiteboard and marker for small classes, and students can respond to posed questions in a standard discussion format. For large courses, technology can help to facilitate the response collection. Students can text in answers about their goals using text-ready clickers or web-based platforms, and you can show the list of responses on a projection screen. Then, after giving groups a few minutes to discuss the question of how to best achieve the goals, you can post a clicker question to get a quick snapshot of how the discussions went. The question can be something as simple as this:

Which of these goals do you think you can achieve on your own, outside of class?

- Acquiring basic knowledge of science content
- Practicing scientific skills like data analysis and lab techniques
- Developing transferable skills like critical thinking and problem solving

This is a great way to introduce the course structure and goals, because it gives the students a feeling of ownership over how class time should be spent, and it conveys that you have given consideration to how you can help them achieve their goals. It also establishes a tone of collaboration, and it gets them talking to one another on day one.

You can follow up by getting them excited about the types of things they will be doing in class. If you have a few case studies or team projects planned that you think will be interesting to them, give them a sneak preview. Also tell them about the types of simple activities that help them engage in class each day. Try a think-pair-share exercise, with some conversation from you in between, and tell them that this type of discussion is an example of the ways they will work together in class.

Show your students data about the benefits of active learning (see Appendix A). Tell them that you structure your class this way because studies indicate that students will get higher grades and feel more engaged in class and also because you want to be sure that everyone has an equal opportunity to succeed.

Finally, an introduction to Bloom's taxonomy (see Appendix C) fits well here, as it helps students think about the level of questions and tasks they will be assigned, and it is often reflected nicely in the goals the students listed. Explain that recall of basic facts and definitions is a lower-order thinking skill, and that may be what students are most familiar and comfortable with. However, the in-class activities will include higher-order tasks, like analyzing data and making predictions. These skills are more challenging, and that is why students will work on them together. You can also remind them that higher-order skills build on lower ones, so they will need to take responsibility for knowledge and comprehension on their own by completing assigned work before class.

Pre-Class Assignments

Beyond assigning readings from the textbook, there are several types of assignments that you may employ to prepare your students for a particular activity in class.

If you are removing much lecture time from your class, or if you have an activity planned that specifically warrants it, asking students to watch videos before class can be helpful. Some instructors teaching flipped classes choose to record entire lectures for students to watch before class or select from some really excellent ones already available online. Even if you don't need your students to watch a complete lecture, there are many short videos that can be assigned to add clarity or context to a particular topic. Supplemental readings can also help ensure that time in class is spent effectively.

To encourage students to take reading and media assignments seriously, some instructors include a pre-class quiz. You can design your own short quizzes based on the textbook reading or other supplemental readings or media you assign to students. Using your campus LMS can automate the administration and scoring of quizzes that you create, or you can have students turn in a paper quiz as a "ticket" to get into class each day (which you may choose to grade for accuracy or just completion).

In the Classroom

ENGAGING STUDENTS THROUGH QUESTION AND RESPONSE One simple first step toward implementing active learning in your course is to pause every few minutes to ask the class a question. This can be informative for you, in that it allows you to check whether students are keeping up with the content, and it can give students an idea about which topics are most important and how exam questions might be structured. This strategy, if done well, can engage students in deep thinking, challenge misconceptions, and even spark debate among class members. For best results, ask questions at a variety of Bloom's levels, beyond simple recall of recently stated facts. The Test Bank provided with *The Cell* includes some multiple-choice questions that reach higher cognitive levels and would be great choices for in-class questioning.

When presenting a multiple-choice question, a show of hands may be sufficient to collect answers in a small class. You can also have each student write the letter of his or her response on a sheet of paper and hold it up, or create reusable response cards by printing letters on card stock and keeping them together in a binder clip.

For larger classes, technology can be a major asset for asking students questions and collecting their responses. Both cell phones and personal response devices (commonly known as clickers) can be used by students to respond to questions in class. While some systems permit only A–E responses, others allow free-response and numerical answers. For a multiple-choice question, you can get an instant report of how many students chose each answer and then display a graph to the class. This technique is hugely helpful for you and for students, as it gives a snapshot of what the class knows at any moment.

- Did everyone get it right? Great, no need to spend more time on that topic—moving on!
- Were answers all over the place? You may want to back up and explain the concept in a different way, solicit students' questions about the topic, or ask if they can explain why they answered a certain way.
- Is the class split between two ideas? This is a great opportunity to turn questioning into a group activity by instructing students to debate among themselves. Tell them to spend two minutes arguing for their choice with the folks around them and try to change some minds. Re-poll and see if the answers have shifted.

If you are considering incorporating personal response technology into your class, consult with your campus teaching center. Some schools adopt a single brand of clicker devices or a single web-based service to minimize the cost to students, and many offer seminars or one-on-one training in implementation. If you are eager to learn more about the pedagogy behind using clickers or other technology in your classroom, see Bruff (2009) or consider the Teaching with Technology Conference: https://www.magnapubs.com/teaching-with-technology-conference/

ASSIGNING SIMPLE WRITING TASKS Getting students writing, even if just for a minute, is a great way to engage them in the classroom. One simple tool for adding active learning to a lecture-based course is to provide empty outlines for students to complete as they follow along with a lecture, video, or peer presentation. This strategy focuses attention on the main ideas and increases engagement in what may otherwise be a passive listening activity. If you already have lecture notes prepared for your classes, creating empty outlines likely won't take much additional effort. You can also assign the outline as an end-of-class review activity, and you can task small groups with completing it together after the lecture. For large classes, asking students to work in groups will also help make your review of their work more manageable.

UTILIZING GRAPHIC ORGANIZERS A graphic organizer is "a visual and graphic display that depicts the relationships between facts, terms, and/or ideas within a learning task" (Strangman et al., 2003). These can take a variety of forms and names, such as concept maps, flow charts, spider maps, and network trees. They often include main ideas in bounded text (circles or boxes), with relationships and subcategories drawn outward in linear or radial arrays. Creating a graphic organizer requires consideration of how ideas intersect, and they can help students see big-picture ideas. When students create them as reading notes, they improve reading comprehension and vocabulary. These can be used by students outside of class for studying, or they can be assigned in class as individual or group activities.

Graphic organizers are especially well suited for tying multiple chapters together at the end of a major unit of study, and they help instructors see misconceptions and missing connections. Some instructors assign them as final exam review activities, with students filling poster boards with all of the main ideas from a semester. When assigning a graphic organizer activity in class, keep in mind that they often take longer to create than you might imagine. Pencil and paper work well, but there are also a number of tools online for creating digital diagrams. (Lucidchart.com is a good free site.) This activity can also be modified to fit a shorter class time or for use on multiple-choice exams if you make a skeleton for students to complete. You can create your own organizer (or find one online), delete key words, and ask students to fill in the blanks. This modification also works well for large courses, since you can then use clickers to collect student responses.

Useful Active Learning Tools

DEBATE TEAMS Breaking into small groups, students debate topics that have multiple valid angles. A representative from each side of the debate can then present arguments to the whole class for further discussion, or a student can lead the class through a "decision" exercise.

MATRIX Matrices are tables that help students categorize and arrange a series of concepts, definitions, or outcomes. More linear and restrictive than graphic organizers, tables are often less daunting for students to create, as they offer a more predictable structure. Structure-and-function tables are perfect for organizing information. Venn diagrams or similarly constructed tables are excellent for highlighting similarities and differences of two or more groups or processes that students often confuse. A defining-features matrix is a great way to organize information about traits of related structures—list common features in rows and structures in columns, and ask students to check off which traits each structure has. You can provide the set-up of the table, with row and column headers labeled or, for added challenge, task students with deciding what categories of information are important to include.

MINUTE PAPER A minute paper—completed in just 60 seconds—can be focused in a number of ways. You might ask students to write about the most important or interesting idea they learned in class that day or about which concept was most confusing. In *The Cell*'s Active Learning Guide you'll find minute papers used in a variety of ways to keep students actively engaged and get them to organize and share their thoughts. Papers can be collected for instructor review, or they can be swapped (anonymously) for small-group or class discussion.

SEQUENCE MAP Sequence maps help students understand a series of steps or events by arranging them in the proper order. You may choose to provide templates, in the form of handouts, with a specified number of boxes or fields to fill in. Alternatively, you can ask students to name different steps, then have them work independently to organize the steps correctly in a sequence map.

SMALL-GROUP DISCUSSION Students form small groups to discuss a complex topic that typically has multiple levels. Again, this can be followed with a classroom exercise, assigned for further study, or wrapped up before moving on.

SPIDER MAP Students place a central concept in the middle of a piece of paper and draw lines radiating out to connect to related, second-level concepts. Third and fourth levels may be used, if necessary.

T TABLE This is a simple, two-column table of pros and cons, terms and definitions, or any two characteristics that can be compared side-by-side. T tables are useful for getting students to focus on important details they may otherwise skip over.

THINK-PAIR-SHARE In this exercise you pose a question and give students a short time to think about it on their own. Then ask them to pair up with a classmate to discuss their answers. Finally, ask some or all pairs to share what they discussed. Think-pair-share is especially helpful for encouraging participation of shy students, who may be hesitant to speak in front of the whole class. By sharing with just one person first, the student can practice his or her response and potentially get reinforcement from a peer who has the same answer.

Assessment

Assessment of student learning in an active learning classroom takes many forms. Some informal assessment comes from simply listening in on students' conversations as they work on assignments. This is a great way to determine whether they are grasping key concepts and to figure out where they are stuck. As for formal assessment, frequent low-stakes assessment is a good way to help students stay on track.

Formative assessments, whose main goal is to inform instructors and students about learning progress, can take many forms, both in and out of class. Pre-class quizzes provide timely information for instructors about what to cover in class while also focusing students on the concepts that will be most important for the day's activity. Wrap-up questions and post-class quizzes can reinforce key ideas for students and help instructors reflect on the efficacy of a particular activity.

Instructors can choose how much weight to give individual assessments or whether to score them for completion only. It is important to find the right balance in this regard. If in-class activities are scored too leniently or infrequently, students may not be motivated to put forth appropriate effort. However, if activities are weighted heavily or graded stringently, students may become too focused on finding the right answers and less able to think creatively.

Summative assessments, like exams and projects, are meant to assess demonstrated learning gains. These are naturally higher-stakes assessments, as they typically represent a larger portion of the course grade. You can choose questions intended for in-class work and repurpose them for use on exams instead.

The Cell includes a test bank for each chapter, with several questions in various formats, aligned with specific learning objectives. Strive to align exam questions with the learning objectives you set, and consider those objectives when you design or choose formative assessments for in-class activities to give students appropriate practice. Even if backward course design is not feasible for the entire course at once, you can apply it one unit at a time to be sure you assess the concepts and skills that you believe are most important.

Time to Get Started

The possibilities for how to use the active learning materials provided with this textbook are plentiful, as are the types of activities available for you to explore. Now that you know why active learning is important and how to structure your course to include it, the next task is to explore the myriad resources available in this guide and on the independent websites recommended here. Don't let the task overwhelm you—remember that you can start small, just one activity at a time, to improve the learning experience for your students. Every moment that your students are engaged and active in the classroom is a moment of success. After each activity, take time to reflect on what worked well, and keep going back for more.

Recommended Resources

Angelo, T. A. and K. P. Cross. 1993. *Classroom assessment techniques: A handbook for college teachers* (2nd ed.). San Francisco, CA: Jossey-Bass.

This book has dozens of tools that can be used both for assessment and for in-class engagement. Each technique includes notes for implementation and extension and examples of its use in a variety of course settings. A few of the ideas posed in this Active Learning Guide (minute paper, defining features matrix) come from this text.

Mintzes, J. J., and W. H. Leonard, (Eds.). 2006. *Handbook of college science teaching*. Arlington, VA: National Science Teachers Association Press.

This edited volume contains multiple chapters that describe techniques for active learning in a college science course, including some described in this Guide (concept mapping, case studies, and reading literature). It also includes chapters on use of technology, student motivation, diversity, and the science of learning.

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CHAPTER 1

Part I **Fundamentals and Foundations**

Introduction to Cells and Cell Research

Chapter Overview

Understanding the molecular biology of cells is one of the most active and fundamental areas of research in the biological sciences. This is true not only from the standpoint of basic science, but also with respect to the numerous applications of cell and molecular biology to medicine, biotechnology, and agriculture. Especially with the ability to obtain rapid sequences of complete genomes, progress in cell and molecular biology is opening new horizons in the practice of medicine. Striking examples include genome editing; the identification of genes that contribute to susceptibility to a variety of common diseases, such as heart disease, rheumatoid arthritis, and diabetes; the development of new drugs specifically targeted to interfere with the growth of cancer cells; and the potential use of stem cells to replace damaged tissues and treat patients suffering from conditions like diabetes, Parkinson's disease, Alzheimer's disease, and spinal cord injuries.

Because cell and molecular biology is such a rapidly growing field of research, it is important to understand its experimental basis as well as the current state of our knowledge. This chapter focuses on how cells are studied and reviews some of their basic properties, including the unity and the diversity of present-day cells in terms of their evolution from a common ancestor and the properties of different kinds of cells that make them particularly valuable as experimental models.

Chapter Outline

1.1 The Origin and Evolution of Cells
- How did the first cell arise?
- The evolution of metabolism
- Prokaryotes
- Eukaryotic cells
- The origin of eukaryotes
- The development of multicellular organisms

1.2 Experimental Models in Cell Biology
- *E. coli*
- Yeasts
- *Caenorhabditis elegans* and *Drosophila melanogaster*
- *Arabidopsis thaliana*
- Vertebrates
- Animal cell culture
- Viruses
  - **Key Experiment** HeLa Cells: The First Human Cell Line
  - **Molecular Medicine** Viruses and Cancer

1.3 Tools of Cell Biology: Microscopy and Subcellular Fractionation
- Light microscopy
- Fluorescence microscopy and GFP
- Following protein movements and interactions
- Sharpening the focus and seeing cells in three dimensions
- Super-resolution microscopy: breaking the diffraction barrier
- Electron microscopy
- Subcellular fractionation

Section Reviews

1.1 The Origin and Evolution of Cells

The first cell is thought to have arisen at least 3.8 billion years ago by the enclosure of self-replicating RNA in a phospholipid membrane. The earliest reactions for generation of metabolic energy were a form of anaerobic glycolysis, followed by the evolution of photosynthesis and oxidative metabolism. Two domains of prokaryotic cells, Bacteria and Archaea, diverged early in evolution. Eukaryotic cells, which are larger and more complex than prokaryotic cells, contain a nucleus and cytoplasmic organelles.They evolved as a branch from the Archaea, with mitochondria and chloroplasts originating by endosymbiosis. Multicellular organisms then evolved from associations between unicellular eukaryotes, and division of labor led to the development of the many kinds of specialized cells that make up present-day plants and animals.

1.2 Experimental Models in Cell Biology

Some organisms are widely used in cell and molecular biology because they can easily be studied in the laboratory. *E. coli* is the basic model for fundamental aspects of biochemistry and molecular biology, and yeasts are the simplest model for eukaryotic cells. *C. elegans* and *Drosophila* are widely used for studies of animal development, and *Arabidopsis thaliana* is the model plant. The closest model for human biology is the mouse. Cell culture provides a way to study animal cells outside of intact organisms, and animal viruses are simple models for studies of many aspects of cell biology.

1.3 Tools of Cell Biology: Microscopy and Subcellular Fractionation

The light microscope, with a resolution of 0.2 µm, can be used to visualize cells and larger subcellular organelles. Fluorescence microscopy and the use of GFP allows specific proteins to be visualized and their movements and interactions in living cells to be studied. The use of fluorescent probes in super-resolution microscopy provides a resolving power approximately tenfold greater than that of the light microscope. Electron microscopy, with a resolution a hundredfold greater than light microscopy, is used to analyze details of cell structure. Subcellular fractionation provides the tools to isolate organelles for biochemical analysis.

Key Terms

adenosine 5′-triphosphate (ATP)
amphipathic
Arabidopsis thaliana
bright-field microscopy
Caenorhabditis elegans
cell wall
chloroplasts
confocal microscopy
cyanobacteria
cytoskeleton
density-gradient centrifugation
differential centrifugation
differential interference-contrast microscopy
Drosophila melanogaster
electron tomography
embryonic stem (ES) cells
endoplasmic reticulum (ER)
endosymbiosis
epithelial cells
equilibrium centrifugation
erythrocytes
Escherichia coli (E. coli)
Eukarya
eukaryotic cells
fibroblast
fluorescence microscopy
fluorescence recovery after photobleaching (FRAP)
fluorescence resonance energy transfer (FRET)
genes
glycolysis
Golgi apparatus
granulocytes
green fluorescent protein (GFP)
hydrophilic
hydrophobic
immortal cell lines
lymphocytes
lysosomes
macrophages
mitochondria
monocytes
multiphoton microscopy
neurons
nucleoid
nucleus
oxidative metabolism
peroxisomes
phase-contrast microscopy
phospholipids
photosynthesis
plasma membrane
primary cultures
prokaryotic cells
resolution
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super-resolution microscopy
transcription
translation
transmission electron microscopy
ultracentrifuge
vacuoles
velocity centrifugation
yeasts
zebrafish

Additional Media and Supplements for Use in the Classroom

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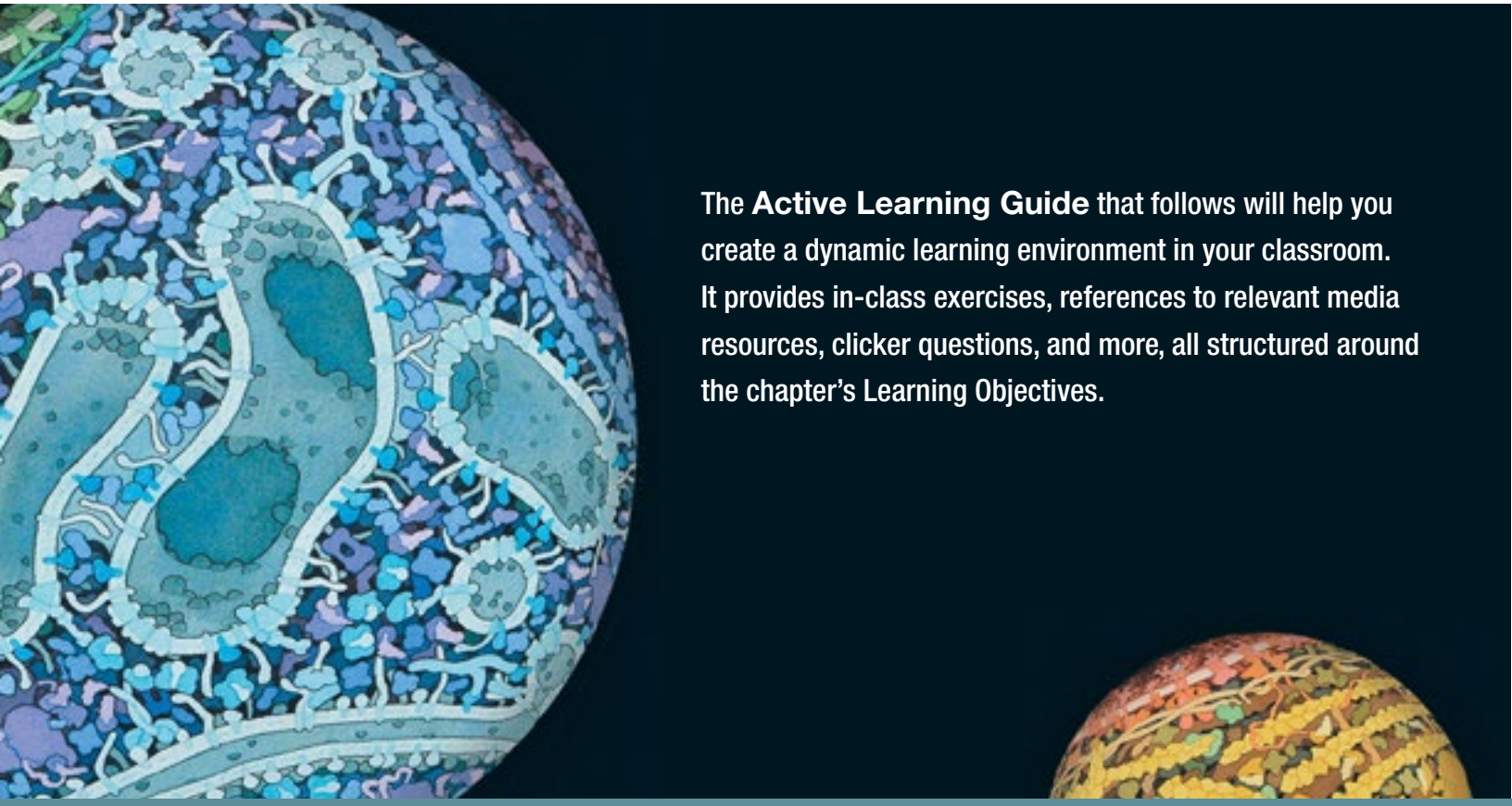
All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website



The **Active Learning Guide** that follows will help you create a dynamic learning environment in your classroom. It provides in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the chapter's Learning Objectives.

CHAPTER 1 Introduction to Cells and Cell Research

Active Learning Activities for the Classroom

1.1 The Origin and Evolution of Cells

Learning Objectives

You should be able to:

1.1.1 Explain how the first cell originated.
1.1.2 Describe the major steps in evolution of metabolism.
1.1.3 Illustrate the structures of eukaryotic and prokaryotic cells.
1.1.4 Outline the evolution of eukaryotic cells and multicellular organisms.

Media Available on Companion Website oup.com/uk/cooper8e

Video 1.1 *Paramecium* Feeding
Micrograph 1.1 *E. coli*

Active Learning Exercises

1. Have students do a **think-pair-share** exercise in which they discuss what features of RNA make scientists believe this was the initial genetic system. (LO 1.1.1)

   Answer: *Unlike DNA, RNA is self-replicating and carries genetic information.*

2. Have students form **small discussion groups** and share thoughts about why early cells could survive without their own metabolic pathways but eventually had to evolve metabolism. (LO 1.1.2)

   Answer: *The first organisms could live off the abundant supply of reduced organic molecules but eventually had to evolve the ability to generate energy and synthesize the molecules necessary for their replication.*

3. Have students **draw** typical prokaryotic and eukaryotic cells and label all components. (LO 1.1.3)

   Answer: *These drawings are shown in every biology textbook as "convenient fiction." While all of the components can be found in one cell or another, all are never found in the same cell. This can work well as a take-home assignment or as an unlabeled handout for students to fill in. It can be expanded by asking students to identify the function of each structure in the drawings.*

4. Have students write a minute paper to answer the question: "Given that prokaryotic cells are much simpler than eukaryotic cells, why have they not gone extinct over the course of Earth's history?" (LO 1.1.3)

   Answer: *Life evolved to be successful in a particular niche. Bacteria and Archaea are successful in their niches. There is no reason that being more complex is any better than being less complex. Survival is the key, and prokaryotes are incredibly successful.*

5. Have students use their smart devices to research the organism *Elysia chlorotica*. Next, have them form **debate teams** and discuss both sides of this question: "Is the *Elysia/Vaucheria* relationship an example of endosymbiosis?" (LO 1.1.4)

   Answer: *Probably not, because the plastids cannot be passed on from one generation to the next via the* Elysia *egg cells, as they are with true plants. However, the relationship does involve limited horizontal gene transfer from plastid to sea slug.*

Clicker Questions

1. The first self-replicating biomolecule in the evolution of life was DNA.
   a. True
   b. False

2. Why was glycolysis most likely the first complicated metabolic pathway to evolve?
   a. It served as the eventual precursor to photosynthesis.
   b. It could break down organic molecules and generate ATP.
   c. It could synthesize the organic molecules needed for metabolism.
   d. It served as the central branch point for feeding carbon into amino acid synthesis.

3. One way in which prokaryotic cells differ from eukaryotic cells is that prokaryotic cells typically have
   a. more complex metabolisms.
   b. more organelles.
   c. smaller nuclei.
   d. smaller genomes.

4. Eukaryotic cells have multiple organelles. This has allowed eukaryotes to
   a. greatly simplify their metabolism and be much more efficient than prokaryotic cells.
   b. evolve cells that are smaller and more complicated than prokaryotic cells.
   c. evolve cells that perform limited but specialized functions.
   d. increase the efficiency of metabolic pathways by keeping them separate.

5. Multicellular organisms evolved from
   a. the endosymbiosis of mitochondria and chloroplasts.
   b. the association of unicellular prokaryotes.
   c. the association of unicellular eukaryotes.
   d. the association of early archaea with bacterial cells.

Answers: *1: b; 2: b; 3: d; 4: c, d; 5: c*

1.2 Experimental Models in Cell Biology

Learning Objectives

You should be able to:

1.2.1 Explain the advantages of *E. coli* for studying basic concepts of molecular biology.
1.2.2 Contrast yeast with *E. coli* as a model system.
1.2.3 Summarize the simple models for studying plant and animal development.
1.2.4 Describe the advantages and disadvantages of studying vertebrates.
1.2.5 Summarize the principles of animal cell culture.
1.2.6 Explain how viruses can be used to study cell biology.

Media Available on Companion Website oup.com/uk/cooper8e

Key Experiment HeLa Cells: The First Human Cell Line

Active Learning Exercises

1. Ask students to find this paper online: Wade (2002) Unculturable bacteria—the uncharacterized organisms that cause oral infections. *J Roy Soc Med* 95(2): 81–83. Then have them form think-pair-share groups to discuss the consequences to all medical research (not just oral medicine) brought about by unculturable bacteria. (LO 1.2.1)

   Answer: *There is no definitive answer; the goal is to make students aware that many bacteria cannot be grown in culture, which obviously hampers research on those microbes.*

2. Have students make a **spider map** with "model system" at the center. Each leg of the map will connect to one of the seven systems described in the text: *Escherichia coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster*, *Arabidopsis thaliana*, *Danio rerio*, and *Mus musculus.* Beside each species name, have students add information, such as the common name, haploid genome size, number of protein-coding genes, and type of research the system would be used for. (LO 1.2.1, LO 1.2.2, LO 1.2.3)

   Answer: *Students may have to look up some of the common names. Genome size and number of protein-coding genes are listed in Table 1.2.*

3. Have students use their smart devices to research the USDA APHIS (United States Department of Agriculture Animal and Plant Health Inspection Service). Ask them to prepare a **T Table** in which they **compare and contrast** the regulations surrounding animal health inspection and those surrounding plant health inspection. (LO 1.2.4)

   Answer: *The animal rules, which are much more numerous, focus mostly on animal welfare, less on the spread of disease. The plant rules focus solely on preventing the spread of disease and pests. Plants are not considered to have a welfare. This is one reason animal research, especially vertebrate research, is at a disadvantage.*

4. Have students write a **minute paper** on the difference between a mortal and an immortal cell line. (LO 1.2.5)

   Answer: *Mortal cell lines can only be transferred for 50–100 cell doublings, whereas immortal cell lines can be subcultured indefinitely. Students' answers should include some knowledge that embryonic and cancer cells make good immortal cell lines.*

Clicker Questions

1. *Saccharomyces cerevisiae* is a yeast used for
   a. making bread.
   b. genetic studies.
   c. metabolic studies.
   d. brewing beer.

2. Prokaryotic model systems can be used in the study of eukaryotic cell and molecular biology because
   a. prokaryotic systems are very simple, so they are easy to work with.
   b. the fundamental properties of all cells have been conserved during evolution.
   c. studies of one model system can always be applied to other model systems.
   d. eukaryotic systems share all the features of prokaryotic systems.

3. While studies of model systems are important to science, only human studies are beneficial to medical research.
   a. True: Though all life forms share common features, human cell and molecular biology are unique.
   b. False: All advancements in science, regardless of model system, are applicable to human studies.
   c. True: Medical research is valuable only if it advances to the clinical stage. Studies on other organisms cannot advance to that stage.
   d. False: Many metabolic pathways, developmental patterns, and even genes are shared across microbe, plant, and animal groups.

4. Plant cell culture has several advantages over animal cell culture. What is one main advantage?
   a. In many instances, an entire adult plant capable of reproduction can be regenerated from cells in plant tissue culture.
   b. Plant cells in tissue culture can be used to generate tissues and organs needed for human transplant studies.
   c. Plant cells in tissue culture readily mutate, creating plants that are useful for further study.
   d. Animal cells in tissue culture can be used only for simple biomedical or clinical studies.

5. To study viruses in tissue culture you must first
   a. grow mammalian or plant cells in culture so the viruses have a host.
   b. sterilize the virus particles to remove contaminating bacterial cells.
   c. remove all DNA and RNA from the virus particles to avoid cross-contamination of genetic material.
   d. degrade the viral protein coat to allow experimental reagents to enter the virus particles.

Answers: *1: a, b, c, d; 2: b; 3: d; 4: a, 5: a*

1.3 Tools of Cell Biology: Microscopy and Subcellular Fractionation

Learning Objectives

You should be able to:

1.3.1 Summarize the uses and limitations of the light microscope.
1.3.2 Explain how fluorescence microscopy is used to visualize specific proteins.
1.3.3 Describe how GFP can be used to study proteins in living cells.
1.3.4 Explain super-resolution microscopy.
1.3.5 Compare electron microscopy and light microscopy.
1.3.6 Summarize procedures for isolation of subcellular organelles.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 1.1 Subcellular Fractionation
Video 1.2 Super-Resolution Light Microscopy
Data Analysis Problem 1.1 Fractionation of a Sample from Rat Liver
Data Analysis Problem 1.2 Electron Microscopy of Isolated Ribosomes
Data Analysis Problem 1.3 Equilibrium Density Gradient Centrifugation of DNA Samples
Data Analysis Problem 1.4 Electron Microscopic Analysis of a Nuclear Fraction from Rat Liver

Data Analysis Problem 1.5 Electron Microscopic Analysis of a Subcellular Fraction

Data Analysis Problem 1.6 Analysis of Protein Synthesis in Adenovirus-Infected Cells

Active Learning Exercises

1. Have students form **small discussion groups** and use the equations under "Light microscopy" to answer the question: "What effect would increasing refractive index have on image resolution?" (LO 1.3.1)

   Answer: *Increasing the refractive index (η) would increase the numerical aperture (NA) via the equation NA = η sin α. The resulting larger NA would decrease resolution in the equation Resolution = 0.6 1λ/NA. The latter equation gives the value by which two objects separated by less than this distance appear as a single image, rather than being distinguished from one another. Therefore, increasing the refractive index would decrease the calculated value for resolution and therefore increase the resolving power of a light microscope.*

2. Biological membranes are called a "fluid mosaic" because they are a mixture of lipids and proteins that can diffuse (move) within the plane of the membrane (i.e., fluid). However, the various lipids and proteins can diffuse at different rates. Have students write a **minute paper** in which they briefly describe how FRAP works to determine rate of molecular diffusion. Have them include an answer to the question: "How would the size of the lipid molecules affect the rate of diffusion?"

   Answer: *(A description of FRAP is in the text.) All other things being equal, the larger the lipid molecule, the slower the rate of diffusion.*

3. Have students prepare a **T Table** to compare electron microscopy with light microscopy. Ask them to associate each characteristic with one of the two types (LO 1.3.5):
   a. source = electron gun
   b. can view living specimens
   c. images are in color
   d. source = light bulb
   e. operates in a vacuum
   f. maximum magnification ≈ 200,000x
   g. operates at normal atmospheric pressure
   h. specimen must be dead
   i. uses glass lenses
   j. uses magnetic lenses
   k. images are in black and white
   l. maximum magnification ≈ 1,000x

   Answer: *Light microscopy = b, c, d, g, i, l; electron microscopy = a, e, f, h, j, k.*

Clicker Questions

1. If you wanted to visualize the movement of individual microtubules during the anaphase stage of mitosis, which microscopy technique would be the best choice?
   a. transmission electron microscopy
   b. confocal microscopy
   c. bright-field microscopy
   d. fluorescence recovery after photobleaching

2. Super-resolution microscopy allows microscope designers to
   a. break the "diffraction barrier" that limits the maximum resolution achievable with standard light microscopy.
   b. combine transmission electron microscopy with scanning electron microscopy to conduct correlative studies.
   c. localize and isolate individual fluorescently labeled cellular components.
   d. determine the rate of diffusion of individual fluorescently labeled cellular components.

3. Differential centrifugation is in subcellular fractionation studies of Archaea, Bacteria, and Eukarya.
   a. True
   b. False

Answers: *1. b; 2: a, c; 3: a (The text covers only subcellular fractionation within the context of isolating eukaryotic organelles, but differential centrifugation can also be used to isolate membranes, nucleoids, and ribosomes from Archaea and Bacteria.)*

Instructor's Manual: **Resources**

CHAPTER

2

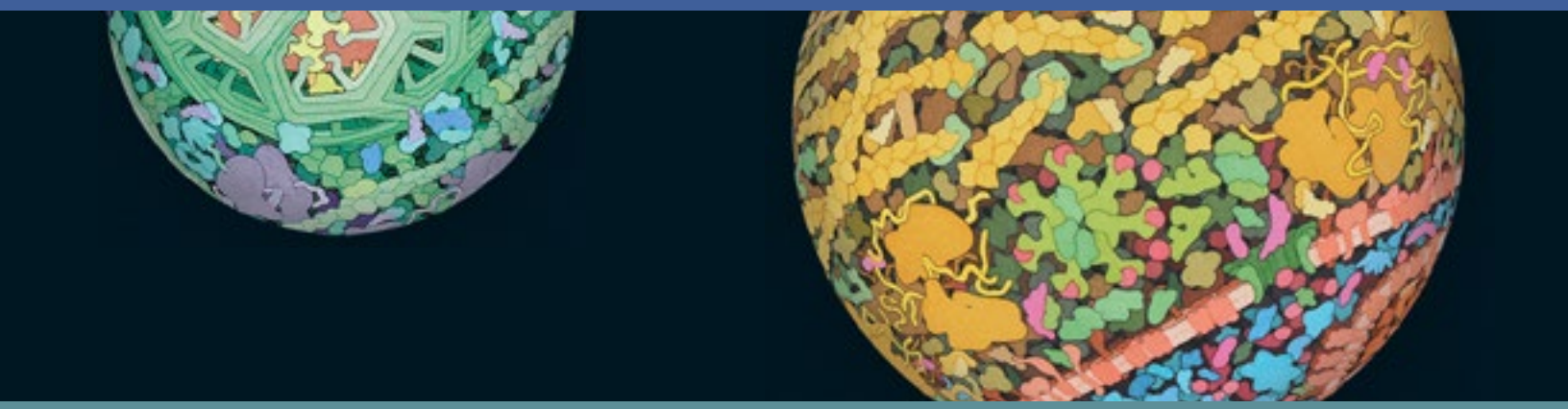
Part I **Fundamentals and Foundations**

Molecules and Membranes

Chapter Overview

Cells are incredibly complex and diverse structures, capable not only of self-replication—the very essence of life—but also of performing a wide range of specialized tasks in multicellular organisms. Yet, cells obey the same laws of chemistry and physics that determine the behavior of nonliving systems. Consequently, modern cell biology seeks to understand cellular processes in terms of chemical and physical reactions.

This chapter considers the chemical composition of cells and the properties of the molecules that are ultimately responsible for all cellular activities. Proteins are given particular emphasis because of their diverse roles within the cell, including acting as enzymes that catalyze almost all biological reactions and serving as key components of cell membranes. Membranes are critical to cell structure and function because they serve as barriers that separate distinct aqueous compartments. For example, the plasma membrane separates the contents of a cell from the external environment, while the nuclear membrane separates the contents of the nucleus from the cytoplasm. Membranes consist of both lipids and proteins and are impermeable to most water-soluble molecules, with proteins carrying out the selective transport of molecules across the phospholipid bilayer.



Chapter Outline

Section Reviews

2.1 The Molecules of Cells

Covalent bonds and four types of noncovalent bonds mediate the formation of and interactions between the molecules of cells. Four classes of organic compounds are the unique constituents of biological systems: carbohydrates, lipids, nucleic acids, and proteins. Carbohydrates, including simple sugars and polysaccharides, are the major nutrients of cells and serve as structural components and markers for cell recognition processes. Lipids are the principal components of cell membranes. Nucleic acids are the informational molecules of cells, with hydrogen bonding between complementary bases directing self-replication. Proteins, which are polymers of 20 different amino acids, are the most diverse macromolecules and are responsible for carrying out most cell functions.

2.2 Enzymes as Biological Catalysts

Almost all chemical reactions within cells are catalyzed by enzymes, which function by bringing substrates together, altering their conformations to approach the transition state, and forming bonds with reaction intermediates. Coenzymes are small molecules that function in conjunction with enzymes by carrying chemical groups between substrates. The activities of enzymes are regulated to meet the physiological needs of the cell. Enzymes can be controlled by the binding of small molecules, by interactions with other proteins, and by covalent modifications.

2.3 Cell Membranes

Phospholipid bilayers are the basic structures of cell membranes, which also contain glycolipids and, in eukaryotic cells, cholesterol or related compounds. Proteins can either be inserted into the lipid bilayer or associated with the membrane indirectly, by protein–protein interactions. Some proteins span the lipid bilayer; others are anchored to one side of the membrane. Lipid bilayers are permeable only to small, uncharged molecules. Ions and most polar molecules are transported across cell membranes by specific transport proteins, the action of which can be coupled to the hydrolysis or synthesis of ATP.

Key Terms

activation energy
active site
active transport
adenine
allosteric regulation
α helix
amino acids
amphipathic
β barrel
β sheet
carbohydrates
carrier proteins
cellulose
channel proteins
chitin
cholesterol
coenzymes
cytosine
deoxyribonucleic acid (DNA)
2′-deoxyribose
domains
enzymes
fats
fatty acids
feedback inhibition
fluid mosaic
glycerol phospholipids
glycogen
glycolipids
glycosidic bond
guanine
induced fit
integral membrane proteins
lipids
messenger RNA (mRNA)
monosaccharides
nicotinamide adenine dinucleotide (NADH)
nucleosides
nucleotides
oligonucleotides
oligosaccharide
passive transport
peptide bond
peripheral membrane proteins
phosphodiester bond
phospholipid bilayers
phosphorylation
polynucleotides
polypeptides
polysaccharides
primary structure
product (*P*)
prosthetic groups
purine
pyrimidine
quaternary structure
ribonucleic acid (RNA)
ribose
ribosomal RNA
secondary structure
sheet
sphingomyelin
starch
steroid hormones
substrate
tertiary structure
thymine
transfer RNA
transition state
transmembrane proteins
triacylglycerols
triglycerides
uracil
X-ray crystallography

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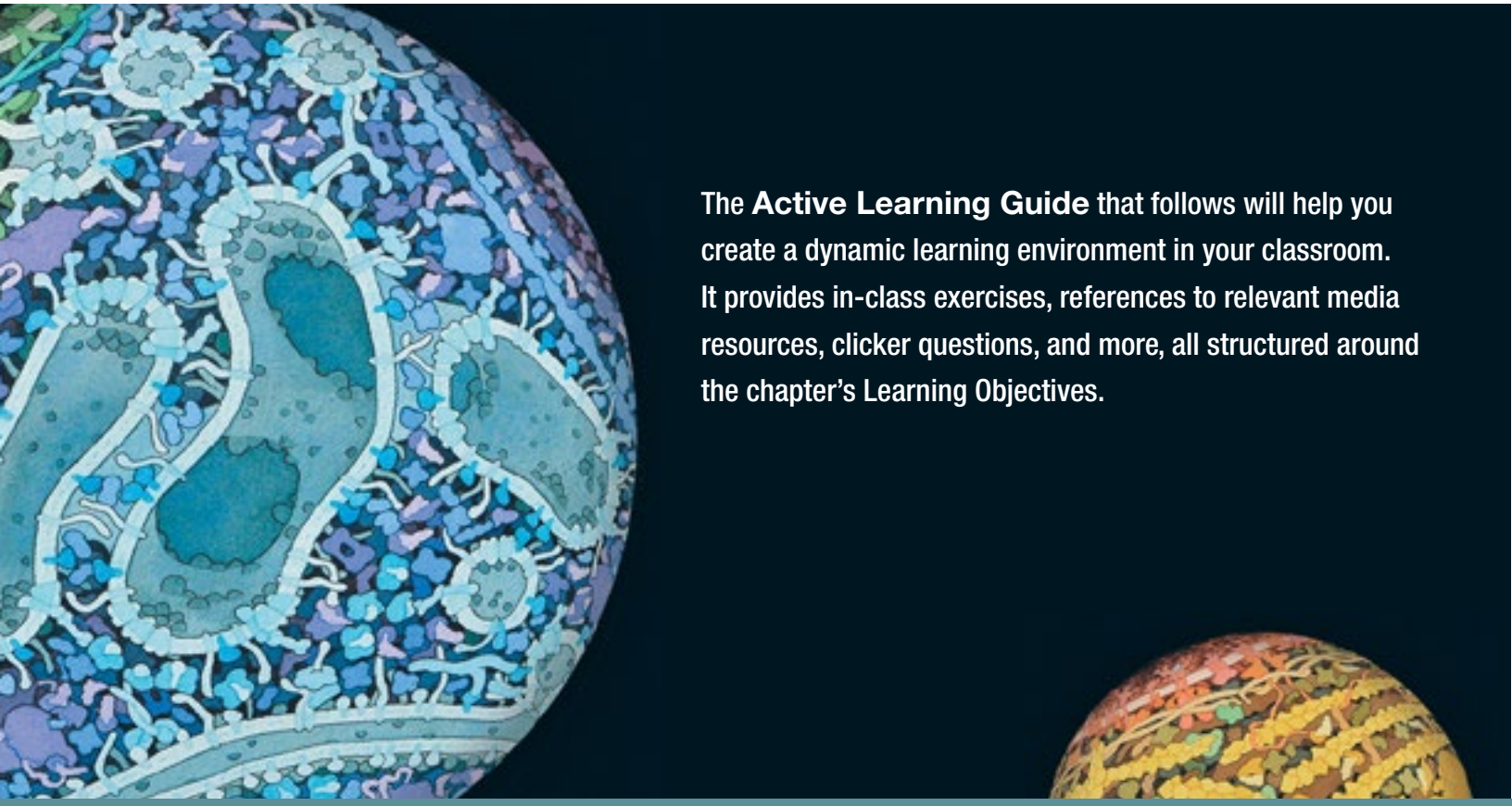

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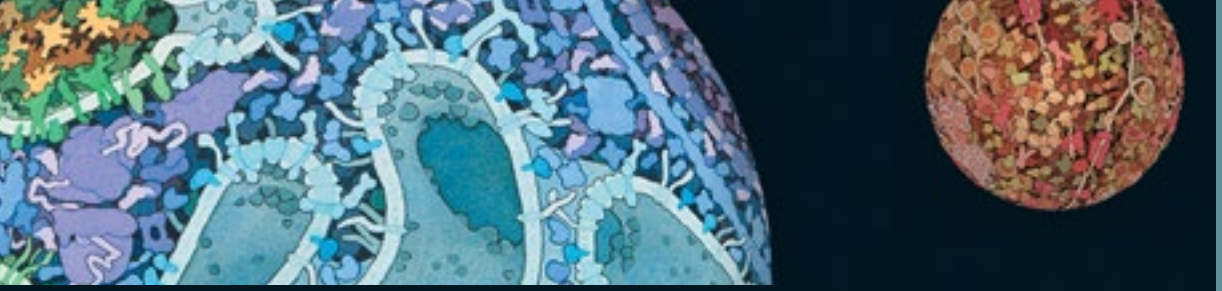


CHAPTER 2 Molecules and Membranes

Active Learning Activities for the Classroom

2.1 The Molecules of Cells

Learning Objectives

You should be able to:

2.1.1 Explain the properties of different types of chemical bonds.
2.1.2 Diagram the structure of a simple carbohydrate.
2.1.3 Compare the structures of fatty acids, phospholipids, and steroid hormones.
2.1.4 Contrast the structures of RNA and DNA.
2.1.5 Summarize the properties of the different groups of amino acids.
2.1.6 Explain the roles of noncovalent bonds in protein folding.

Media Available on Companion Website oup.com/ukcooper8e

Key Experiment The Folding of Polypeptide Chains
Animation 2.1 Bond Formation
Video 2.1 What Is a Protein?
Data Analysis Problem 2.2 Electrophoretic Mobility of Hemoglobin Variants
Data Analysis Problem 2.3 The Effect of Heating on DNA Samples

Active Learning Exercises

1. Though motor oil is a mixture of different molecules, the bulk of the recipe is made of 18- to 34-carbon, straight-chain alkanes. Have students form small **discussion groups** to discuss why those molecules would make a good engine lubricant. (LO 2.1.1)

   Answer: *The atoms in the chain are connected via covalent bonds, the strongest of the four chemical bond types. Therefore, the oil molecules can endure high engine temperatures without breaking down. Further, alkanes are hydrophobic and do not "stick" together or to surfaces. They are slippery. Heat-stable and slippery make for good engine oil.*

2. Have students construct a **spider map** with the word "nucleotides" in the center and one leg for each nucleotide. At the end of each leg include the name of a nucleotide and whether it is a purine or a pyrimidine, contains deoxyribose or ribose, and is found in DNA or RNA. (LO 2.1.4)

   Answer: *There should be eight legs in the spider map. DNA has four nucleotides: A, T, C and G, each with a deoxyribose sugar. RNA has A, U, C and G, each with a ribose sugar. The point is to make students realize that the adenine in DNA is a similar but different molecule than the adenine in RNA. Why does that matter? Because the enzymes that synthesize DNA (DNA polymerase) and RNA (RNA polymerase) need to be able to tell the difference between the different but closely related forms of nucleotides and that little OH group on ribose is enough information to allow them to do so.*

3. Have students use their smart devices to research and write a **minute paper** answering the question: "What are the most abundant carbohydrate, lipid, and protein molecules on Earth?" (LO 2.1.2, LO 2.1.3, LO 2.1.5)

   Answer: *The most abundant carbohydrate is cellulose, a polymer of glucose found in plant cell walls. The most abundant lipids are MGDG (monogalactosyl diglyceride) and DGDG (digalactosyl diglyceride) found in plant photosynthetic membranes. The most abundant protein is ribulose-bis-phosphate carboxylase oxygenase, a protein used by plants in the process of photosynthesis.*

4. Have students use their smart devices to research the chemistry that underlies how a hairdresser does a perm (generally, making curly or wavy hair from straight hair). Have them discuss in **think-pair-share** groups. (LO 2.1.5)

   Answer: *Hair is treated with a solution of sodium thioglycolate (NaGly), which is a reductant. The NaGly breaks the disulfide bonds in the hair protein (keratin). Hair is then wrapped into a curly shape, and an oxidant (usually hydrogen peroxide) is added to reform the disulfide linkages.*

Clicker Questions

1. What kind of crystals would form if all of the water were removed from a salt solution containing sodium ions, magnesium ions, and chloride ions? (LO 2.1.1)
   a. $Mg(Cl)_2$ and NaCl
   b. MgCl and $Na(Cl)_2$
   c. MgNa and $Mg(Cl)_2$
   d. $Na(Mg)_2$

2. Carbohydrates differ from hydrocarbons in that (LO 2.1.2)
   a. carbohydrates are composed of carbon and hydrogen.
   b. hydrocarbons are composed of carbon and hydrogen.
   c. carbohydrates are composed of carbon and water.
   d. hydrocarbons are composed of carbon and water.

   (Hint: Point out to students the derivation of the term: "carbo" = carbon and "hydrate" = water, whereas "hydro" = hydrogen and "carbon" = carbon.)

3. If a steroid hormone were covalently modified by the addition of multiple hydrophilic side groups it would be _____ likely to dissolve in the bloodstream. (LO 2.1.3)
   a. more
   b. less

4. Taken together, what is the total number of unique nucleotides in DNA and RNA? (LO 2.1.4)
   a. 4
   b. 5
   c. 8

5. Using your skills as a molecular biologist, you synthesize a fungal gene that codes for a protein with the amino acid sequence given below. Where would you expect to find that protein when the gene is expressed in a fungal cell? (LO 2.1.5)

   Met-Phe-Tyr-Val-Val-Asn-Asp-Ser-Gln-Val-Ala-Ala-Gly

   a. The entire protein would be embedded in a membrane, with no part of it in the cytoplasm.
   b. The two ends would be embedded in a membrane, and the middle would be in the cytoplasm.
   c. The two ends would be in the cytoplasm, and the middle would be embedded in a membrane.
   d. The entire protein would be in the cytoplasm, with no part of it in a membrane.

Answers: 1: a; 2: b, c; 3: a; 4: c; 5: b

2.2 Enzymes as Biological Catalysts

Learning Objectives

You should be able to:

2.2.1 Explain why enzymes affect the kinetics of chemical reactions without changing the equilibrium between reactants and products.
2.2.2 Summarize the mechanisms of enzymatic catalysis.
2.2.3 Distinguish between enzymes and coenzymes.
2.2.4 Explain why regulating the activity of enzymes is important to cell function.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 2.2 Catalysts and Activation Energy
Animation 2.3 Enzyme-Catalyzed Reactions
Data Analysis Problem 2.1 The Effect of a Reducing Agent on Protein Structure
Data Analysis Problem 2.4 Enzyme Activity of an RNA Molecule

Active Learning Exercises

1. One Learning Objective for section 2.2 reads, "Explain why enzymes affect the kinetics of chemical reactions without changing the equilibrium between reactants and products." Neither "kinetics" nor "equilibrium" are defined in the text. Have students research the meaning of these critical terms, then define and use the terms correctly in a **minute paper**. (LO 2.2.1)

   Answer: *Kinetics is the study of enzyme reaction mechanisms. Equilibrium is the point in a chemical reaction in which the rate of the forward reaction equals the rate of the reverse reaction. Both reactions still proceed, but their rates are equal, so there is no net change in concentration of substrate or product.*

2. Have students form **small discussion groups** in which they compare and contrast the three enzyme reaction mechanisms described in the text: 1) binding multiple substrates, 2) induced fit, and 3) direct participation in the catalytic process. (LO 2.2.2)

   Answer: *1) The binding of two or more substrates to the active site accelerates the reaction by holding the substrates in the proper position and orientation, akin to holding two pieces of paper together long enough for glue to dry. 2) Induced fit distorts the substrate molecules and weakens critical bonds, similar to snapping a twig in two. 3) In direct participation, specific amino acids in or near the active site react with the substrate and form bonds with reaction intermediates.*

3. Table 2.1 lists seven coenzymes and gives a related vitamin and a chemical reaction type for each. Have students add a fourth column to that **table** that describes the reaction and shows the functional group involved. (LO 2.2.3)

   Answer: *NAD^+, $NADP^+$, and FAD are common electron carriers that remove electrons from (i.e., oxidize) one substrate and deliver those electrons to (i.e., reduce) a second substrate; vitamin B1 transfers an aldehyde group (-COH) between molecules; pantothenate transfers an acetyl group (-COOH); folate transfers a methyl group (-CH3); vitamin B6 transfers an amino group (-NH2); biotin transfers either a carbon (CO2) or a carboxyl (-COOH). The purpose of this exercise is to show students that all of these reactions involve the transfer of either electrons or small (three to four atoms) functional groups. In spite of the fact that many biomolecules are huge, a lot of biochemistry involves small reactions.*

4. Have students **in pairs or small groups** discuss this experimental scenario and the question that follows. You set up the chemical reaction aA + bB → cC and run it under four conditions: 1) At room temperature in the absence of the proper enzyme, 2) at 100°C in the absence of the proper enzyme, 3) at room temperature with the proper enzyme and 4) at 100°C with the proper enzyme. Under which set of conditions would you expect the yield of product C to be the highest?

   Answer: *There is no correct answer. The amount of product C produced is a function of the equilibrium constant of the reaction, NOT the path by which the reaction proceeds and would be the same regardless of reaction conditions.*

Clicker Questions

1. Enzymes are biological catalysts that must be continually replaced via protein synthesis because they are consumed by the reactions they mediate. (LO 2.2.1)
   a. True
   b. False

2. What role does protein tertiary structure play in enzyme specificity? (LO 2.2.2)
   a. Protein tertiary structure is a result of hydrophobic and intermolecular interactions. These interactions make the enzymes very specific.
   b. Protein tertiary structure is fixed and unchanging. Because 3° structure never changes, enzymes can bind only one substrate and are therefore very specific.
   c. Protein tertiary structure determines the shape of the active site, which determines the specific substrate that can be bound.
   d. Protein tertiary structure constantly changes in response to environmental factors. This allows enzymes to adapt to and be specific for any substrate and any time.

3. In protein tertiary structure and enzyme specificity, allosteric regulators (LO 2.2.2)
   a. bind to sites other than the active site and change the binding affinity of the enzyme for its substrate.
   b. bind to the active site and prevent the enzyme's normal substrate from binding.
   c. bind to sites other than the active site and alter protein tertiary structure.
   d. bind to the enzyme's normal substrate and create a regulator/substrate complex that is too large to fit in the active site.

4. Why do humans need vitamins as part of their diet, whereas plants do not? (LO 2.2.4)
   a. Plant metabolism is so much simpler than human metabolism that plants do not need vitamins.
   b. Plants do not actually perform metabolism or use enzymes. Therefore vitamins (enzyme cofactors) are not needed.
   c. Ingesting vitamins allows human metabolism to be much more complex than that of plants.
   d. Plant metabolism is more sophisticated than human metabolism. Plants make all their own vitamins.

5. Refer to the chemical reaction below. (LO 2.2.4)

$$aA + bB \rightarrow cC$$

   You set up this reaction and run it under four sets of conditions: 1) At room temperature in the absence of the proper enzyme, 2) at 100°C in the absence of the proper enzyme, 3) at room temperature with the proper enzyme, and 4) at 100°C with the proper enzyme. Under which set of conditions would you expect the reaction rate to be the fastest?

   a. RT minus enzyme
   b. 100°C minus enzyme
   c. RT plus enzyme
   d. 100°C plus enzyme

Answers 1: b; 2: c; 3: a,c; 4: d; 5: c

2.3 Cell Membranes

Learning Objectives

You should be able to:

2.3.1 Illustrate the hydrophobic and hydrophilic interactions that lead to the formation of lipid bilayers.

2.3.2 Explain the difference between integral and peripheral membrane proteins.

2.3.3 Distinguish molecules that can diffuse through a lipid bilayer from those that require transporters to cross a membrane.

Media Available on Companion Website oup.com/uk/cooper8e

Key Experiment The Structure of Cell Membranes

Animation 2.4 Passive Transport

Video: 2.2 Ordering Effect of Cholesterol in a Lipid Bilayer

Active Learning Exercises

1. Have students form **think-pair-share** groups to answer the following question: Plastoquinol (PQ) is a hydrophobic molecule with a ringed head group and a 40-carbon-long tail. It is found in the photosynthetic electron transport chain of chloroplasts. Given the length of the membrane lipids shown in Figure 2.11 and the bilayer structure shown in Figure 2.34, where would you expect PQ to reside in the photosynthetic membrane? (LO 2.3.1)

   Answer: *Membrane lipids have 16–18 carbons, meaning a membrane is roughly 32–36 carbons thick—too thin for the 40+ carbon-long plastoquinol to sit in the membrane like cholesterol does, perpendicular to the membrane surface. Therefore, PQ lies parallel to the membrane surface, near the center of the membrane.*

2. Have students create a **matrix** in which they divide membrane proteins into peripheral versus integral, then divide those categories into the ways those membrane associations are maintained. (LO 2.3.2)

   Answer: *See Figure 2.36. Integral proteins all have at least one membrane-spanning, hydrophobic alpha helix. Peripheral proteins may be associated several different ways.*

3. Have students write a **minute paper** that answers the question, "What is the difference between simple diffusion and passive transport?" (LO 2.3.3)

   Answer: *Passive transport requires a channel or carrier protein and simple diffusion does not.*

Clicker Questions

1. Lipid bilayers form the basis of almost all cell membranes. Would it be possible for a cell to have a lipid monolayer as a membrane? In protein tertiary structure and enzyme specificity, allosteric regulators (LO 2.3.1)
   a. bind to sites other than the active site and change the binding affinity of the enzyme for its substrate.
   b. bind to the active site and prevent the enzyme's normal substrate from binding.
   c. bind to sites other than the active site and alter protein tertiary structure.
   d. bind to the enzyme's normal substrate and create a regulator/substrate complex that is too large to fit in the active site.
   e. Yes. Lipid droplets, in many cells, are surrounded by a lipid monolayer with the hydrophobic tails pointing toward the lipid and the hydrophilic heads pointing toward the cytoplasm.
   f. No. Lipid droplets in cells must be surrounded by a lipid bilayer with the hydrophilic heads pointing toward the lipid droplet and hydrophobic tails pointing toward the cytoplasm.

2. Referring to the β barrel shown in Figure 2.37: What would happen if those cells were placed in a solution that contained a peptidase (an enzyme that degrades proteins)? (LO 2.3.1)
   a. The peptidase would digest the β barrel and cause a pore to form in the membrane.
   b. The peptidase would digest the loops on the outside of the cell and leave the β barrel intact.
   c. The peptidase would degrade the lipids of the membrane and release the β barrel.
   d. The peptidase would degrade the entire β barrel protein, but the membrane would seal any pore formed.

3. Figure 2.38 shows that many molecules can diffuse freely through a lipid bilayer. What determines the direction and rate of that diffusion? (LO 2.3.3)
   a. The properties of the membrane lipids
   b. The properties of the diffusing species
   c. The number and variety of other molecules in solution
   d. The concentration difference across the membrane

4. What key feature(s) of the Singer–Nicolson membrane model distinguished it from other models? (LO 2.3.3)
   a. It assumed that the lipids and proteins were arranged in separate layers.
   b. It assumed that the lipids and proteins were intermixed within the structure of the membrane.
   c. It was based on thermodynamic considerations of lipid-protein-water interactions.
   d. It accounted only for membranes that had less than 10% protein and 90% lipid.

5. Which statement about passive transport and active transport is correct? (LO 2.3.3)
   a. Both rely on membrane-spanning proteins.
   b. Both rely solely on a concentration gradient.
   c. Active transport requires energy input.
   d. Passive transport requires a membrane spanning protein.

Answers: *1: a; 2: b; 3: d; 4: b; 5: c*

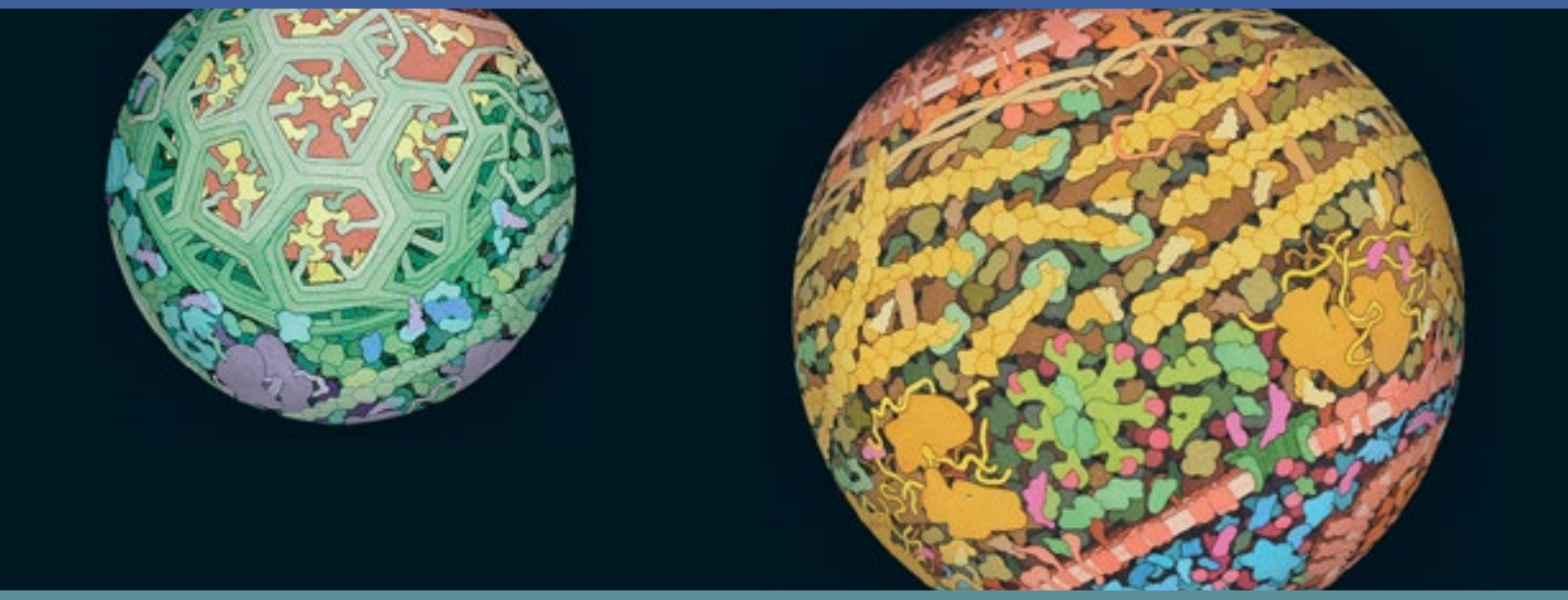
CHAPTER 3

Part I **Fundamentals and Foundations**

Bioenergetics and Metabolism

Chapter Overview

Almost all cellular activities, including movement, membrane transport and the synthesis of cell constituents, require energy. Consequently, the generation and utilization of metabolic energy is fundamental to all of cell biology. All cells use ATP as their source of metabolic energy, and the mechanisms that cells use for the generation of ATP, either from the breakdown of organic molecules or from photosynthesis, are discussed in this chapter. In addition, this chapter presents an overview of the network of chemical reactions that constitute the metabolism of the cell and are responsible for the synthesis of major cell constituents, including carbohydrates, lipids, proteins, and nucleic acids.



Chapter Outline

3.1 Metabolic Energy and ATP
- The laws of thermodynamics
- The role of ATP

3.2 Glycolysis and Oxidative Phosphorylation
- Glycolysis
- The citric acid cycle
- The derivation of energy from lipids
- Electron transport and oxidative phosphorylation
- Chemiosmotic coupling
  - **Key Experiment** The Chemiosmotic Theory

3.3 Photosynthesis
- Electron transport
- ATP synthesis
- Synthesis of glucose

3.4 The Biosynthesis of Cell Constituents
- Carbohydrates
- Lipids
- Proteins
  - **Key Experiment** Antimetabolites, Cancer, and AIDS
- Nucleic acids

Section Reviews

3.1 Metabolic Energy and ATP

The behavior of cells is governed by the first and second laws of thermodynamics. Gibbs free energy combines the effects of entropy and enthalpy to predict the direction of biochemical reactions, which proceed in the energetically favorable direction. ATP serves as a store of free energy, which can be used to drive energy-requiring reactions within cells.

3.2 Glycolysis and Oxidative Phosphorylation

The breakdown of glucose provides a major source of cellular energy. Glycolysis is the initial stage of glucose breakdown in all cells. In aerobic cells, the oxidation of glucose is then completed by the Krebs cycle, yielding 36 to 38 molecules of ATP. Most of this ATP is derived from electron transport reactions in which electrons from NADH and $FADH_2$ are transferred through a series of carriers in the inner mitochondrial membrane of eukaryotic cells. The energy-yielding reactions of electron transport are coupled to the generation of a proton gradient across the inner mitochondrial membrane and the energy stored in this gradient is harvested by ATP synthase, which couples ATP synthesis to the energetically favorable return of protons to the mitochondrion.

3.3 Photosynthesis

Energy from sunlight is absorbed by chlorophylls, exciting electrons to a higher energy state. These high-energy electrons are then transferred through a series of membrane carriers, coupled to the synthesis of ATP and the reduction of $NADP^+$ to NADPH. The ATP and NADPH produced by these reactions are then used to synthesize glucose from CO_2 and H_2O.

3.4 The Biosynthesis of Cell Constituents

Biosynthetic reactions are driven by energy and reducing power, usually in the form of ATP and NADPH. Additional energy is required to drive the polymerization of simple sugars, amino acids, and nucleotides to form polysaccharides, proteins, and nucleic acids, respectively.

Key Terms

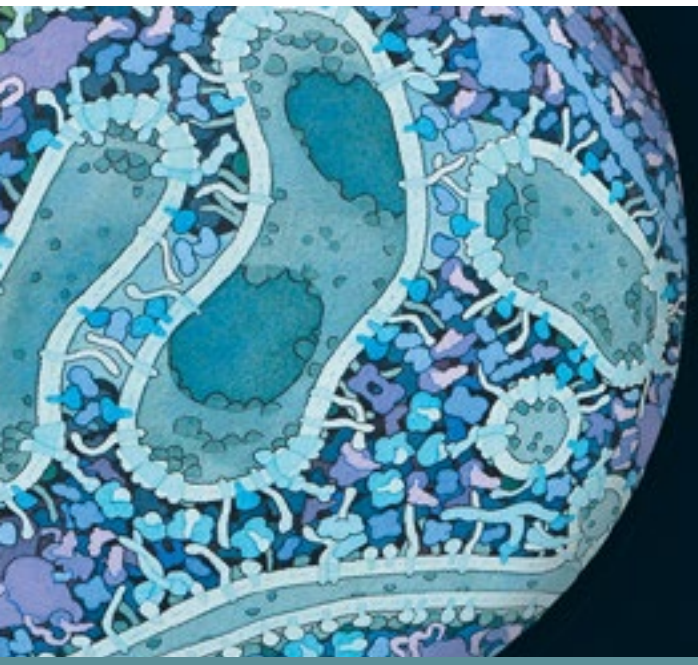
adenosine 5′-triphosphate (ATP)
anabolism
ATP synthase
Calvin cycle
catabolism
chemiosmotic coupling
chlorophylls
citric acid cycle
coenzyme A (CoA-SH)
coenzyme Q
cyclic electron flow
cytochrome *bf* complex
cytochrome *c*
cytochrome oxidase
dark reactions
electrochemical gradient
electron transport chain
enthalpy
entropy
flavin adenine dinucleotide ($FADH^2$)
Gibbs free energy (*G*)
gluconeogenesis
glycolysis
high-energy bonds
Krebs cycle
light reactions
NADP reductase
nitrogen fixation
oxidative phosphorylation
photocenters
photosystem I
photosystem II
ubiquinone

Additional Media and Supplements for Use in the Classroom

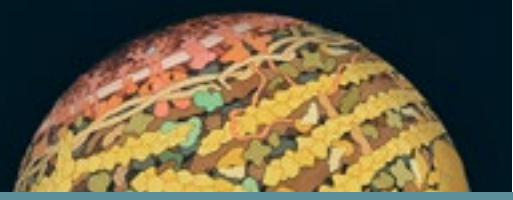
Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

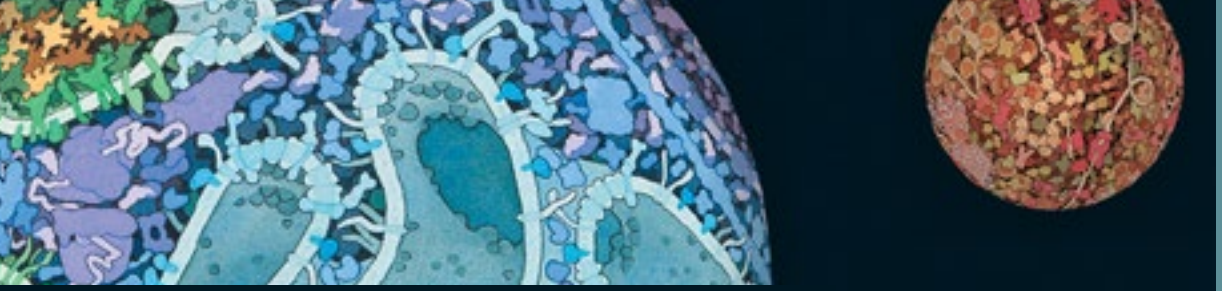
All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website



The **Active Learning Guide** that follows will help you create a dynamic learning environment in your classroom. It provides in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the chapter's Learning Objectives.





CHAPTER 3 Bioenergetics and Metabolism

Active Learning Activities for the Classroom

3.1 Metabolic Energy and ATP

Learning Objectives

You should be able to:

3.1.1 Interpret the first and second laws of thermodynamics.

3.1.2 Explain how changes in Gibbs free energy determine the direction of chemical reactions.

3.1.3 Summarize the role of ATP in cell physiology.

Active Learning Exercises

1. Have students form **think-pair-share** groups and answer this question: "Why is the second law of thermodynamics dependent on the first law of thermodynamics?" (LO 3.1.1)

   Answer: *The second law defines what happens when energy is converted or used (entropy increases). The first law lays out the fact that energy is converted or used (energy is neither created or destroyed, it is converted).*

2. Have students write a **minute paper** in which they use text to describe the relationship between the terms in the equation: $\Delta G = \Delta H - T\Delta S$. (LO 3.1.2)

   Answer: *The equation says that every chemical reaction is associated with a change in energy (ΔG) (as described by the 1st and 2nd laws of thermodynamics). All of that energy change is represented by a loss or gain of heat (ΔH) plus a loss of gain of entropy (ΔS). So, the equation explains what the energy is converted into as it is used to do work.*

3. Have students form **small discussion groups** to consider the question "Why is ATP needed for so many biochemical reactions?" (LO 3.1.3)

   Answer: *Many biochemical reactions have a ΔG >0 and would not proceed without the input of energy. Therefore, ATP hydrolysis (which releases energy) is coupled to the reaction that needs energy, and the two separate reactions proceed at the same time.*

Clicker Questions

1. The first and second laws of thermodynamics describe what happens to energy in the biosphere: it is eventually converted to heat or disorder. If that is the case, where does the energy come from to power the biosphere? (LO 3.1.1)
   a. Plant and animal agriculture
   b. The sun, via photosynthesis
   c. The earth's core, via geothermal sources
   d. Nutrients in the soil, taken up by plants

2. A value >0 for ΔG means that the reaction as written will (LO 3.1.2)
   a. need energy input to proceed.
   b. proceed spontaneously.
   c. release energy.
   d. generate heat.

3. Biochemists are more interested in the value of ΔG than $\Delta G°$ because (LO 3.1.2)
   a. the $\Delta G°$ value for any reaction can be found on the Internet and does not need to be calculated.
   b. enzymes change the ΔG of a reaction, knowing $\Delta G°$ is only useful for non-enzymatic reactions.
   c. ΔG is always larger than $\Delta G°$, meaning that all chemical reactions will proceed to equilibrium.
   d. the calculation of $\Delta G°$ is based on chemical concentrations that never exist inside a cell.

4. The adenine moiety found in ATP is also found in (LO 3.1.3)
   a. the electron carriers NADH, NADPH and $FADH_2$.
   b. coenzyme A.
   c. the nucleic acid RNA.
   d. the nucleic acid DNA.

5. To calculate the total free energy change of two coupled reactions—a chemical reaction coupled to the hydrolysis of ATP—one would need to (LO 3.1.3)
   a. add together the free energy changes of both reactions.
   b. take the ΔG of the first reaction and subtract 7.3 kcal/mol.
   c. subtract the ΔG of the first reaction from the free energy change of ATP hydrolysis.
   d. do nothing. The total free energy change is the same as the ΔG of the first reaction.

Answers: *1: b; 2: a; 3: d; 4: a, b, c, d; 5: a, b*

3.2 Glycolysis and Oxidative Phosphorylation

Learning Objectives

You should be able to:

3.2.1 Summarize the reactions of glycolysis and the citric acid cycle.

3.2.2 Describe the breakdown of lipids.

3.2.3 Compare the mechanisms of ATP formation during glycolysis and oxidative phosphorylation.

3.2.4 Explain chemiosmotic coupling.

Media Available on Companion Website oup.com/uk/cooper8e

Key Experiment The Chemiosmotic Theory

Animation 3.1 Glycolysis

Animation 3.2 The Citric Acid Cycle

Video 3.1 ATP Synthase in Action

Active Learning Exercises

1. Have students form **small discussion groups** and calculate the net free energy change in the following reaction to determine if the reaction will proceed spontaneously. (LO 3.2.1)

   1,3-*bis*phosphoglycerate + ADP + Pi → 3-phospohglycerate + ATP

   Answer: *The textbook gives the value of $\Delta G^{\circ\prime}$ = –11.5 kcal/mol for the 1,3 bPG → 3-PG reaction and 7.3 kcal/mol for the ADP + P → ATP reaction. Adding those together yields –11.5 + 7.3 = –4.2 kcal/mol net change. The reaction will proceed spontaneously.*

2. Instruct students to prepare a **sequence map** that lays out the steps in the breakdown of lipids. Then choose a student to share his or her map with the class. (LO 3.2.2)

   Answer: *See Figure 3.5.*

3. Have students write a **minute paper** in which they compare the oxidation of glucose during respiration to the oxidation of glucose in a burning marshmallow. What happens to the energy that is released? (LO 3.2.3)

   Answer: *In both processes, the high-energy electrons in the carbon–carbon bonds of the glucose are transferred from the glucose molecule to molecular oxygen. In the case of cellular respiration, much of the energy is captured and stored in ATP. In the case of the burning marshmallow, the energy is converted to light and heat and lost to the environment.*

4. In **small discussion groups,** have students consider how the waste products of cellular respiration, CO_2 and H_2O, relate to fire extinguishers. (LO 3.2.4)

   Answer: *After most of the energy (in the form of high-energy electrons) from the glucose molecules has been extracted to make ATP via substrate level or chemiosmosis, all the atoms and the electrons that carried that energy still remain. The carbon atoms are lost as CO_2, and the electrons end up on oxygen to form water. Because the energy was stored in the ATP, CO_2 and H_2O are low-energy molecules that are good at extinguishing fires.*

Clicker Questions

1. Glucose brings carbon atoms and electrons to glycolysis and the citric acid cycle. The carbon atoms are lost _____, whereas the electrons end up _____. (LO.3.2.1)
   a. in the CAC as CO_2; in water
   b. in glycolysis; as NAD^+
   c. in the electron transport chain; in ATP
   d. in the CAC as CO_2; in ATP

2. Glucose brings carbon atoms and energy to glycolysis and the citric acid cycle. The carbon atoms are lost _____, whereas the energy ends up _____. (LO.3.2.1)
   a. in the CAC as CO_2; in water
   b. in glycolysis; as NAD^+
   c. in the electron transport chain; in ATP
   d. in the CAC as CO_2; in ATP

3. Why are lipids, and not polysaccharides, the main form of energy storage in animals? (LO.3.2.2)
   a. Lipids are more easily digested than polysaccharides.
   b. Lipids have substantially more energy stored as starch.
   c. Lipids are hydrophobic, while polysaccharides are hydrophilic.
   d. Animals lack the metabolic pathways to synthesize polysaccharides.

   (*Note:* Have students discuss their answer choices. Then initiate a discussion with this explanation: Animals are mobile and, as such, need to minimize weight. Lipids pack more energy per gram than polysaccharides and they do not bind water. Animals store fat. Plants, on the other hand, are sessile. They "don't mind" if their energy storage form also binds a lot of water weight because they are stuck in one place. Plants store starch (and all the water that is bound to it). The one instance in which this is not true for plants is seeds, which often store oils (peanut oil, soybean oil, corn oil, canola oil, and many others are all extracted from seeds) and may need to be transported long distances. This also relates to why marathon runners gain a few pounds and feel bloated when they carbo load. The added glycogen binds water, which is heavy.)

4. The ATP made via substrate-level phosphorylation is different from the ATP made by chemiosmosis. (LO.3.2.3)
   a. True: The mechanisms of synthesis are fundamentally different.
   b. False: ATP is the same molecule regardless of how or where it is made.

5. Electrons are used to make ATP as they move through the electron transport chain, and they never make it to the end of the chain. (LO.3.2.3)
   a. True: Electrons are nothing more than packets of energy. When they give up their energy, they cease to exist.
   b. False: The electrons are used to reduce oxygen to the level of water. They have lost much of their energy, but they still exist as discrete electrons.

6. Because chemiosmotic ATP synthesis relies on the flow of electrons through an electron transport chain, chemiosmosis is considered to be a redox reaction. (LO.3.2.3)
   a. True: Any reaction that relies on the transfer of electrons from one molecule to the next is, by definition, a redox reaction.
   b. False: The ETC is a series of redox reactions, but the ATP synthase is powered directly by the flow of protons across the membrane.

7. In the electron transport chain, negatively charged electrons (e^-) and positively charged protons (H^+) start on the _____ side of the membrane and end up on the _____ side. This is called _____. (LO.3.2.4)
   a. matrix (both); cytoplasmic (both); chemiosmosis
   b. matrix (e^-); cytoplasmic (H^+); an electron transport
   c. matrix (H^+); cytoplasmic (e^-); oxidative phosphorylation
   d. matrix (both); matrix (e^-) and cytoplasmic (H^+); an electrochemical gradient

Answers: *1: a; 2: d; 3: b, c; 4: b; 5: b; 6: b; 7: d*

3.3 Photosynthesis

Learning Objectives

You should be able to:

3.3.1 Explain the role of chlorophyll in harvesting energy from sunlight.

3.3.2 Describe the mechanisms used for generation of ATP and NADPH in chloroplasts.

3.3.3 Summarize the reactions of the Calvin cycle.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 3.3 The Light Reactions

Animation 3.4 The Calvin Cycle

Active Learning Exercises

1. Have students form **small groups** and discuss what is incorrect about the following passage: Energy from sunlight is absorbed by chlorophylls, exciting electrons to a higher energy state. These high-energy electrons are then transferred through a series of membrane carriers, coupled to the synthesis of ATP and the reduction of $NADP^+$ to NADPH. (LO 3.3.1)

   Answer: *The excited electrons of the antenna chlorophyll do not leave the individual chlorophyll molecules and are not transferred through the electron transfer chain. Energy is transferred from antenna chlorophyll to antenna chlorophyll via resonance transfer (see Figure 3.11). Ultimately, an electron is extracted from water and moved through the electron transport chain (see Figure 3.12).*

2. A major difference between ATP synthesis in mitochondria and ATP synthesis in chloroplasts is that the mitochondrial ATP is exported to the cytoplasm, but the chloroplast ATP molecules never leaves the stroma. Have students form **small groups** to discuss this question: How does the energy in photosynthetic ATP exit the chloroplast? (LO 3.3.2)

   Answer: *The high-energy terminal phosphate on ATP is transferred to glyceraldehyde-3-phosphate (G3P). The G3P then leaves the chloroplast as a phosphorylated (and reduced, high-energy) molecule. Note: G3P exits via a G3P/PO_4 antiporter. If all the chloroplast did was export G3P, it would very quickly run out of the PO_4 groups needed for chemiosmosis.*

3. Have students form **think-pair-share** groups to consider the relative life spans of the products of the light-dependent reaction and the light-independent reactions of photosynthesis. How does that relate to petroleum and coal? (LO 3.3.2, LO 3.3.3)

   Answer: *The ATP and NADPH produced by the light-dependent reactions have life spans of less than a millionth of a second. However, the life span of reduced carbon is indefinite. The energy in fossil fuels was stored by the light-independent reactions of photosynthesis some 100–500 million years ago.*

Clicker Questions

1. Chlorophyll is a unique molecule in the way that energy migrates through the photosystem antenna.
   a. True: The energy migrates as resonance transfer from one chlorophyll molecule to the next, not as a redox reaction.
   b. False: The energy migrates as electrons moving from one chlorophyll molecule to the next, a form of the very common oxidation/reduction.

2. Cyclic electron flow around photosystem I generates
   a. NADPH but not ATP.
   b. ATP and NADPH.
   c. a proton gradient and NADPH.
   d. G3P and ATP.

3. The substrates for the light-dependent reactions are
   a. photons, H_2O, and $NADP^+$.
   b. CO_2 and H_2O.
   c. H_2O and photons.
   d. protons and electrons.

4. The substrates for the light-independent reactions are
   a. H_2O, CO_2, and NADPH.
   b. CO_2, NADPH, and ATP.
   c. NADPH, G3P, and PSII.
   d. glucose and O_2.

5. Consider a chloroplast in the light. If the pH of the lumen is ~5.0, what would you expect the pH of the stroma to be?
   a. ~3.0
   b. ~5.0
   c. ~7.0
   d. ~8.0

6. The primary end product of photosynthesis is glucose.
   a. True: Glucose is used to make starch, which is exported from the chloroplast and stored in the cytoplasm before it is excreted as waste.
   b. False: The primary end product is G3P, which is exported to the cytoplasm and used as the basis for every carbon-based molecule in the plant (and ultimately humans).

Answers: *1: a; 2: c; 3: a; 4: b; 5: d; 6: b*

3.4 The Biosynthesis of Cell Constituents

Learning Objectives

You should be able to:

3.4.1 Explain the difference between gluconeogenesis and glycolysis.
3.4.2 Describe the synthesis of lipids.
3.4.3 Summarize how amino acids and proteins are synthesized.
3.4.4 Summarize the pathways of nucleic acid synthesis.

Media Available on Companion Website oup.com/uk/cooper8e

Key Experiment Antimetabolites, Cancer, and AIDS
Data Analysis Problem 3.1 Regulation of Aspartate Transcarbamoylase Activity
Data Analysis Problem 3.2 Analysis of a DNase Regulating Protein
Data Analysis Problem 3.3 The Bohr Effect

Active Learning Exercises

1. Have students form **think-pair-share** groups and use their smart devices to research and answer the question "Why would an organism use an energy-requiring pathway like gluconeogenesis to generate a molecule (glucose) that is then respired for energy production?" (LO 3.4.1)

   Answer: *Gluconeogenesis is not just reverse glycolysis. It is used to generate glucose from non-carbohydrate precursors, such as fatty acids and amino acids. Some organs can use glucose only for respiration, and if they cannot get it directly, they must synthesize it from whatever reduced carbon is available.*

2. Figure 3.17 shows the assimilation of nitrogen into organic compounds. Have students use their smart devices to research the concept of "symbiotic nitrogen fixation." Now have them **redraw** Figure 3.17 to include this new information. (LO 3.4.2)

   Answer: *Most nitrogen-fixing bacteria are in a symbiotic relationship with a plant. The plant provides reduced carbon to the bacterium. In return, the bacterium provides bioavailable nitrogen to the plant. Therefore, the arrow between "N_2" and "Ammonia" should be labeled to indicate this relationship.*

Clicker Questions

1. If an animal cell could *not* perform gluconeogenesis, its ability to synthesize _____ would be reduced. (LO 3.4.1)
   a. glycogen
   b. starch
   c. proteins
   d. nucleic acids

2. Figure 3.18 shows a series of synthetic reactions taking place in a cell. Which two cellular compartments would have to be involved? (LO 3.4.2)
   a. mitochondrion and chloroplast
   b. chloroplast and cytoplasm
   c. cytoplasm and nucleus
   d. mitochondrion and cytoplasm

   (*Note:* The glucose → pyruvate steps are in the glycolytic pathway (cytoplasm), and the CAC is in the mitochondrial matrix. In plants, the essential amino acids are all made in the chloroplast, but that is not indicated in the figure.)

3. There is some clinical evidence that RNA supplements (either dietary or via injection) can shorten the time needed for recovery from a skin burn. Which hypothesis below might explain this? (LO 3.4.3)
   a. Burn recovery requires high rates of cellular respiration to supply the ATP needed for repair. The additional RNA would be expected to stimulate ATP synthesis.
   b. Burn recovery requires substantial gene expression and protein synthesis. The additional RNA supports those processes.
   c. Burn recovery requires high rates of mitosis to replace damaged cells. The additional RNA would be expected to support chromosome duplication.

4. The synthesis of lipids differs from the breakdown in lipids in that (LO 3.4.1)
   a. synthesis releases energy, and breakdown requires energy input.
   b. synthesis starts with glucose, and breakdown produces acetyl groups.
   c. synthesis requires energy input, and breakdown releases energy.
   d. synthesis takes place in the cytoplasm, and breakdown takes place in the mitochondrion.

5. If plants could write textbooks, they would have no need for the term "essential amino acid." (LO 3.4.3)
   a. True: Plants can synthesize all 20 amino acids; humans invented the term "essential amino acids" to denote the ones we cannot make.
   b. False: Essential and nonessential have to do with different forms of metabolic pathways, not whether the pathway is found in plants or humans.

Answers: *1: a; 2: d; 3: b; 4: c; 5: a*

CHAPTER 4

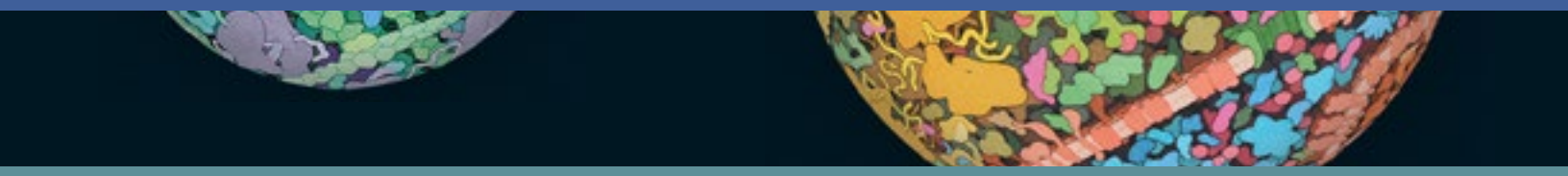
Part I **Fundamentals and Foundations**

Fundamentals of Molecular Biology

Chapter Overview

Contemporary molecular biology is concerned principally with understanding the mechanisms responsible for transmission and expression of the genetic information that governs cell structure and function. As reviewed in Chapter 1, all cells share a number of basic properties, and this underlying unity of cell biology is particularly apparent at the molecular level. Such unity has allowed scientists to choose simple organisms (such as bacteria) as models for many fundamental experiments, with the expectation that similar molecular mechanisms are operative in organisms as diverse as *E. coli* and humans. Numerous experiments have established the validity of this assumption, and it is now clear that the molecular biology of cells provides a unifying theme to understanding diverse aspects of cell behavior.

Initial advances in molecular biology were made by taking advantage of the rapid growth and readily manipulable genetics of simple bacteria, such as *E. coli*, and their viruses. The development of recombinant DNA then allowed both the fundamental principles and many of the experimental approaches first developed in prokaryotes to be extended to eukaryotic cells. The application of recombinant DNA technology has had a tremendous impact, initially allowing individual eukaryotic genes to be isolated and characterized in detail and more recently allowing the determination of the complete sequences of cellular genomes. The early development of molecular biology, recombinant DNA, and the experimental approaches used to investigate the function of eukaryotic genes are discussed in this chapter.



Chapter Outline

Section Reviews

4.1 Heredity, Genes, and DNA

Genes are carried on chromosomes, with DNA as the genetic material. DNA is a double helix in which hydrogen bonds form between purines and pyrimidines on opposite chains. Because base pairing is specific—A with T and G with C—the two strands of DNA are complementary. DNA replicates by semiconservative replication in which the two strands separate and each serves as a template for synthesis of a new progeny strand.

4.2 Expression of Genetic Information

The order of nucleotides in DNA specifies the order of amino acids in proteins. DNA serves as a template for synthesis of mRNA (transcription) and mRNA serves as a template for protein synthesis on ribosomes (translation). Thus the central dogma states that information flows from DNA to RNA to protein. Transfer RNAs serve as adaptors between amino acids and mRNA, with each amino acid specified by a codon consisting of three nucleotides. DNA can also be synthesized from RNA by reverse transcription, first discovered in retroviruses.

4.3 Recombinant DNA

Restriction endonucleases cleave specific DNA sequences, yielding defined fragments of DNA molecules. Either genomic DNA fragments or cDNAs synthesized by reverse transcriptase can be ligated to a vector that is able to replicate in an appropriate host cell and isolated as molecular clones. The nucleotide sequences of cloned DNA fragments can be readily determined, and proteins encoded by cloned genes can be expressed at high levels in either bacteria or eukaryotic cells.

4.4 Detection of Nucleic Acids and Proteins

Amplification of DNA by PCR is a sensitive method for detecting and isolating small amounts of specific DNA or RNA molecules. Nucleic acid hybridization allows the detection of specific DNA or RNA sequences either after separation by gel electrophoresis or within cells. Antibodies can be used to detect specific proteins either in cells or cell extracts.

4.5 Gene Function in Eukaryotes

Cloned genes can be introduced into complex eukaryotic cells and multicellular organisms for functional analysis. The effect of engineered mutations can be studied by *in vitro* mutagenesis of cloned DNAs, which can be introduced into chromosomal gene copies by homologous recombination. The CRISPR/Cas system uses homologous guide RNAs to efficiently target desired cellular genes. Gene expression at the level of mRNA can also be blocked by antisense nucleic acids or RNA interference.

Key Terms

allele
antibodies
antigens
antisense nucleic acids
cDNA
central dogma
chromosomes
codons
CRISPR/Cas system
dideoxynucleotides
diploid
DNA ligase
dominant
embryonic stem (ES) cells
expression vector
gel electrophoresis
genes
gene transfer
genetic code
genotype
haploid
homologous recombination
immunoblotting
in situ hybridization
in vitro mutagenesis
in vitro translation
knockout
liposomes
meiosis
messenger RNAs (mRNAs)
molecular clone
molecular cloning
monoclonal antibodies
mutations
next-generation sequencing
Northern blotting
nucleic acid hybridization
origin of replication
phenotype
plasmids
polymerase chain reaction (PCR)
real-time PCR
recessive
recombinant molecule
restriction endonucleases
retroviruses
reverse transcriptases
reverse transcription
ribosomal RNA (rRNA)
RNA interference (RNAi)
RNA polymerase
SDS-polyacrylamide gel electrophoresis (SDS-PAGE)
semiconservative replication
Southern blotting
transcription
transfection
transfer RNAs (tRNAs)
transformation
transgenic mice
transient expression
translation
vector
Western blotting

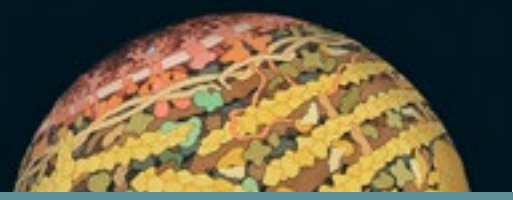
Additional Media and Supplements for Use in the Classroom

Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website

The **Active Learning Guide** that follows will help you create a dynamic learning environment in your classroom. It provides in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the chapter's Learning Objectives.



CHAPTER 4 Fundamentals of Molecular Biology

Active Learning Activities for the Classroom

4.1 Heredity, Genes, and DNA

Learning Objectives

You should be able to:

4.1.1 Explain the relationship between genes and chromosomes.
4.1.2 Summarize the experiment that established DNA as the genetic material.
4.1.3 Diagram the structure of DNA.
4.1.4 Summarize the experimental evidence for semiconservative replication.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 4.1 Bacterial Transformation
Animation 4.2 Avery, MacLeod & McCarty
Data Analysis Problem 4.1 Agarose Gel Electrophoresis of Polyethylene Glycol–Treated DNA Samples
Data Analysis Problem 4.2 Analysis of Clones of Herpes Simplex Virus DNA
Data Analysis Problem 4.3 The Effect of DNA Methylation on Restriction Endonuclease Cleavage
Data Analysis Problem 4.4 The Fate of a Gene in Fruit Fly Ovary during Egg Development
Data Analysis Problem 4.5 Analysis of a Clone of a Human cDNA Library Coding for a Lysosomal Enzyme

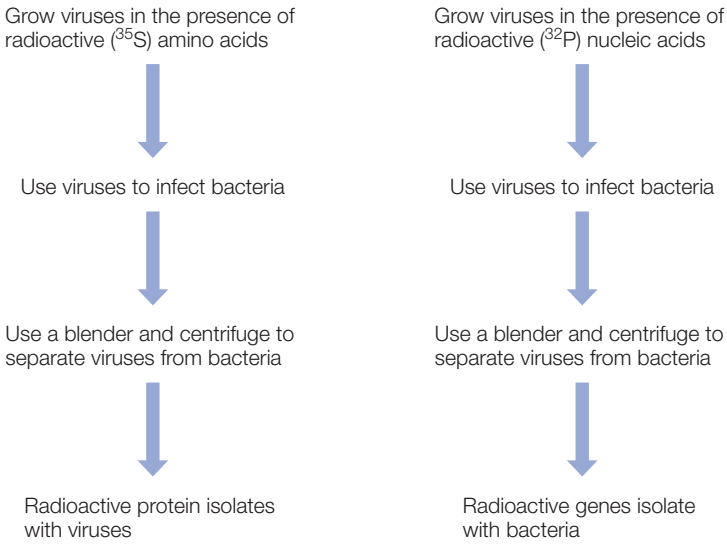
Active Learning Exercises

1. Have students write a **minute paper** in which they describe how all of the following are connected: diploid, meiosis, gametes, haploid, and fertilization. (LO 4.1.1)

   Answer: *Many adult cells are diploid, meaning they carry two copies of each chromosome. The process of meiosis produces haploid gametes. Fertilization of one gamete (typically an egg cell) by another gamete (sperm) restores the diploid condition.*

2. Ask students to use their smart devices to research "Hershey–Chase experiment" and construct a **sequence map** that details the steps Alfred Hershey and Martha Chase took to confirm that DNA was the genetic material. (LO 4.1.2)

   Answer: *Students must first know, or be told, what Hershey and Chase knew at the time: a) viruses are made of a protein coat surrounding a few genes and b) when a virus infects a bacterial cell, the genes enter the bacterial cell, but the viral protein coat does not. The Hershey–Chase experiments sought to determine whether the viral protein or the viral genes were entering and infecting the bacterial cells. A version of the correct response is given below.*



3. James Watson and Francis Crick were awarded the 1962 Nobel Prize in Physiology or Medicine for their elucidation of DNA structure. Have students form **small discussion groups** and use their smart devices to answer the question, "What roles did the experiments of Rosalind Franklin, Maurice Wilkins, and Erwin Chargaff play in the Watson–Crick discovery?" (LO 4.1.3)

   Answer: *Wilkins and Franklin generated the X-ray crystallographic data Watson and Crick used, and Chargaff had already shown that A=T and C=G.*

4. Adenine and guanine are purines, while thymine and cytosine are pyrimidines (see section 2.1 and Figure 4.5). Have students form **think-pair-share** groups and consider the implications of those chemical structures on the structure of DNA. (LO 4.1.3)

   Answer: *The purine molecules are both the same length but longer than the pyrimidine molecules. Therefore, the A–T base pair is the same length as the C–G base pair, and the two strands of the DNA molecule are kept parallel.*

Clicker Questions

1. The only role for a gene is to contain the information to make a protein. (LO 4.1.1)
   a. True: Genes contain the information to make a protein.
   b. False: Some genes code for tRNAs and rRNAs.

2. Human skin cells have about 20,000 genes and ~40,000 alleles, but human sperm cells have ~20,000 genes and ~20,000 alleles. (LO 4.1.1)
   a. True
   b. False

3. In complimentary base paring between the two strands of DNA, adenine forms two hydrogen bonds with thymine, and cytosine forms three hydrogen bonds with guanine. What is the significance of this difference in hydrogen bonding? (LO 4.1.3)
   a. This ensures that A and C will always be on the left strand and T and G on the right strand.
   b. This ensures that A will always pair with T and C will always pair with G.
   c. This ensures that the two strands will always be antiparallel to each other.

4. In Watson and Crick's 1953 seminal paper on DNA structure, the researchers made the statement, "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." To what were they referring? (LO 4.1.4)
   a. The constant ratio of A to T and C to G
   b. The double-stranded helical structure of the DNA molecule
   c. The relationship between DNA structure and RNA structure
   d. The semiconservative model of DNA replication

5. In the 1950s there was considerable debate over whether proteins or nucleic acids were the genetic material. This was because (LO 4.1.2)
   a. chromosomes are made of both proteins and nucleic acids.
   b. many experiments pointed to proteins as being the genetic material.
   c. nucleic acids had already been shown to carry genes.
   d. both proteins and nucleic acids can contain genetic information.

Answers: *1: b; 2: a; 3: b; 4: d; 5: a*

4.2 Expression of Genetic Information

Learning Objectives

You should be able to:

4.2.1 Describe the roles of mRNA, tRNA, and rRNA in protein synthesis.

4.2.2 Summarize the experimental evidence for a triplet code.

4.2.3 Predict the effects of specific mutations on the amino acid sequence of an encoded protein.

4.2.4 Summarize the experimental evidence for reverse transcription.

Media Available on Companion Website oup.com/uk/cooper8e

Key Experiment: The DNA Provirus Hypothesis

Animation 4.3 The "Central Dogma"

Animation 4.4 DNA Mutations

Animation 4.5 HIV Reproduction

Active Learning Exercises

1. Have students prepare a **matrix** similar to the one below and fill it in with information that compares and contrasts mRNA, tRNA, and rRNA. (LO 4.2.1)

   Answer: *The answers are in italics in the table below. You may choose to hand out a blank table with only the bolded terms written in or have students draw their own.*

	Site of synthesis	Location	Function
mRNA	nucleus	nucleus and cytoplasm	deliver genetic instructions to ribosome
tRNA	nucleus	cytoplasm	deliver proper amino acid to ribosome
rRNA	nucleus	ribosome	protein synthesis

2. Have students write a **minute paper** answering the question "Why can it be said that the triplet code has redundancy but no ambiguity?" (LO 4.2.2)

   Answer: *There are 64 possible combinations of a triplet code using four bases (4x4x4=64), but there are only 20 amino acids used in protein synthesis. So, while there may be multiple codons for each amino acid (redundancy), each codon is specific for a single amino acid (no ambiguity).*

3. A particular gene codes for a protein that is 50 amino acids long, with two membrane-spanning alpha helices. The protein has five regions: region A has 10 hydrophilic amino acids, B has 10 hydrophobic amino acids, C has 10 hydrophilic amino acids, D has 10 hydrophobic amino acids, and E has 10 hydrophilic amino acids. Regions A and E are on the cytoplasmic side of the cell membrane. Region C is on the external side of the membrane. Have students form **small discussion groups** and consider what would happen if some of the amino acids in region D were changed to hydrophilic. (LO 4.2.3)

   Answer: *Region A would still be on the cytoplasmic side, B would span the membrane, and the other three regions would be on the external side.*

4. Some drugs used to treat AIDS (acquired immune deficiency syndrome) are reverse transcriptase inhibitors (RTIs). Have students form **think-pair-share** groups and explain why that is the case. (LO 4.2.4)

   Answer: *HIV, the virus that causes AIDS, is an RNA-containing retrovirus. It uses reverse transcriptase as part of its infection cycle. (See Figure 4.12.)*

Clicker Questions

1. mRNA, tRNA and rRNA are all synthesized by the same RNA polymerase. (LO 4.2.1)
   a. True
   b. False

2. Of the 64 possible codons, only 61 code for an amino acid. The other three (LO 4.2.2)
   a. are start codons.
   b. are interruption codons.
   c. are stop codons.
   d. are resume codons.

3. A particular enzyme has a lysine (positively charged) residue in its active site. A mutation changes that to a glycine (neutral). What effect would you expect that to have on enzyme activity? (LO 4.2.3)
   a. Enzyme activity would not be changed because glycine is neutral.
   b. Enzyme activity would cease completely.
   c. Enzyme activity would increase because the charged lysine repels substrate molecules.
   d. It would probably alter the enzyme's substrate-binding affinity.

4. There are 64 triplet codes for 20 amino acids. What is the evolutionary significance of this redundancy? (LO 4.2.3)
   a. It allows for the presence of silent mutations in genes.
   b. It means that all gene mutations will lead to an altered protein.
   c. It allows for one mutation to affect multiple proteins.
   d. It increases the chances of lethal gene mutations.

   (Note: A silent mutation is one in which a change in the DNA—usually a base substitution in the third member of a triplet—causes a change in the corresponding codon but causes no change in the resulting protein. The gene has been mutated, but the gene product (protein) is unchanged because of the redundancy in the triplet code.)

5. Howard Temin made this statement in his 1964 paper on the Rous sarcoma virus (RSV): "RNA tumor viruses have a DNA genome when they are in cells and an RNA genome when they are in virions." To what was he referring? (LO 4.2.4)
   a. the triplet code
   b. reverse transcription
   c. semiconservative DNA replication
   d. bacterial transformation

Answers: *1: a; 2: c; 3: d; 4: a; 5: b*

4.3 Recombinant DNA

Learning Objectives

You should be able to:

4.3.1 Predict the average sizes of DNA fragments produced by cleavage with a restriction endonuclease with a known recognition site.

4.3.2 Summarize how a fragment of host DNA is cloned in a plasmid vector.

4.3.3 Explain how molecular cloning allows a unique fragment of DNA to be isolated from a mixture.

4.3.4 Describe how DNA is sequenced with dideoxynucleotides.

4.3.5 Identify the key features of a vector used to express cloned genes.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 4.6 Restriction Endonucleases

Animation 4.7 Recombinant DNA Molecules

Animation 4.8 Sequencing a DNA Strand

Active Learning Exercises

1. Have students form **small discussion groups** to explore why the restriction sites produced by a restriction enzyme are called "palindromic." Students may wish to use their smart devices to look up the meaning of the word "palindrome." (LO 4.3.1)

   Answer: *"Palindromic" means the sequence of nucleotides is the same on the two sticky ends, but in reverse order.*

2. Instruct students to create a **sequence map** depicting the steps in constructing a cDNA library. (LO 4.3.3)

   Answer: *See Figure 4.17.*

3. Instruct students to create a **sequence map** of the steps in gene sequencing using dideoxynucleotides. (LO 4.3.4)

   Answer: *A gene is digested using restriction enzymes into multiple, distinct fragments. Each fragment is isolated and placed downstream from a synthetic primer. The reaction is given normal A, T, C, and G and fluorescently labeled ddA, ddT, ddC, and ddG. Each nucleotide gets a different color label. The DNA synthesis reaction is allowed to run and incorporates the proper nucleotide. If a dd-nucleotide is incorporated, the chain is terminated and the last nucleotide in that chain is the correct fluorescently labeled dd-nucleotide. Electrophoresis is used to separate the fragments. If there were 100 nucleotides in the full-length fragment, there should be 100 fragments of 1, 2, 3, etc. nucleotides long and each terminated with a fluorescent label, the color of which is specific for A, T, C, or G.*

4. Have students write a **minute paper** explaining why some genes are expressed in mammalian cells and not in *E. coli*. (LO 4.3.5)

   Answer: *Because eukaryotic proteins are often modified after synthesis (called "post-translational modification") by the addition of sugars of lipids. Expressing eukaryotic genes in a prokaryote yields proteins that lack such modifications. However, expressing eukaryotic genes in a eukaryote cell line will generate the proper modifications.*

Clicker Questions

1. Would the restriction enzyme EcoRI be able to cut RNA? Be prepared to explain your answer. (LO 4.3.1)
   a. Yes
   b. No

   (Note: EcoRI recognizes a sequence that contains T (thymine). RNA does not contain thymine.)

2. A restriction enzyme is to a DNA ligase as (LO 4.3.2)
   a. a hammer is to a nail.
   b. a can of paint is to a paint brush.
   c. scissors are to glue.
   d. gasoline is to an automobile.

3. The end goal of molecular cloning is to (LO 4.3.3)
   a. produce multiple copies of a single stretch of DNA.
   b. generate a large number of haploid mutant cells.
   c. generate a population of cells that each contains identical DNA molecules.

4. In sequencing a gene using fluorescent dideoxynucleotides, a unique DNA fragment is generated for every base pair in the gene. (LO 4.3.4)
   a. True
   b. False

5. Expression vectors must contain (LO 4.3.5)
   a. a promotor sequence.
   b. a sequence for ribosome binding.
   c. the gene of interest.
   d. an antibiotic selectable marker.

Answers: *1: b; 2: c; 3: a, c; 4: a; 5: a, b, c, d*

4.4 Detection of Nucleic Acids and Proteins

Learning Objectives

You should be able to:

4.4.1 Explain how DNA is amplified by the polymerase chain reaction (PCR).

4.4.2 Summarize the methods used to separate and detect fragments of DNA or molecules of RNA.

4.4.3 Describe how antibodies are used to detect proteins.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 4.9 Polymerase Chain Reaction

Animation 4.10 Nucleic Acid Hybridization

Animation 4.11 Southern Blotting

Animation 4.12 Monoclonal Antibodies

Micrograph: Figure 4.25 Immunofluorescence

Active Learning Exercises

1. Have students prepare a **flow chart** of the steps in the polymerase chain reaction. (LO 4.4.1)

   Answer: *Based on Animation 4.9*

2. Have students form **small discussion groups** and use their smart devices to answer the question "What are the 'labeled probes' used in Southern and Northern blots?" (LO 4.4.2)

   Answer: *First, the sequence of the gene to be identified must be known. Then, a short piece of single-strand DNA (using nucleotides labeled with 32P) is synthesized and used as the probe. The probe will only hybridize to a piece of DNA on the filter blot that is complementary to its nucleotide sequence.*

3. Have students prepare a **matrix** similar to the one below (or provide them with a template) that compares and contrasts Southern blots, Northern blots, and Western blots. (LO 4.4.2, LO 4.4.3)

   Answer: *Shown in italics below*

Blot type	Probe	Detection system	Molecule detected
Southern	*^{32}P-labeled ssDNA*	*X-ray film*	*DNA*
Northern	*^{32}P-labeled ssDNA*	*X-ray film*	*RNA*
Western	*Fluorescent antibody*	*Chemiluminescence*	*Protein*

Clicker Questions

1. DNA in every organism is replicated by an enzyme complex called DNA polymerase (DNA pol). What is unique about the DNA pol used in PCR? (LO 4.4.1)
   a. It is heat-stable and remains active after the heat denaturing steps.
   b. It was isolated from a bacterium that lives in hot springs.
   c. It is used up in every cycle and has to be replenished with fresh DNA pol.
   d. It makes single-stranded DNA from double-stranded DNA.

2. Electrophoresis is (LO 4.4.2)
   a. an identification technique; a separate technique must be used for separation.
   b. an amplification technique that greatly increases the amount of DNA or RNA for analysis.
   c. a blotting technique to ensure that isolated gene fragments or proteins are not lost.
   d. a separation technique; a separate technique must be used for identification.

3. Both PCR and Northern blots can be used to monitor gene expression. (LO 4.4.2)
   a. True: PCR can be used to amplify mRNAs present in a cell and Northern blots can identify specific RNAs in a cell extract.
   b. False: PCR can be used to amplify mRNAs present in a cell, but Northern blots are used to identify specific genes in a cell mixture.

4. Electrophoresis separates molecules based on their surface charges. What is a fundamental difference between nucleic acid electrophoresis and protein electrophoresis? (LO 4.4.2)
   a. Nucleic acids are positively charged and must be treated with SDS to shield those charges and give them an overall negative charge.
   b. Proteins will bind directly to the polyacrylamide of the gel and must be treated with SDS to prevent that binding.
   c. Nucleic acids are naturally charged but proteins must be treated with SDS to give them an overall negative charge.
   d. Proteins need to be purified before they will separate on a gel; nucleic acids do not.

5. DNA probes, RNA probes, and antibodies all share what key trait? (LO 4.4.3)
   a. They are extremely specific for their target molecules.
   b. They recognize and bind to multiple genes and proteins.
   c. They can bind and debind different molecules, depending on reaction conditions.
   d. They are all radioactively labeled and are detected using X-ray film.

Answers: *1: a, b; 2: d; 3: a; 4: c; 5: a*

4.5 Gene Function in Eukaryotes

Learning Objectives

You should be able to:

4.5.1 Distinguish transient expression from stable transformation of animal cells in culture.
4.5.2 Construct primers for the introduction of a desired mutation into a cloned DNA.
4.5.3 Summarize the methods used to introduce mutations into homologous cellular genes.
4.5.4 Describe the CRISPR/Cas system.
4.5.5 Explain the difference between antisense RNA and RNA interference.

Media Available on Companion Website oup.com/uk/cooper8e

Key Experiment: RNA Interference
Video 4.1 RNA Interference

Active Learning Exercises

1. Have students use their smart devices to research *Agrobacterium tumefaciens* and prepare a **sequence map** showing the steps in *Agrobacterium tumefaciens*-mediated plant cell transformation. (LO 4.5.1)

   Answer: *Construct a plasmid containing the gene(s) you want to insert into the plant genome. Then acquire a commercial strain of A.t. and transform it with the plasmid. Infect the plant (root, shoot, leaves) with the transformed A.t., which in turn will insert the plasmid into the plant genome.*

2. In **small discussion groups**, have students consider the question "Why are antibiotic resistance genes usually included as part of a transformation vector?" (LO 4.5.2)

   Answer: *Any cell that is successfully transformed will be able to express both the gene of interest and the antibiotic resistance gene. Cell cultures are then treated with the antibiotic, and only the transformed cells survive.*

3. Have students write a **minute paper** in which they explain, in their own words, how homologous recombination works. They may need to use their smart devices to find out more. (LO 4.5.3)

   Sample answer: *Homologous recombination is a naturally occurring form of DNA editing used to repair harmful breaks. Scientists take advantage of that process (and the repair enzymes already present in the cell) by introducing a foreign stretch similar to the gene they wish to replace.*

4. Ask students to form **think-pair-share** groups and, using their smart devices, find out why the CRISPR/Cas system is considered to be a prokaryotic immune system. (LO 4.5.4)

   Answer: *Prokaryotes have an innate CRISPR/Cas system that they use to remove and degrade foreign DNA they pick up as a plasmid or via viral infection.*

5. Have students construct a simple **matrix** to compare and contrast antisense RNA with RNA interference. (LO 4.5.5)

   Answer: *In a one-step process, antisense RNA binds directly to a specific mRNA sequence and blocks transcription. RNA interference is a multistep process in which the RNAi molecule is cleaved and then recruits an RNase to degrade a specific piece of mRNA.*

Clicker Questions

1. The difference between transient gene expression and stable gene expression is that (LO 4.5.1)
   a. the percentage of cells successfully transformed is much higher in stable expression.
   b. in transient expression the introduced gene is not transported to the nucleus.
   c. selectable markers are not needed in transient expression experiments.
   d. in stable expression the introduced gene is integrated into the host cell's genome.

2. Why would a scientist want to perform a gene knockout? (LO 4.5.2)
   a. To see if their transformation was successful
   b. To learn the function of the knockout gene
   c. To make sure a mutant gene is the only one expressed
   d. To select for the proper transformed cells

3. Homologous recombination can be used to study both cells in culture and mature organisms. (LO 4.5.3)
   a. True
   b. False

4. The CRISPR/Cas system is an advance over previous methods of cell transformation because it (LO 4.5.4)
   a. allows for mutations to be targeted to very precise locations.
   b. allows for multiple genes to be mutated in a single experiment.
   c. allows for genetic transformations without the use of selectable markers.

5. There would be no effect if antisense RNA for a plant gene were introduced into mouse cells in tissue culture. (LO 4.5.5)
   a. True
   b. False
   c. Maybe

Answers: *1: d; 2: b, c; 3: a; 4: a; 5: c*

CHAPTER 5

Part I **Fundamentals and Foundations**

Genomics, Proteomics, and Systems Biology

Chapter Overview

Recent years have seen major changes in the way scientists approach cell and molecular biology, with large-scale experimental and computational approaches being applied to understand the complexities of biological systems. Traditionally, cell and molecular biologists studied one or a few genes or proteins at a time. This was changed by genome sequencing projects, which introduced large-scale experimental approaches that generated vast amounts of data to the study of biological systems. The complete genome sequences of a wide variety of organisms, including many individual humans, provide a wealth of information that forms a new framework for studies of cell and molecular biology and opens new possibilities in medical practice. Not only can the sequences of complete genomes be obtained and analyzed, but it is also now possible to undertake large-scale analyses of all of the RNAs and proteins expressed in a cell. These global experimental approaches form the basis of the new field of systems biology, which seeks a quantitative understanding of the integrated behavior of complex biological systems. This chapter considers the development of these new technologies and their impact on understanding the molecular biology of cells.

Chapter Outline

Section Reviews

5.1 Genomes and Transcriptomes

Bacterial and yeast genomes are compact, with protein-coding sequences accounting for most of the DNA. The *S. cerevisiae* genome contains about 6000 genes. Protein-coding sequences account for 10–25% of the genomes *C. elegans*, *Drosophila*, and *Arabidopsis*, which contain approximately 19,000, 14,000, and 26,000 genes, respectively. The human genome contains approximately 20,000 protein-coding genes—not much more than the number of genes found in simpler animals like *Drosophila* and *C. elegans*, and fewer than in *Arabidopsis* and other plants, emphasizing the lack of relationship between gene number and complexity of an organism. Enormous progress in the technology of DNA sequencing has now made it feasible to determine the complete sequence of individual genomes and of all the RNAs expressed in a cell.

5.2 Proteomics

Characterization of the complete protein complement of cells is a major goal of proteomics. Mass spectrometry provides a powerful tool for protein identification, which can be used to identify either isolated proteins or proteins present in mixtures. The protein compositions of subcellular organelles can be analyzed by mass spectrometry or large-scale immunofluorescence. The purification of protein complexes from cells and analysis of interactions of proteins introduced into yeast can identify interacting proteins and may lead to elucidation of the complex networks of protein interactions that regulate cell behavior.

5.3 Systems Biology

Systems biology uses large-scale datasets for quantitative experimental analysis and modeling of biological systems, including genome-wide screens of gene function, regulation of gene expression, and quantitative modeling of regulatory networks. Synthetic biology is an engineering approach to designing new biological systems, including genetic circuits, metabolic pathways, and synthetic genomes.

Key Terms

bioinformatics
crosstalk
DNA microarray
feedback loops
feedforward relay
immunoprecipitation
network
next-generation sequencing
open-reading frame
proteome
proteomics
RNA-seq
mass spectrometry
synthetic biology
systems biology
tandem mass spectrometry
transcriptome
yeast two-hybrid system

Additional Media and Supplements for Use in the Classroom

Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website

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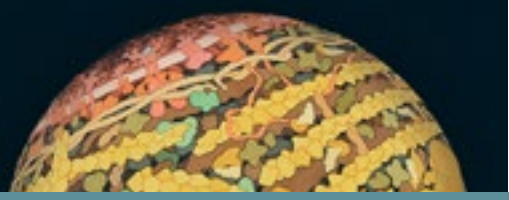

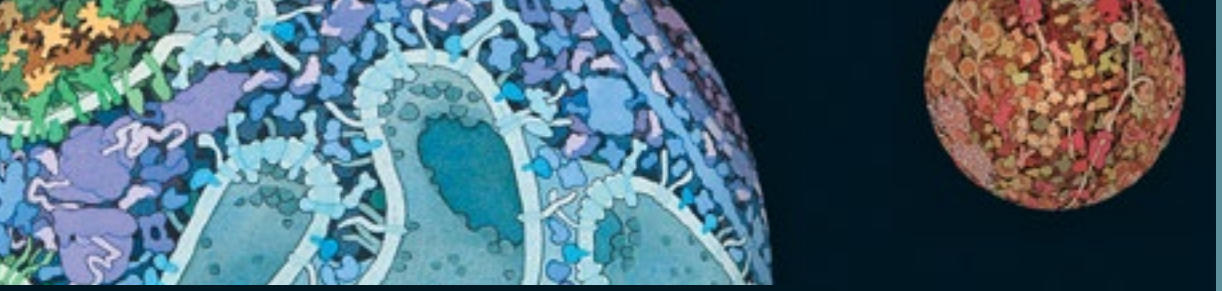

CHAPTER 5 Genomics, Proteomics, and Systems Biology

Active Learning Activities for the Classroom

5.1 Genomes and Transcriptomes

Learning Objectives

You should be able to:

- **5.1.1** Compare the numbers of genes in bacterial and yeast genomes.
- **5.1.2** Summarize the contributions of coding and noncoding sequences to the genomes of *Drosophila*, *C. elegans*, and *Arabidopsis*.
- **5.1.3** Compare the approximate size and amount of protein-coding sequence in the human genome with that of *Drosophila*.
- **5.1.4** Explain why studies of other vertebrates are useful in understanding human genomics.
- **5.1.5** Outline the basic approach used in next-generation sequencing.
- **5.1.6** Describe the global methods used to study gene expression.

Media Available on Companion Website oup.com/uk/cooper8e

Key Experiment The Human Genome
Animation 5.1 Next-Generation Sequencing
Animation 5.2 DNA Microarray Technology
Video 5.1 A Brief Introduction to *C. elegans*
Data Analysis Problem 5.1 Microarray Analysis of Gene Expression in Retina Cells
Data Analysis Problem 5.2 Spectral Karyotyping

Active Learning Exercises

1. Have students form **small discussion groups** and explain how the Venter group counted the number of genes in *H. influenzae* without identifying any actual genes. (LO 5.1.1)

   Answer: *A gene is a stretch of DNA that codes for a molecule of RNA. That is not exactly what the Venter group looked for. The Venter group looked for open reading frames—long stretches of DNA (approximately 100 base pairs) that lack a chain-terminating codon. They were operating on the assumption that any stretch that long without a chain-terminating codon must be a gene.*

2. Have students form small **pro/con teams** and debate the reasoning behind this statement: "For example, the genome of the apple contains about 57,000 protein-coding genes, further emphasizing the lack of a relationship between gene number and complexity of an organism." (LO 5.1.2)

   Answer: *This debate could go in any direction. Pro: Apples clearly are not as complex as humans (the most "complex" species on the planet) so it is surprising that they have so many genes. Con: By having 56,000 genes, apples are clearly more "complex" than humans (with only 20,000 genes). At the very least, an apple has a more complex genome and proteome.*

3. Lead a class discussion on the pros and cons of having one's genome sequenced. Sequencing has the potential to identify genetic flaws (susceptibility to hundreds of diseases and conditions). Should that information be shared with doctors, health insurers, and life insurers? Have students write a **minute paper** on whether or not they would choose to have their genomes sequenced. (LO 5.1.4)

   Answer: *There is no right or wrong answer for this question. The point is to get students to think about how genome sequencing technology might impact their lives.*

4. Have students make a sequence map of the steps in next-generation genome sequencing. (LO 5.1.5)

   Answer: *See Figure 5.5. The point of this exercise is to get students to look closely at the details of next-generation sequencing and describe them in their own words.*

5. Have students form **think-pair-share** groups and discuss an answer to the question: "What is the advantage of RNA sequencing over DNA sequencing?" (LO 5.1.6)

   Answer: *Only about one-half of the genes in any cell are "turned on" (i.e., transcribed) at any given time. RNA sequencing tells you which mRNAs are present and, therefore, which genes are active, in a cell at any given time or under any given conditions.*

Clicker Questions

1. The size of an organism's genome is measured by the number of genes it contains. (LO 5.1.1)
   a. True
   b. False

2. In general, the larger an organism's genome, the larger the (LO 5.1.2)
   a. number of protein-coding genes.
   b. number of chromosomes.
   c. amount of non–protein-coding sequences.
   d. number of nuclei per cell.

3. An unexpected result that came from sequencing the human genome is that (LO 5.1.3)
   a. it is the same size as the *Drosophila* genome.
   b. it has more chromosomes than virtually any other organism has.
   c. it contains surprisingly few protein-coding genes.
   d. it has very few non–protein-coding sequences.

4. Many human genes are also found in other organisms. (LO 5.1.4)
   a. True
   b. False

5. DNA sequencing can reveal details of an entire genome, but RNA sequencing (LO 5.1.6)
   a. can locate and identify the non–protein-coding regions of the genome.
   b. is used to pick out the open reading frames in a genome.
   c. is the main technique used when comparing genomes between species.
   d. determines which genes are actively transcribed.

Answers: *1: b; 2: a, c; 3: c; 4: a; 5: d*

5.2 Proteomics

Learning Objectives

You should be able to:

5.2.1 Explain how proteins are identified by mass spectrometry.

5.2.2 Summarize the approaches used for analysis of the proteome of subcellular organelles.

5.2.3 Describe the approaches used for identification of protein interactions.

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Data Analysis Problem 5.3 Two-Dimensional Fractionation of Proteins Synthesized in a Virus-Infected Cell

Active Learning Exercises

1. Have students form **small discussion groups** and use their smart devices to research the underlined portion of the sentence: "Computer algorithms can then be used to compare the experimentally determined mass spectrum with a database of theoretical mass spectra representing tryptic peptides of all known proteins, allowing identification of the unknown protein." (LO 5.2.1)

   Answer: *Using mass spectrometry to identify a cell's proteome must be preceded by sequencing the organism's genome. Once the sequence is known, researchers can identify trypsin digestion sites and the size and composition of the resulting fragments. The mass spectrometry data are then compared to the predicted (i.e.,*

theoretical) fragmentation pattern. The key point is that the study of proteomics using mass spectrometry depends on the availability of reliable genomic data for the species being studied. This is why sequencing novel genomes is so important.

2. Have students create (or fill in) a **matrix** that compares the main features of mass spectrometry and immunofluorescence. (LO 5.2.2)

   Answer: *The goal is to highlight how the two techniques are based on completely different approaches while seeking to answer 1) What is the protein? and 2) Where is the protein? The answers are not obvious, so students might require guidance/ discussion/hints to get them on track.*

	Identity confirmed by:	Location confirmed by:
Mass spectrometry	Comparing fragments generated to database	Accurate subcellular fractionation techniques
Immunofluorescence	Specificity of antibody used	Direct visualization

3. Have students form **think-pair-share** groups and work out the steps involved in a yeast two-hybrid system. (LO 5.2.3)

   Answer: *The steps are shown in Figure 5.13 and explained in the accompanying figure legend and text. It is a rather complicated assay that students may need to think through completely to understand.*

Clicker Questions

1. What would happen if alternative splicing were not possible in a cell? (LO 5.2.1)
   a. The number of protein-coding sequences would be increased.
   b. The number of genes that could be identified in the genome would remain the same.
   c. The number of genes being transcribed at any given time would be reduced.
   d. The number of proteins found in a cell would be reduced.

2. Adding a phosphate group to an amino acid would change the mass of the molecule by how much? (LO 5.2.1)
   a. 31 g/mol
   b. 95 g/mol
   c. 97 g/mol
   d. 194 g/mol

3. In order to apply immunofluorescent microscopy to protein localization studies, scientists must first (LO 5.2.2)
   a. raise antibodies against the protein in a living animal.
   b. sequence the gene that codes for the protein of interest.
   c. determine the molecular mass of the protein of interest.
   d. isolate the subcellular organelle in which the protein is found.

4. Protein–protein interactions require a physical binding of one protein to another. (LO 5.2.3)
   a. True
   b. False

Answers: *1: b, d; 2: c; 3: a; 4: a*

5.3 Systems Biology

Learning Objectives

You should be able to:

5.3.1 Contrast the approaches of traditional biological experimentation and systems biology.
5.3.2 Summarize the methods used for large-scale screens of gene function.
5.3.3 Explain the approaches used to identify gene regulatory sequences.
5.3.4 Illustrate the types of interactions between pathways in a regulatory network.
5.3.5 Define synthetic biology.

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Molecular Medicine Malaria and Synthetic Biology

Active Learning Exercises

1. Have students use their smart devices to research and write a **minute paper** describing an example of a complex biological system that was elucidated using bioinformatics and systems biology. (LO 5.3.1)

   Answer: *Answers will vary. The Wikipedia entry for "systems biology" has many examples.*

2. Ask students in **small discussion groups** to describe the differences among *in vivo*, *in vitro*, and *in silico* experiments and give examples of when to use each one. (LO 5.3.2)

   Answer: In vivo *means "in life." Experiments are conducted on intact, living organisms.* In vitro *(literally "in glass") means experiments are conducted in a test tube or Petri dish.* In silico *(from silicon-based computer chips) means experiments are conducted on a computer. Examples will vary.*

3. Have students prepare a T table in which they compare and contrast the five types of signaling networks shown in Figure 5.19. (LO 5.3.4)

   Answer: *Example below.*

Negative feedback	A downstream element of a pathway inhibits an upstream element
Positive feedback	A downstream element of a pathway stimulates an upstream element
Feedforward relay	The activity of one component of a pathway stimulates a distant downstream component
Stimulatory crosstalk	One pathway stimulates the other
Inhibitory crosstalk	One pathway inhibits the other

4. Synthetic biology has the potential to create a fully synthetic cell; in effect, creating life. Have students form pro/con **debate teams** and consider this question, "Should scientists be allowed to create life in the laboratory?" (LO 5.3.5)

   Answer: *Potential pros: a life form could be tailored to produce molecules or drugs that are helpful to humans. Potential cons: the creation of life may raise ethical, moral, or religious concerns.*

Clicker Questions

1. As a discipline of study, systems biology relies heavily on computer science and computational power. (LO 5.3.1)
   a. True
   b. False

2. Studying global patterns of gene expression is usually done by (LO 5.3.2)
   a. sequencing an organism's entire genome.
   b. comparing gene expression patterns among different organisms.
   c. monitoring environmentally induced signal transduction arrays.
   d. using microarrays to determine which mRNAs are present at any given time.

3. Why is it harder to identify regulatory sequences than protein-coding sequences? (LO 5.3.3)
   a. Regulatory sequences are much shorter than protein-coding sequences.
   b. Protein-coding sequences have many stop codons, which makes them easy to identify.
   c. False gene regulatory sequences appear randomly in the genome.
   d. Signaling networks that lack regulatory sequences are fairly common.

4. Studies of signaling pathways and gene expression patterns are linked because (LO 5.3.4)
   a. changes in gene expression patterns are sensed by signaling pathways.
   b. activating a signaling pathway often leads to changes in gene expression.
   c. all signaling pathways work by directly altering gene-expression patterns.

5. Synthetic biology has the potential to create life. (LO 5.3.5)
   a. True
   b. False

Answers: *1: a, d; 2: a, c; 3: b; 4: a*

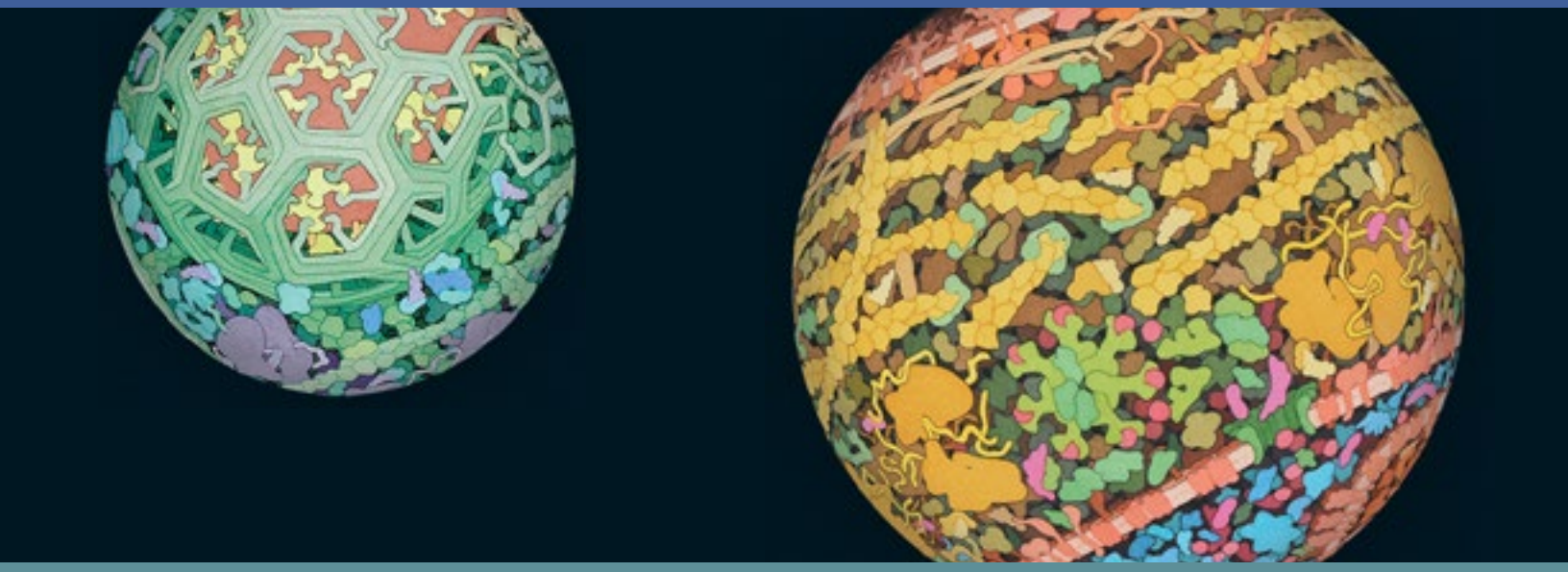
CHAPTER

Part II **The Flow of Genetic Information**

6 Genes and Genomes

Chapter Overview

As the genetic material, DNA provides a blueprint that directs all cellular activities and specifies the developmental plan of multicellular organisms. An understanding of gene structure and function is therefore fundamental to an appreciation of the molecular biology of cells. The development of gene cloning represented a major step toward this goal, enabling scientists to dissect complex eukaryotic genomes and probe the functions of eukaryotic genes. Advances in DNA sequencing then brought us to the exciting point of knowing the complete genome sequences of thousands of bacteria, of yeast, and of many species of plants and animals, including humans. This chapter will focus on the organization of eukaryotic genes and the types of sequences in the genomes of higher eukaryotes, many of which play important roles in gene regulation rather than encoding proteins.



Chapter Outline

Section Reviews

6.1 The Structure of Eukaryotic Genes

Most eukaryotic genes have a split structure in which segments of coding sequence (exons) are interrupted by noncoding sequences (introns). In mammals, introns account for more than ten times as much DNA as exons. Although they are removed from mRNAs, introns have multiple cellular functions. Some proteins or RNAs are encoded within introns of larger genes. In addition, introns contain transcriptional regulatory sequences and allow alternative splicing.

6.2 Noncoding Sequences

About two-thirds of mammalian genomes are composed of sequences other than protein-coding genes. Many genes encode regulatory RNAs, including miRNAs and lncRNAs. Mammalian genomes encode more lncRNAs than proteins. Over 50% of mammalian DNA consists of highly repetitive DNA sequences, some of which are present in 10^5–10^6 copies per genome. These sequences include simple-sequence repeats as well as transposable elements that have moved throughout the genome by either RNA or DNA intermediates. In addition, many eukaryotic genes are present in multiple copies, called gene families, which have arisen by duplication of ancestral genes. Many members of gene families (pseudogenes) have been inactivated by mutations and no longer represent functional genes.

6.3 Chromosomes and Chromatin

The DNA of eukaryotic cells is wrapped around histones to form nucleosomes and chromatin fibers. Chromatin fibers are loosely packed in transcriptionally active euchromatin but tightly packed in heterochromatin and metaphase chromosomes of cells undergoing mitosis. Centromeres are specialized regions of eukaryotic chromosomes that serve as the sites where sister chromatids are joined and the sites of spindle fiber attachment during mitosis. Centromere function is determined by a variant H3-like histone, which is epigenetically maintained at cell division.

Key Terms

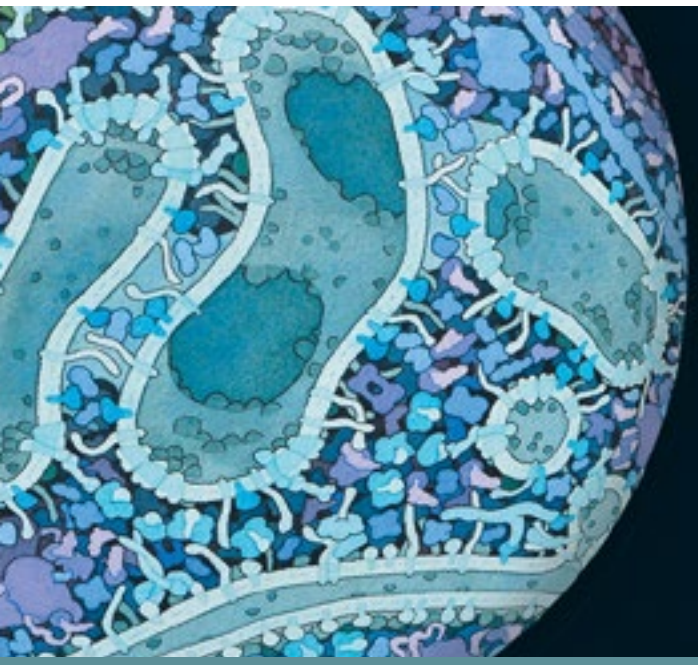
3′ and 5′ untranslated region (UTR)
alternative splicing
CENP-A
centromere
chromatin
DNA transposon
epigenetic inheritance
euchromatin
exon
gene
gene family
heterochromatin
histone
intron
kilobases (kb)
kinetochore
long interspersed element (LINE)
long noncoding RNAs
microRNAs (miRNAs)
nested genes
nucleosome
nucleosome core particle
processed pseudogene
pseudogene
retrotransposition
retrotransposon
retrovirus-like element
RNA interference (RNAi)
RNA splicing
short interspersed element (SINE)
simple-sequence repeat
telomerase
telomere
transposable element
X chromosome inactivation

Additional Media and Supplements for Use in the Classroom

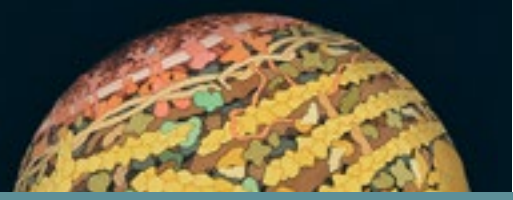
Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

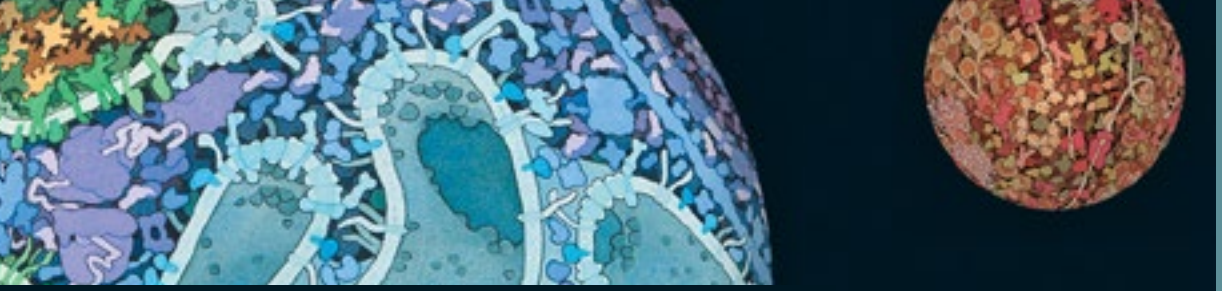
All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website



The **Active Learning Guide** that follows will help you create a dynamic learning environment in your classroom. It provides in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the chapter's Learning Objectives.





CHAPTER 6 Genes and Genomes

Active Learning Activities for the Classroom

6.1 The Structure of Eukaryotic Genes

Learning Objectives

You should be able to:

6.1.1 Diagram the structure of typical genes in bacteria, yeast, and humans.

6.1.2 Explain how an intron can encode a functional protein.

6.1.3 Show how alternative splicing can generate multiple different proteins from a single gene.

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Key Experiment The Discovery of Introns

Active Learning Exercises

1. Have students use their smart devices to research "largest genome" and then write a **minute paper** on the relationship between genome size and polyploidy. (LO 6.1.1)

   Answer: *The largest genome sequenced to date is that of* Paris japonica*, a small, rare plant native to mountains in Japan.* P. japonica *is octoploid (eight sets of chromosomes) as compared to diploid humans (two sets of chromosomes). In this case, the increase in genome size is due largely to polyploidy, not an increase in the number of unique genes. Polyploidy is fairly common in plants, yet quite rare in animals.*

2. Have students form **small groups** to summarize the primary conclusion from the Key Experiment described on page 191 of the textbook. (LO 6.1.2)

   Answer: *Scientists knew that mature mRNAs were shorter than immature mRNAs, but they thought the ends were cut off. Removal of internal sequences—introns—was a complete surprise.*

3. Provide students with a version of the **T table** below with the Value column left blank. From the information on pages 192–194 of the textbook, have students complete the table by filling in the blank column. (LO 6.1.3)

   Answer: *See below. The text uses a lot of percentages and numbers. Bringing some of them together should help students navigate the ocean of data.*

Characteristic	Value
Size of genome (in millions of base pairs)	3,200
Number of genes	21,000
Percent of genes that can be alternatively spliced	90%
Average number of different proteins coded for by a single gene	4
Percent of genome accounted for by introns	~35%
Average percentages of exons and introns in a gene	10% / 90%
Average number of introns per gene	9
Percent of the genome sequences that regulate gene expression	10–20%
Percent of genes that are nested genes	<1%

Clicker Questions

1. If all of the DNA in the human genome coded for proteins, about how many proteins would there be? (LO 6.1.1)
   a. There would be enough genes to code for approximately 10,000,000 proteins.
   b. Each gene would be about 100 times longer.
   c. Each cell would contain much less DNA.
   d. The human genome would be as complex as that of *Arabidopsis*.

2. What is a major difference between prokaryotic genes and eukaryotic genes? (LO 6.1.2)
   a. Prokaryotic genes are more complex.
   b. Prokaryotic genes are more numerous.
   c. Prokaryotic genes lack introns.
   d. Prokaryotic genes are expressed at higher levels.

3. Introns are fairly rare in the human genome. (LO 6.1.2)
   a. True
   b. False

4. Why was electron microscopy used in the discovery of introns? (LO 6.1.2)
   a. Because living cells can be viewed in the electron microscope.
   b. Because electron microscopy can be used to manipulate genes.
   c. Because electron microscopy allowed direct visualization of the introns.

5. Functions of introns include (LO 6.1.3)
   a. regulation of translation.
   b. regulation of transcription.
   c. regulation of splicing.
   d. containing nested genes.

Answers: *1: a; 2: c; 3: b; 4: c; 5: b, c, d*

6.2 Noncoding Sequences

Learning Objectives

You should be able to:

6.2.1 Distinguish miRNAs from lncRNAs.

6.2.2 Describe the different types of repetitive DNA sequences.

6.2.3 Explain how transposable elements can affect gene expression.

6.2.4 Distinguish processed pseudogenes from pseudogenes that arose by DNA duplication.

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Key Experiment The ENCODE Project

Data Analysis Problem 6.2 Analysis of a Specific Form of Satellite DNA by Fluorescence *In Situ* Hybridization

Active Learning Exercises

1. Have students prepare a **T table** similar to the one shown below that details the various types of non-coding RNAs. (LO 6.2.1)

   Answer: *See table below. Note that long noncoding RNAs perform multiple functions. Chromosome inactivation is the one example given in the textbook.*

Type of RNA molecule	Function
tRNA	Delivers the proper amino acid to the ribosome
rRNA	Plays a structural and functional role in ribosome function (translation)
miRNA	Regulates gene expression at the level of transcription via RNA interference (RNAi)
lncRNA	Regulates gene expression at the level of chromosome inactivation

2. Have students form **small discussion groups** to compare and contrast non-coding RNAs from repetitive sequences. (LO 6.2.1, LO 6.2.2)

   Answer: *Non-coding RNAs are RNA molecules that are transcribed from genes but are not translated into a protein. Repetitive sequences are stretches of DNA that are (usually) not transcribed or translated. Both play important roles in the regulation of gene expression.*

3. Have students prepare a **sequence map** of the steps in the functioning of a retrotransposon such as a SINE (short interspersed element) or a LINE (long interspersed element). (LO 6.2.3)

   Answer: *See Figure 6.10. Basic steps are: 1) A SINE or LINE is expressed via transcription to yield a molecule of RNA. 2) Reverse transcription then makes a double-stranded DNA (dsDNA) copy of the RNA. 3) The dsDNA is then integrated into a different site in the genome.*

4. In **think-pair-share** groups, have students use their smart devices to research the plant *Erythranthe peregrine* and answer the question: "How can a new species arise instantaneously?" (LO 6.2.4)

   Answer: Erythranthe guttata *from western North America and* Erythranthe lutea *from the Andes of South America were introduced to Scotland and planted next to each other. They cross-fertilized and the triploid offspring, named* E. × robertsii*, were sterile. However, a whole genome duplication occurred in* E. × robertsii *that yielded an entirely new hexaploid species,* Erythranthe peregrine*.*

Clicker Questions

1. MicroRNAs (miRNAs) are inhibitory, while long, non-coding RNAs (lncRNAs) are regulatory. (LO 6.2.1)
   a. True
   b. False

2. RNA interference leads to (LO 6.2.1)
   a. an increase in transcription of a specific gene.
   b. the expression of long tandem repeats.
   c. the enzymatic destruction of specific mRNAs.
   d. post-transcriptional regulation of gene expression.

3. The major difference between retrovirus-like elements and retroviruses is that (LO 6.2.2)
   a. after replication, retroviruses assemble into viral particles and exit the host cell.
   b. retrovirus-like elements are not integrated into the host cell's genome.
   c. before replication, retroviruses must be released from the host cell.
   d. retrovirus-like elements are exceedingly rare in the human genome.

4. What would happen if a transposable element were integrated into a gene that codes for a protein that controls a stop point in the cell cycle? (LO 6.2.3)
   a. Mitosis could not proceed and the cell cycle would be halted.
   b. The cell cycle would proceed unchecked, resulting in cancerous growth.
   c. The transposable element would be excised and the gene repaired.
   d. Reverse transcriptase would make a copy of the gene and restore function.

5. The human genome contains about 21,000 functional genes and 11,000 non-functional pseudogenes. (LO 6.2.4)
   a. True
   b. False

   Answers: *1: a; 2: c, d; 3: a; 4: b; 5: a*

6.3 Chromosomes and Chromatin

Learning Objectives

You should be able to:

6.3.1 Diagram the structure of chromatin.

6.3.2 Describe the functions of centromeres and their epigenetic transmission.

6.3.3 Summarize the role of telomeres in chromosome maintenance.

Media Available on Companion Website oup.com/uk/cooper8e

Micrograph Interphase chromatin

Data Analysis Problem 6.1 Nuclease Digestion of Chromatin

Data Analysis Problem 6.5 Regulation of Chromatin Structure by a Nuclear Enzyme

Active Learning Exercises

1. Have students use their smart devices to research and write a **minute paper** answering the question, "What is the function of histones?" (LO 6.3.1)

   Answer: *The text defines histones but does not assign a specific function to them. They have two functions: 1) compacting the very long DNA molecules and 2) gene regulation via many different covalent modifications.*

2. Have students form **small discussion groups** and explain why centromere specification is an example of epigenetic inheritance. (LO 6.3.2)

   Answer: *Any information that is passed from one generation to the next that is not specified in a DNA sequence is called epigenetic. The CENP-A histones mark the location of the centromere and recruit more CENP-A histones to that site in the newly formed chromosomes.*

3. Have students use their smart devices to research "Hayflick limit," form **think-pair-share** groups, and relate that concept to cancer cells. (LO 6.3.3)

   Answer: *The Hayflick limit describes the observation that human cells in culture will only divide 40–60 times before they senesce and die. The limit is a consequence of normal cells lacking telomerase, so the telomeres get shortened each round of division and eventually become too short to support mitosis. Cancer cells have very active telomerase enzymes and can therefore repair their telomeres and continue to divide beyond the Hayflick limit.*

Clicker Questions

1. Why do eukaryotes need histones, whereas prokaryotes do not? (LO 6.3.1)
   a. Prokaryotes lack a nucleus, so their chromosome is fully exposed to the cytoplasm.
   b. Histones are needed to ensure alternate gene splicing goes correctly in eukaryotes.
   c. Histones are needed to compact the very long DNA molecules in eukaryotes.

2. The centromere is a region on the chromosome where two sister chromatids are attached during prophase and metaphase of mitosis. However, the centromere "disappears" when the sister chromatids separate at anaphase. How is that region of the chromosome marked so that the cell knows where the centromere should be placed in the next round of mitosis? (LO 6.3.1)
   a. Kinetochore proteins remain bound to the mitotic spindle fibers until the next round of mitosis.
   b. The centromere region is always in the exact middle of every chromosome.
   c. The chromosomes specify a new centrosome site each round of mitosis.
   d. CENP-A histones are used to mark where the centromere should be.

3. The kinetochore is (LO 6.3.2)
   a. the site at which spindle microtubules attach.
   b. a region where the two sister chromatids are attached.
   c. composed of proteins associated with the centromere.
   d. a relatively short sequence of DNA.

4. Most prokaryotes lack telomeres because (LO 6.3.3)
   a. their genomes are so small they do not need telomeres.
   b. their chromosomes lack histones, which are needed for telomerase activity.
   c. their genomes are mostly RNA-based, so DNA repair mechanisms are not needed.
   d. their chromosomes are circular and do not have ends to protect.

Answers: *1: c; 2: d; 3: a, c; 4: d*

CHAPTER 7

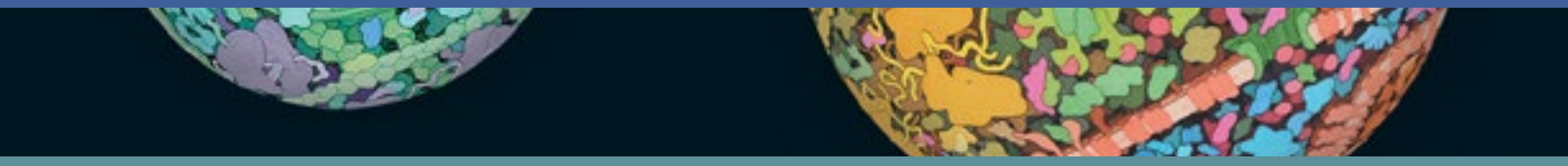
Part II **The Flow of Genetic Information**

Replication, Maintenance, and Rearrangements of Genomic DNA

Chapter Overview

The fundamental biological process of reproduction requires the faithful transmission of genetic information from parent to offspring. Thus, the accurate replication of genomic DNA is essential to the lives of all cells and organisms. Each time a cell divides, its entire genome must be duplicated, and complex enzymatic machinery is required to copy the large DNA molecules that make up both prokaryotic and eukaryotic chromosomes. In addition, cells have evolved mechanisms to correct mistakes that occur during DNA replication and to repair DNA damage that can result from the action of environmental agents, such as radiation. Abnormalities in these processes result in a failure of accurate replication and maintenance of genomic DNA—a failure that can have disastrous consequences, such as the development of cancer.

Despite the importance of accurate DNA replication and maintenance, cell genomes are far from static. In order for species to evolve, mutations and gene rearrangements are needed to maintain genetic variation between individuals. In addition, some DNA rearrangements are programmed to regulate gene expression during the differentiation and development of individual cells and organisms. In humans, a prominent example is the rearrangement of antibody genes during development of the immune system. A careful balance between maintenance and variation of genetic information is thus critical to the development of individual organisms as well as the evolution of a species.



Chapter Outline

Section Reviews

7.1 DNA Replication

Different DNA polymerases play distinct roles in DNA replication and repair in both prokaryotic and eukaryotic cells. All known DNA polymerases synthesize DNA only in the 5′ to 3′ direction by the addition of deoxyribonucleotides to a preformed primer. As a consequence, one new DNA strand (the leading strand) is synthesized in a continuous manner at the replication fork whereas the other strand (the lagging strand) is formed by the joining of small fragments of DNA that are synthesized backward with respect to the overall direction of replication. DNA polymerases and various other proteins act in a coordinated manner to synthesize both leading and lagging strands of DNA. DNA polymerases increase the accuracy of replication both by selecting the correct base for insertion and by proofreading newly synthesized DNA to eliminate mismatched bases. DNA replication starts at origins of replication, which contain binding sites for proteins that initiate the process. In higher eukaryotes, origins may be defined by chromatin structure rather than DNA sequence. Telomeric repeat sequences at the ends of chromosomes are maintained by the action of a reverse transcriptase (telomerase) that carries its own template RNA.

7.2 DNA Repair

A few types of common DNA lesions are repaired by direct reversal of the damage, but most are repaired by excision of the damaged DNA. The resulting gap is filled by newly synthesized DNA, using the undamaged complementary strand as a template. Mismatch repair specifically removes mismatched bases from newly synthesized DNA strands. If other mechanisms fail, specialized DNA polymerases are capable of replicating DNA across from a site of DNA damage, although the action of these polymerases may result in a high frequency of incorporation of incorrect bases. Double-strand breaks are repaired by recombination to rejoin the damaged strands, either by homologous recombination with an undamaged chromosome or by nonhomologous rejoining of the broken ends of a single DNA molecule.

7.3 DNA Rearrangements and Gene Amplification

Programmed DNA rearrangements of immunoglobulin and T cell receptor genes play a critical role in development of the vertebrate immune system. Additional diversity is provided to immunoglobulin genes by somatic hypermutation and class switch recombination, both of which result from enzymatic deamination of cytosines in DNA. Gene amplification results from repeated replication of a chromosomal region. In some cases, gene amplification provides a mechanism for increasing gene expression during development. It can also occur in cancer cells, resulting in the elevated expression of genes that contribute to uncontrolled cell proliferation.

Key Terms

activation-induced deaminase (AID)
antigen
AP endonuclease
autonomously replicating sequence (ARS)
base-excision repair
class switch recombination
DNA glycosylase
DNA ligase
DNA polymerase
double-strand break
excinuclease
exonuclease
gene amplification
helicase
homologous recombination
immunoglobulin
lagging strand
leading strand
mismatch repair
nucleotide-excision repair
Okazaki fragment
origin recognition complex (ORC)
origins of replication
photoreactivation
primase
proofreading
pyrimidine dimer
Rad51
RecA
recombinational repair
replication fork
reverse transcriptase
RNase H
single-stranded DNA-binding protein
somatic hypermutation
T cell receptor
telomerase
telomere
topoisomerase
translesion DNA synthesis

Additional Media and Supplements for Use in the Classroom

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All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website

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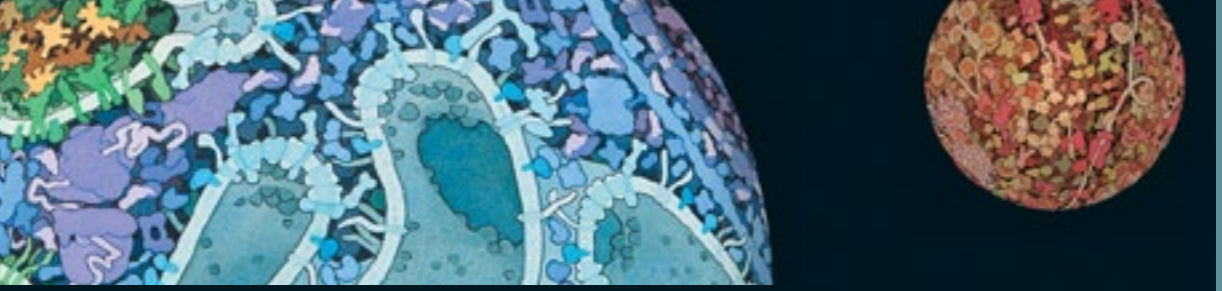


CHAPTER 7 Replication, Maintenance, and Rearrangements of Genomic DNA

Active Learning Activities for the Classroom

7.1 DNA Replication

Learning Objectives

You should be able to:

- **7.1.1** Compare the roles of DNA polymerases in *E. coli* with those in mammalian cells.
- **7.1.2** Contrast the mechanisms of synthesis of the leading and lagging strands of DNA.
- **7.1.3** Identify the proteins found at replication forks of bacteria and mammalian cells.
- **7.1.4** Describe the mechanisms that ensure accurate DNA replication.
- **7.1.5** Compare origins of replication in bacteria and mammalian cells.
- **7.1.6** Summarize the action of telomerase.

Media Available on Companion Website oup.com/uk/cooper8e

Key Experiment Telomerase Is a Reverse Transcriptase
Animation 7.1 DNA Replication Fork
Video 7.1 Mechanism of DNA Replication
Data Analysis Problem 7.1 Enzymatic Activity of SV40 Antigen
Data Analysis Problem 7.2 The Activity of Telomerase
Data Analysis Problem 7.3 Replication of SV40 DNA
Data Analysis Problem 7.4 *In Vitro* Analysis of an Enzyme Involved in DNA Replication

Active Learning Exercises

1. Have students write a **minute paper** explaining how the discovery of DNA polymerase by Kornberg in 1956 fit with the discovery of the structure of DNA by Watson and Crick in 1953. (LO 7.1.1)

   Answer: *Watson and Crick recognized that their double-helix model of DNA meant that the complimentary strands could be faithfully replicated. Kornberg found the enzyme that reads a single strand and generates a double-strand product.*

2. Have students construct a **sequence map** of the steps in the synthesis of the lagging strand of DNA. (LO 7.1.2)

   Answer: *See Figures 7.3 and 7.4 in the textbook. The double-stranded DNA is open, and DNA polymerase begins replicating the leading strand in the 5′ to 3′ direction. When the replication fork is large enough, a second DNA Pol uses an RNA primer and begins synthesizing the lagging strand, resulting in Okazaki fragments. The Okazaki fragments are connected by ligase but contain the short RNA primers, which must be excised and replaced with DNA nucleotides. RNase H, DNA polymerase δ, and ligase combine to remove the RNA and insert the proper DNA sequence.*

3. Have students prepare a **T table** listing the proteins found at replication forks of mammalian cells and giving the function of each. (LO 7.1.3)

   Answer: *See below. (You may wish to provide students with a partially completed template.)*

Protein	Function
Helicase	unwinds the double-stranded DNA
Single-stranded DNA-binding protein	stabilizes the unwound template DNA
Clamp-loading protein	loads the sliding-clamp proteins
Sliding-clamp protein	loads the polymerase onto the primer and maintain its stable association with the template
DNA polymerase	synthesizes a new strand of DNA from the single-strand template
Primase	synthesizes the RNA primer needed to initiate synthesis of Okazaki fragments
DNA ligase	connects the Okazaki fragments
RNase H and exonucleases	removes the RNA primer between Okazaki fragments
Topoisomerase	breaks and rejoins the new DNA strands to prevent twisting

4. Have students write a **minute paper** in which they explain why telomerases are both a reverse transcriptase and a DNA polymerase. (LO 7.1.6)

   Answer: *Telomerases perform both functions. They carry their own RNA template that is complementary to the DNA sequence of the telomere. Telomerases read that RNA and make a piece of single-stranded DNA (ssDNA). They then read the ssDNA to produce double-stranded DNA.*

Clicker Questions

1. DNA polymerases in eukaryotes are used to (LO 7.1.1, LO 7.1.6)
   a. repair DNA after replication.
   b. replicate DNA.
   c. repair DNA after damage.
   d. replicate telomeres.

2. What role does primase play in DNA replication? (LO 7.1.2)
   a. Primase initiates DNA replication on the leading strand by allowing DNA polymerases to bind.
   b. Primase synthesizes the RNA primer needed to initiate synthesis of Okazaki fragments.
   c. Primase removes the short RNA segments produced during lagging strand replication.
   d. Primase acts as an exonuclease to hydrolyze DNA in the 3′ to 5′ direction.

3. Okazaki fragments are a consequence of (LO 7.1.3)
   a. the need to unwind the DNA molecule during replication.
   b. the circular nature of the prokaryotic chromosome.
   c. the presence of histones in the eukaryotic chromosome.
   d. the ability of DNA polymerase to synthesize only in the 5′ to 3′ direction.

4. What prevents RNA nucleotides from becoming incorporated into a growing DNA strand? (LO 7.1.3)
   a. DNA polymerase discriminates against nucleotides containing the ribose sugar.
   b. Complimentary base pairing means that RNA nucleotides cannot bind to DNA nucleotides.
   c. DNA is synthesized in the nucleus, whereas RNA is synthesized in the cytoplasm.
   d. RNA synthesis is halted during the S phase of mitosis.

5. DNA replication moves in both directions in prokaryotes and eukaryotes. (LO 7.1.4)
   a. True
   b. False

6. Telomerases are necessary in eukaryotes because (LO 7.1.6)
   a. eukaryotic chromosomes contain histones, which must be replicated with the DNA.
   b. telomerases are the only eukaryotic enzymes that can replicate DNA.
   c. eukaryotic telomeres are necessary to preserve the integrity of the kinetochore.
   d. eukaryotic DNA polymerases cannot copy all the way to the end of a chromosome.

Answers: *1: a, b, c, d; 2: b; 3: d; 4: a; 5: a; 6: d*

7.2 DNA Repair

Learning Objectives

You should be able to:

7.2.1 Compare and contrast direct repair of DNA damage with the different types of excision repair.

7.2.2 Explain why defects in DNA repair lead to cancer.

7.2.3 Describe translesion DNA synthesis.

7.2.4 Summarize the mechanisms cells use to repair double-strand breaks.

Media Available on Companion Website oup.com/uk/cooper8e

Video 7.2 Methyl-Directed Mismatch Repair

Molecular Medicine Colon Cancer and DNA Repair

Active Learning Exercises

1. Have students form **think-share-pair** groups and answer this question: "Why does the deamination of cytosine damage DNA?" (LO 7.2.1)

   Answer: *Deaminated cytosine is uracil, meaning that deamination of cytosine is basically a base substitution mutation.*

2. Have students write a **minute paper** explaining how prokaryotes and eukaryotes can tell which is the new strand in mismatch repair. (LO 7.2.1)

   Answer: *In prokaryotes, template strands are methylated; newly synthesized strands are not. This allows repair enzymes to differentiate between the template and the new strand. In eukaryotes, the mismatch is recognized by an enzyme that nicks the new strand. Repair enzymes then excise a portion of the nicked strand, and DNA polymerase replaces it with the proper strand.*

3. Have students prepare a **spider map** with the following four terms as legs: base-excision repair, nucleotide-excision repair, mismatch repair, translesion synthesis. (LO 7.2.1, LO 7.2.3)

   Answer: *Base-excision repair (single, damaged base is replaced), nucleotide-excision repair (oligonucleotide containing the lesion is excised and replaced), mismatch repair (an incorrect base inserted during DNA replication is replaced), translesion synthesis (errors in the template strand are skipped during DNA replication and repaired later).*

Clicker Questions

1. What is the main difference between base-excision repair and nucleotide-excision repair? (LO 7.2.1)
   a. Base excision removes one nucleotide; nucleotide excision replaces an oligonucleotide.
   b. Base excision involves one catalytic step; nucleotide excision have multiple enzymatic steps.
   c. Base excision can repair different types of damage; nucleotide excision only repairs a specific type.
   d. Base excision involves DNA polymerase and ligase; nucleotide excision uses a DNA glycosylase.

2. Defaults in mismatch repair mechanisms affect only genes that regulate cell proliferation, thus leading to colon cancer. (LO 7.2.2)
   a. True. The genes that cause colon cancer are specifically targeted by faulty mismatch repair mechanisms. Other cells in the body replicate their DNA with a different mechanism.
   b. False. Any gene can be the subject of a bad mismatch repair mechanism.

3. How does translesion synthesis differ from excision repair? (LO 7.2.3)
   a. Translesion enzymes skip over mismatched bases; excision acts directly on them.
   b. Translesion enzymes work in the 5′ to 3′ direction; excision enzymes work in the 3′ to 5′ direction.
   c. Excision repair acts before DNA replication; translesion synthesis acts after DNA replication.
   d. Excision repair replaces single base pairs; translesion synthesis replaces large sections of DNA.

4. Recombinational repair of double-strand breaks can introduce (LO 7.2.4)
   a. base substitutions.
   b. base inversions.
   c. base deletions.
   d. base duplications.

5. Homologous recombination repair requires the presence of a centromere because (LO 7.2.4)
   a. the repair requires using the information on the undamaged sister chromatid.
   b. the repair relies on proteins associated with the kinetochore.
   c. the DNA polymerases used in the repair are only expressed during mitosis.

Answers: *1: a; 2: b; 3: a, c; 4: c; 5: a*

7.3 DNA Rearrangements and Gene Amplification

Learning Objectives

You should be able to:

7.3.1 Describe the rearrangements in immunoglobulin heavy and light chains.

7.3.2 Explain how nonhomologous end joining of double-strand breaks and cytosine deamination contribute to immunoglobulin diversity.

7.3.3 Explain why DNA amplification increases gene expression.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 7.2 Light-Chain Genes

Animation 7.3 Heavy-Chain Genes

Active Learning Exercises

1. Have students use their smart devices to **research** the question: "How are immunoglobulins secreted from B lymphocytes?" (LO 7.3.1)

   Answer: *Immunoglobulins are produced on the RER and secreted via the Golgi apparatus.*

2. Have students prepare a **spider map** of the four mechanisms that contribute to antibody diversity. Provide a brief explanation of each mechanism. (LO 7.3.1, LO 7.3.2)

   Answer: *Each mechanism is detailed in a figure in the textbook. Site-specific recombinations (DNA rearrangements and RNA splicing, Figure 7.28), combining different light chains and heavy chains (Figure 7.27), class switch recombination (Figure 7.32), somatic hypermutation (Figure 7.33).*

3. Have students form **small discussion groups** and consider how gene amplification differs from polyploidy. (LO 7.3.3)

   Answer: *In gene amplification, one or two genes are increased in copy number. In polyploidy, an entire genome is increased in copy number.*

Clicker Questions

1. Does gene rearrangement happen before or after transcription? (LO 7.3.1)
   a. Before
   b. After

2. Antibody diversity relies on both gene rearrangement and (LO 7.3.1)
   a. post-translational covalent modifications.
   b. post-translational RNA splicing.
   c. pre-translational covalent modifications.
   d. post-transcriptional RNA splicing.

3. Cytosine deamination is a beneficial process. (LO 7.3.2)
   a. True. Cytosine deamination converts cytosine to uracil and contributes to antibody diversity.
   b. False. Cytosine deamination converts cytosine to uracil and causes DNA damage requiring excision repair.

4. Gene amplification would typically be found only in (LO 7.3.3)
   a. aging tissues.
   b. mature tissues.
   c. damaged tissues.
   d. developing tissues.

Answers: *1: a; 2: d; 3: a; 4: d*

CHAPTER

Part II **The Flow of Genetic Information**

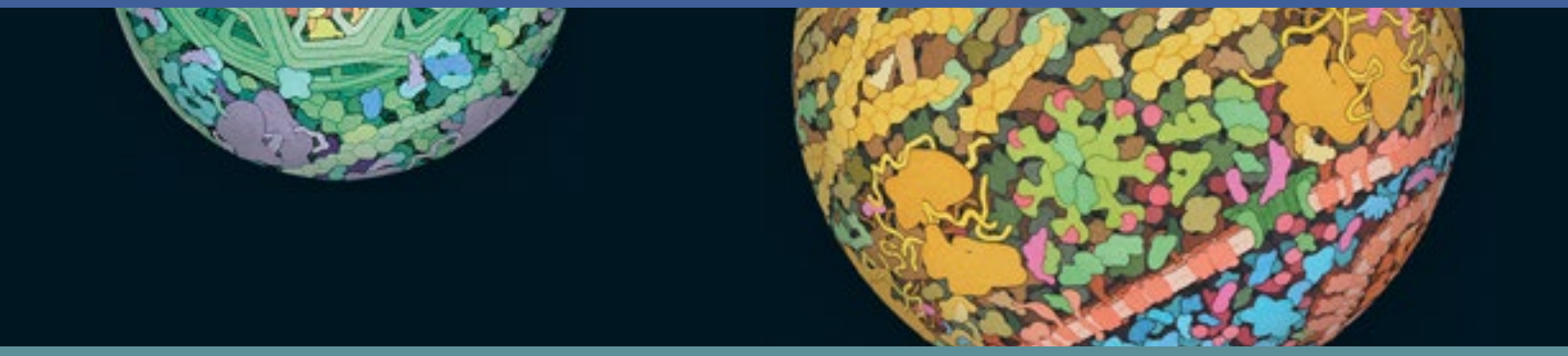
RNA Synthesis and Processing

8

Chapter Overview

Chapters 6 and 7 discussed the organization and maintenance of genomic DNA, the set of genetic instructions governing all cellular activities. These instructions are implemented via the synthesis of RNAs and proteins. Importantly, the behavior of a cell is determined not only by what genes it inherits but also by which of those genes are expressed at any given time. Regulation of gene expression allows cells to adapt to changes in their environments and is responsible for the distinct activities of the multiple differentiated cell types that make up complex plants and animals. Almost all cells in multicellular organisms have the same genomic DNA. Muscle cells and liver cells, for example, contain the same genes. The functions of these cells are determined not by differences in their genomes, but by regulated patterns of gene expression that govern development and differentiation.

The first step in expression of a gene, the transcription of DNA into RNA, is the initial level at which gene expression is regulated. RNAs in eukaryotic cells are then modified in various ways (e.g., introns are removed by splicing) to convert the primary transcript into its functional form. Transcription and RNA processing are discussed in this chapter. The regulation of transcription is discussed in Chapter 9, and the final step in gene expression—the translation of mRNA to protein—is the subject of Chapter 10.



Chapter Outline

Section Reviews

8.1 Transcription in Bacteria

E. coli RNA polymerase consists of α, β, β', ω, and σ subunits. Transcription is initiated by the binding of σ to promoter sequences. After synthesis of about the first ten nucleotides of RNA, the core polymerase dissociates from σ and travels along the template DNA as it elongates the RNA chain. Transcription then continues until the polymerase encounters a termination signal.

8.2 Eukaryotic RNA Polymerases and General Transcription Factors

Eukaryotic cells contain three distinct nuclear RNA polymerases that transcribe genes encoding mRNAs, miRNAs, and lncRNAs (polymerase II), rRNAs (polymerases I and III), and tRNAs (polymerase III). Rather than binding directly to promoter sequences, eukaryotic RNA polymerases require additional proteins (general transcription factors) to initiate transcription. The recruitment of RNA polymerase II to promoters requires a minimum of five general transcription factors. Other factors are required for RNA polymerases I and III to bind their promoters.

8.3 RNA Processing and Turnover

rRNAs and tRNAs are derived by cleavage of long primary transcripts in both bacteria and eukaryotic cells. rRNAs are modified by methylation and pseudouridine formation, and various bases are modified in tRNAs. Eukaryotic pre-mRNAs are modified by the addition of 5′ 7-methylguanosine caps and 3′ poly-A tails, in addition to the removal of introns by splicing, which takes place in large complexes, called spliceosomes, composed of proteins and snRNAs. The snRNAs recognize sequences at the splice sites of pre-mRNAs and catalyze the splicing reaction. Exons can be joined in various combinations as a result of alternative splicing, which provides an important mechanism

for tissue-specific control of gene expression. The sequences of mRNAs can also be modified by RNA editing, in mammalian cells involving either the deamination of cytosine to uridine or of adenosine to inosine. mRNAs in eukaryotic cells are degraded at different rates, providing an additional mechanism for control of gene expression.

Key Terms

7-methylguanosine cap
alternative splicing
general transcription factor
Mediator
mRNP
polyadenylation
poly-A tail
pre-mRNA
pre-rRNA
pre-tRNA
promoter
ribozyme
RNA editing
RNA polymerase
RNase P
self-splicing
small nuclear ribonucleoprotein particle (snRNP)
small nuclear RNA (snRNA)
small nucleolar RNA (snoRNA)
snoRNPs
spliceosome
TATA box
TATA-binding protein (TBP)
TBP-associated factor (TAF)
transcription factor

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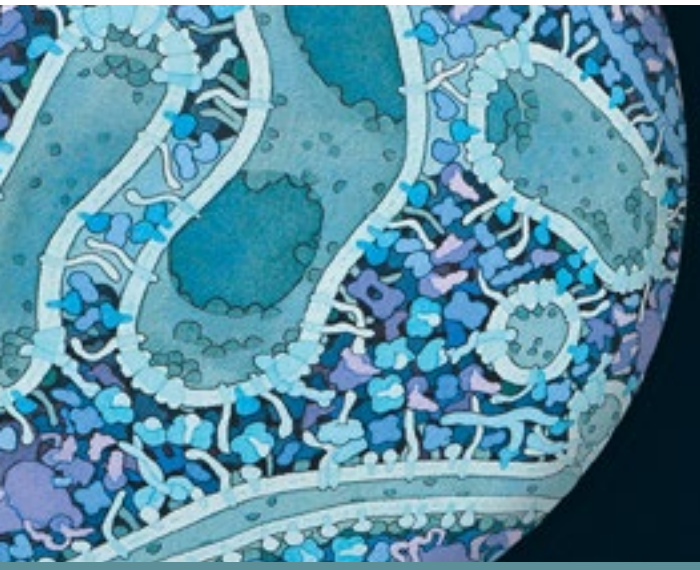

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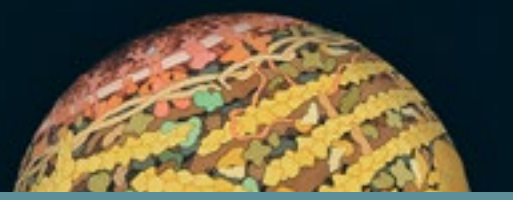

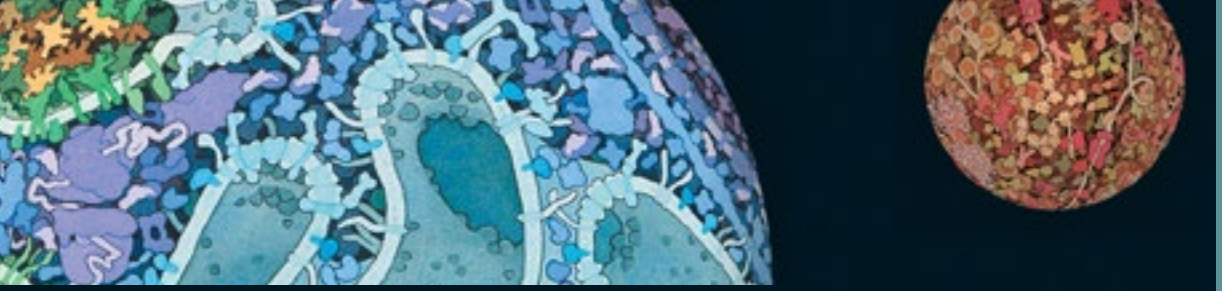

CHAPTER 8 RNA Synthesis and Processing

Active Learning Activities for the Classroom

8.1 Transcription in Bacteria

Learning Objectives

You should be able to:

8.1.1 Explain how *E. coli* RNA polymerase initiates transcription.

8.1.2 Diagram a bacterial promoter sequence.

8.1.3 Describe the processes of transcriptional elongation and termination.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 8.1 Transcription

Video 8.1 DNA Transcription

Data Analysis Problem 8.1 *In vivo* Labeling of Nucleic Acids

Data Analysis Problem 8.4 Pulse–Chase Labeling of Newly Synthesized RNA in *E. coli* Cells

Active Learning Exercises

1. Have students write a **minute paper** describing the relationship between *E. coli* RNA polymerase and *E. coli* promotor sequences and the role the protein σ (sigma) plays in this relationship. (LO 8.1.1, LO 8.1.2)

   Answer: *RNA polymerase binds at a specific promoter region on the DNA. The sigma protein directs RNA Pol to the correct binding site on the promoter at the –10 and –35 positions.)*

2. Have students in **pairs** create a **diagram** of a bacterial promoter sequence. (LO 8.1.2)

   Answer: *See Figure 8.2. Have one student read the description while the other, without looking at the figure, draws the sequence. Then reverse roles.*

3. Call students to the board to create each step in a **sequence map** that illustrates transcriptional elongation and termination. Solicit comments and revisions from the class along the way or after the map is complete. (LO 8.1.3)

   Answer: *See Figure 8.3. (Note: The sequence map can contain only basic information or include more detail, as described in the text.)*

Clicker Questions

1. *E. coli* RNA polymerase differs from *E. coli* DNA polymerase in that (LO 8.1.1)
   a. it reads the template DNA strand in the 3′ to 5′ direction.
   b. it does not need a primer sequence to initiation reading.
   c. it is a multiprotein complex, whereas DNA polymerase is a single enzyme.
   d. the double-stranded DNA gene does not need to be unwound for reading.

2. The promoter sequence is transcribed first, followed by the DNA of the gene. (LO 8.1.2)
   a. True
   b. False

3. The sigma subunit is of the proper size to (LO 8.1.3)
   a. unwind the double-stranded DNA of the gene.
   b. bind to and cause the crab-claw–like β and β' subunits to close.
   c. span between and bind to both the –35 and –10 promoter elements.
   d. span between the promotor and the open reading frame of the gene.

4. The most common way to terminate transcription is by tying a knot at the end of the mRNA molecule. (LO 8.1.3)
   a. True. GC-rich inverted repeats form a stable loop at the end.
   b. False. mRNA is a linear molecule and cannot fold back on itself.

Answers: *1: b; 2: b; 3: c; 4: a*

8.2 Eukaryotic RNA Polymerases and General Transcription Factors

Learning Objectives

You should be able to:

8.2.1 Summarize the roles of different eukaryotic RNA polymerases.

8.2.2 Distinguish between the binding of bacterial and eukaryotic RNA polymerases to promoters.

8.2.3 Describe the functions of the general transcription factors for RNA polymerase II.

8.2.4 Summarize the organization of promoters transcribed by RNA polymerases I and III.

Media Available on Companion Website oup.com/uk/cooper8e

Data Analysis Problem 8.3 Analysis of Cytoplasmic Ribonucleoproteins in Mouse Cells

Active Learning Exercises

1. Have students prepare a **spider map** utilizing the information in Table 8.1. (LO 8.2.1)

   Answer: *There should be three main legs (nuclear genes, mitochondrial genes, chloroplast genes). The "nuclear genes" label should have six additional legs, and the "rRNA" label should have two legs of its own.*

2. Instruct students to write a **minute paper** distinguishing between the binding of bacterial and eukaryotic RNA polymerases to promoters. (LO 8.2.2)

   Answer: *Bacterial RNA polymerase binds to sigma, which directs it to a promotor (indicated by the –10 and –35 promoter regions). Eukaryotic RNA polymerase requires a large, complicated initiation complex composed of multiple transcription factors, none of which are bound directly to the polymerase.*

3. Have students prepare a **sequence map** for the actions of TFIID, TFIIB, TFIIF, TFIIE, and TFIIH. (LO 8.2.3)

   Answer: *TFIID binds to the promoter first and recruits TFIIB. TFIIB and TFIIF then recruit RNA polymerase II and allow it to bind to the promoter. TFIIE binds next and recruits TFIIH to the initiation complex. TFIIH is a helicase that unwinds the DNA double strand. TFIIH also phosphorylates RNA polymerase II, which releases it from the preinitiation complex and allows transcription to proceed.*

4. In **small discussion groups**, have students consider the unique aspects of RNA polymerase I. (LO 8.2.4)

   Answer: *RNA polymerase I transcribes only the genes for rRNAs. rRNA genes are arranged in tandem, unlike other genes. RNA polymerase I is very active in multiple copies to keep up the manufacture of ribosomes.*

Clicker Questions

1. Chloroplast RNA polymerases are similar to bacterial RNA polymerases because (LO 8.2.1)
   a. chloroplasts are found only in plants, which have a simpler genetic machinery.
   b. chloroplasts, like bacteria, are not as large as eukaryotic cells.
   c. chloroplasts perform only photosynthesis; eukaryotic cells perform all other activities.
   d. chloroplasts arose in plants endosymbiotically.

2. A major difference between prokaryotic sigma factor and eukaryotic transcription factors is that (LO 8.2.2)
   a. eukaryotic transcription factors bind upstream of the coding region; sigma factor binds downstream of the coding region.
   b. prokaryotic gene expression can proceed without sigma factor; eukaryotic transcription factors are required for gene expression.
   c. prokaryotic sigma factor binds directly to the polymerase enzyme; transcription factors bind to the DNA and recruit the polymerase.
   d. eukaryotic transcription factors are required only to initiate transcription; prokaryotic sigma factors are needed throughout transcription.

3. What would happen if a yeast cell could not make TFIIE? (LO 8.2.3)
   a. TFIID would not be recruited to the initiation complex.
   b. TFIIB would not be recruited to the initiation complex.
   c. TFIIH would not be recruited to the initiation complex.
   d. Transcription could not proceed.

4. What would happen if a yeast cell could not make TFIIB? (LO 8.2.4)
   a. TFIIF would not be recruited to the initiation complex.
   b. TFIIE would not be recruited to the initiation complex.
   c. TFIIH would not be recruited to the initiation complex.
   d. Transcription could not proceed.

Answers: *1: d; 2: c; 3: c, d; 4: a, b, c, d*

8.3 RNA Processing and Turnover

Learning Objectives

You should be able to:

8.3.1 Summarize the events involved in processing rRNAs and tRNAs.
8.3.2 Diagram mRNA processing.
8.3.3 Describe the roles of snRNAs in mRNA splicing.
8.3.4 Illustrate patterns of alternative splicing.
8.3.5 Describe RNA editing.
8.3.6 Explain how mRNA degradation can be regulated by the environment.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 8.2 RNA Processing
Video 8.2 RNA Splicing
Data Analysis Problem 8.2 Ribosomal RNA Metabolism
Key Experiment The Discovery of snRNPs
Molecular Medicine Splicing Therapy for Duchenne Muscular Dystrophy

Active Learning Exercises

1. Have students write a **minute paper** on the role of the nucleolus in rRNA processing. (LO 8.3.1)

   Answer: *The answer should include, in students' words, the information in Figure 8.12 and the accompanying text.*

2. In **small discussion groups**, have students explain why eukaryotic mRNAs would be subject to more post-transcriptional processing than rRNAs or tRNAs. (LO 8.3.2)

   Answer: *Post-transcriptional processing of mRNAs increases proteome diversity. rRNAs and tRNAs have specific functions, and any alterations in their sequences could be lethal to the cell.*

3. Have students prepare a **T table** that lists the post-transcriptional modifications to mRNA and their function. (LO 8.3.2)

   Answer:

Modification	Function
addition of a 7-methylguanosine cap at 5′ end	Stabilizes RNA and helps align molecule for translation
polyadenylation of the 3′ end	Influences mRNA translation and stability
removal of introns (splicing)	Generates the mature mRNA for translation

4. Have students prepare a **matrix** in which they compare and contrast the composition and function of three types of RNA-binding proteins: snoRNPs, mRNPs, and snRNPs. (LO 8.3.1, LO 8.3.2, LO 8.3.3)

   Answer:

RNA-binding protein	Composition	Function
small ribonucleoprotein particle (snoRNP)	pre-rRNA molecule, single snoRNA and 8-10 proteins	catalyze either ribose methylation or pseudouridine formation in pre-rRNA
messenger ribonucleoprotein particle (mRNP)	pre-mRNA molecule and proteins	responsible for adding cap and tail to pre-mRNA
small nuclear ribonucleoprotein particle (snRNP)	pre-mRNA molecule, 1 or 2 small nuclear RNA molecules and 8–10 proteins	mRNA splicing

5. In **small discussion groups**, have students examine the difference between splicing activators and splicing repressors. (LO 8.3.4)

   Answer: *A splicing activator is demonstrated in Figure 8.21 and a splicing repressor in Figure 8.22.*

6. In **think-pair-share groups**, have students explain the difference between RNA splicing and RNA editing. (LO 8.3.5)

   Answer: *In RNA splicing, portions of a pre-mRNA molecule are deleted and the loose ends reconnected. In RNA editing, individual bases are removed, replaced, or altered in a pre-mRNA molecule.*

Clicker Questions

1. What is particularly unique about RNase P? (LO 8.3.1)
   a. It is capable of initiating translation of both rRNA and tRNA genes.
   b. It is capable of binding both RNA and DNA molecules.
   c. It is composed of a combination of RNA and proteins.
   d. It contains an enzymatic RNA.

2. In order for a molecule of RNA to be self-splicing it must (LO 8.3.3)
   a. be bound to a spliceosome containing at least one snRNA.
   b. be part of a larger, multi-protein splicing assembly.
   c. contain an intron with ribozyme activity.
   d. have all of its introns removed.

3. Alternative splicing is one of many examples of regulation of gene expression. (LO 8.3.4)
   a. True
   b. False

4. RNA editing changes individual codons. This can either alter a protein's amino acid composition or result in a much shorter protein. (LO 8.3.5)
   a. True
   b. False

5. Mammalian mRNAs have different lifetimes, ranging from less than 30 minutes to approximately 20 hours. This is a form of regulation of gene expression. One would expect the shorter-lived mRNAs to code for (LO 8.3.6)
   a. regulatory proteins.
   b. structural proteins.
   c. proteins involved in basic metabolism.
   d. transcription factors.

Answers: *1: d; 2: c; 3: a; 4: a; 5: a, d*

CHAPTER

9

Part II **The Flow of Genetic Information**

Transcriptional Regulation and Epigenetics

Chapter Overview

The preceding chapter discussed the mechanisms of RNA synthesis and processing in both prokaryotic and eukaryotic cells. This chapter deals with the regulation of transcription, which is the primary level at which gene expression is controlled. Regulation of transcription is fundamental to all aspects of cell behavior, from the utilization of nutrients by bacteria to the complex behavior of neurons in the human brain. The mechanisms that determine patterns of gene expression in eukaryotes are multifaceted, including epigenetic control by modification of chromatin. The complex networks that regulate gene expression determine the normal behavior of the many different cell types in the human body. And as one might expect, abnormalities of transcriptional regulation underlie many common diseases, including multiple types of cancer.

Chapter Outline

Section Reviews

9.1 Gene Regulation in *E. coli*

The prototype model for gene regulation in bacteria is the *lac* operon, which is regulated by the binding of a repressor to specific DNA sequences overlapping the promoter. Other bacterial genes are regulated by transcriptional activators, which stimulate rather than inhibit the binding of RNA polymerase to promoters.

9.2 Transcription Factors in Eukaryotes

Transcription of eukaryotic genes is controlled by proteins that bind to regulatory sequences, which can be located either near promoters or in distant enhancers. Transcriptional activators are modular proteins, consisting of distinct DNA binding and activation domains. Some repressors interfere with the binding of activators or general transcription factors to DNA; others contain discrete repression domains that inhibit transcription. In addition to regulation at the level of initiation, eukaryotic transcription is regulated at the level of elongation. Many genes have molecules of RNA polymerase II that have initiated transcription but then paused immediately downstream of the promoter, ready to resume transcription in response to appropriate extracellular signals.

9.3 Chromatin and Epigenetics

Enzymes that catalyze histone acetylation are associated with transcriptional activators, whereas histone deacetylases are associated with repressors. Histones are also modified by phosphorylation and methylation, and specific modifications of histones affect gene expression by serving as binding sites for other regulatory proteins. Chromatin remodeling factors facilitate the binding of transcription factors to DNA by altering the arrangement or structures of nucleosomes. Histone modifications can be transmitted to daughter cells, providing a major mechanism for epigenetic inheritance. Methylation of cytosine residues inhibits the transcription of eukaryotic genes and is also transmitted to daughter cells. Long noncoding RNAs (lncRNAs) can act as scaffolds by forming complexes with proteins that regulate chromatin modification and recruiting these complexes to their target genes.

Key Terms

chromatin immunoprecipitation
chromatin remodeling factors
cis-acting control elements
coactivators
cohesin
corepressors
CTCF
DNA-affinity chromatography
DNase hypersensitive sites
electrophoretic-mobility shift assay
elongation factors
enhancers
epigenetic inheritance
genomic imprinting
histone acetylation
long noncoding RNAs (lncRNAs)
operator
operon
Polycomb proteins
repressor
transcriptional activators

Additional Media and Supplements for Use in the Classroom

Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website

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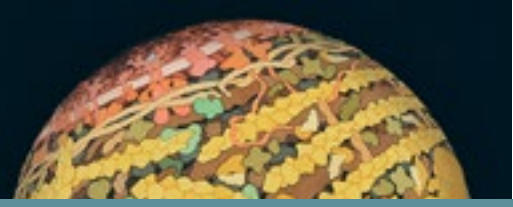

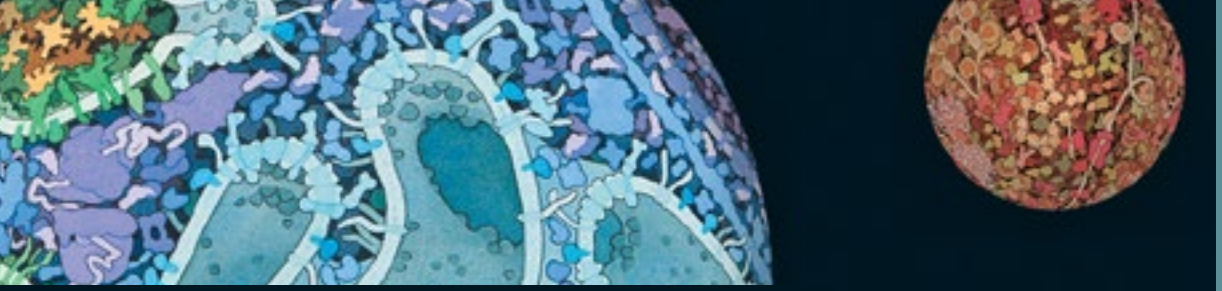

CHAPTER 9 Transcriptional Regulation and Epigenetics

Active Learning Activities for the Classroom

9.1 Gene Regulation in *E. coli*

Learning Objectives

You should be able to:

9.1.1 Explain how lactose regulates transcription of the *lac* operon.
9.1.2 Distinguish between positive and negative control.
9.1.3 Explain why repressors inhibit but activators stimulate transcription.

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Data Analysis Problem 9.1 Electrophoretic Mobility Shift Assay

Active Learning Exercises

1. Have groups of 3–4 students engage in **small group discussions** to consider why would it make more sense to regulate gene expression at initiation than at elongation. Choose one or two groups to share their thoughts with the class. (LO 9.1.1)

   Answer: *The text makes the statement but does not offer an explanation. Therefore, students will have to figure this out on their own. A reasonable answer is that initiation is an early step, whereas elongation is a later step—so regulate initiation. Also, if elongation were regulated, what would become of the partial transcripts? Would they be stored? Preserved? Degraded?*

2. Have students, in groups of 2–3, write a **minute paper** explaining the roles of β-galactosidase, lactose permease, and transacetylase in the metabolism of lactose by *E. coli*. (LO 9.1.1)

   Answer: *In addition to requiring β-galactosidase, lactose metabolism involves the products of two other closely linked genes: lactose permease, which transports lactose into the cell, and a transacetylase, which is thought to inactivate toxic thiogalactosides that are transported into the cell along with lactose by the permease.*

3. Jacob and Monod studied the *lac* operon in the 1950s using only genetic approaches. They "crossed" different strains of bacteria and looked for growth on different carbon sources. The structure of DNA had yet to be revealed by Watson and Crick, and the tools of molecular biology were 25 years in the future. Interestingly, textbooks almost

always ignore the original studies and teach the *lac* operon entirely from the standpoint of molecular biology (refer to Figure 9.2). Have students form **think-pair-share** groups and discuss this seeming enigma. (LO 9.1.1, LO 9.1.2)

Answer: *There is no "correct" answer to this exercise. The point is to get students to realize that the way things are taught are not necessarily the way they were discovered. Students may gain an appreciation of how incredible it was that Jacob and Monod discovered gene expression control without knowing much about DNA or molecular biology.*

4. Have students prepare a **sequence chart** of the steps in lactose-mediated up-regulation of the *lac* operon in *E. coli*. (LO 9.1.1, LO 9.1.3)

   Answer: *See Figure 9.2.*

5. Referring to Figure 9.3, have students make a **spider map** with two pathways. One pathway will outline how high glucose concentrations repress the *lac* operon, while the other pathway will outline how low glucose concentrations have the opposite effect. (LO 9.1.2, LO 9.1.3)

   Answer: *See Figure 9.3.*

Clicker Questions

1. Why is the *lac* operon under transcriptional regulation? (LO 9.1.1)
   a. Transcriptional regulation allows the cell to economize by not investing energy in the synthesis of unnecessary mRNAs and proteins.
   b. Lactose is the preferred, but not the only, β-galactoside that can be enzymatically degraded by β-galactosidase. If the *lac* operon were not under some form of control, all of the β-galactosides in the cell would be degraded.
   c. In the human gut, *E. coli* cells rarely see lactose, a disaccharide found in milk. It would not make sense to synthesize a series of enzymes to degrade a substrate that is rarely encountered.
   d. The presence of too much lactose can be toxic to *E. coli* cells, so there must be a mechanism to prevent its buildup.

2. Discuss a potential response to the Lactose Paradox: If lactose is needed to induce the synthesis of the lactose permease, which is needed for the cell to take up lactose, how does lactose get into an *E. coli* cell to activate the *lac* operon? (LO 9.1.1)
   a. Lactose can freely pass across the cell membrane. The permease is needed only to speed up the rate of uptake.
   b. Lactose can freely pass across the cell membrane. The permease gene is a vestigial remnant that serves no purpose and that natural selection has yet to remove.
   c. The *lac* repressor occasionally falls off (debinds), which allows a minimal level of the three enzymes needed to take up and metabolize lactose.
   d. Occasionally, transcription and translation of the *lac* repressor gene generates a defective *lac* repressor protein. This defective protein cannot repress the expression of the *lac* operon, so a certain number of the permease proteins are always present.

3. Explain how the *lac* operon is regulated. (LO 9.1.1)
   a. It is regulated by an activator protein that is activated by allolactose, thus allowing for transcription.
   b. It is regulated by a repressor protein that is forced to debind by allolactose, thus allowing for transcription.
   c. It is regulated by an activator protein that must bind to the operator to allow for transcription.
   d. It is regulated by a repressor protein that must be removed from the operator to allow for transcription.

4. The lactose operon exemplifies which central principle of the regulation of gene expression? (LO 9.1.1)
   a. Regulation of gene expression is stimulated by repressor proteins and inhibited by activator proteins.
   b. Both positive and negative control of gene expression is mediated by the binding of regulatory proteins to specific DNA sequences.
   c. Regulation of gene expression in prokaryotes is far more complex than regulation of gene expression in eukaryotes.
   d. *Cis*-acting control elements guide prokaryotes to allow gene expression to proceed to the termination stage.

5. Activators are (LO 9.1.2)
   a. proteins that must bind to an upstream *cis*-element for transcription to be initiated.
   b. stretches of DNA to which activator proteins must bind for transcription to be initiated.
   c. proteins that bind to the operator region of an operon and allow transcription to be initiated.
   d. proteins that must be removed from an operator for transcription to be initiated.

6. Explain why repressors inhibit but activators stimulate transcription. (LO 9.1.3)
   a. Repressors bind to specific DNA sequences and inhibit transcription, while activators bind to downstream elements and stimulate transcription.
   b. Repressors bind to activators and remove them from a specific stretch of DNA, which stimulates transcription.
   c. Repressors must be removed from an operator for transcription to proceed, while activators must bind to an operator to stimulate transcription.
   d. Repressors interact directly with activators, such as allolactose.

Answers: *1: a; 2: c; 3: b, d; 4: b; 5: c; 6: c*

9.2 Transcription Factors in Eukaryotes

Learning Objectives

You should be able to:

9.2.1 Compare and contrast promoters and enhancers.

9.2.2 Summarize the experimental approaches used to study the binding of transcription factors to DNA.

9.2.3 Describe how activators and repressors affect transcription.

9.2.4 Explain how transcriptional elongation is controlled.

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Data Analysis Problem 9.1 Electrophoretic Mobility Shift Assay

Key Experiment Isolation of a Eukaryotic Transcription Factor

Active Learning Exercises

1. Have students, in pairs, write a **minute paper** that explains how DNA looping allows distant enhancers to exert control over eukaryotic gene expression. (LO 9.2.1)

   Answer: *See Figure 9.8.*

2. Have students form **think-pair-share** groups to analyze this statement: "*Cis*-acting transcriptional regulators are noncoding regions of DNA. If they don't code for a protein, how do they act to regulate gene expression?" (LO 9.2.1)

   Answer: *Promoters are stretches of DNA that allow for binding of RNA Polymerase II and transcription factors. They represent the "start" site for transcription. Enhancers are stretches of DNA that bind other transcription factors, recruiting them to interact with the promoter and to accelerate transcription.*

3. Chromatin precipitation relies on the ability of an antibody to recognize a specific transcription factor, something antibodies do quite well. Have students, in **small groups**, use their smartphones or computers to research and answer the question, "Where did the antibodies for the chromatin precipitation assay come from?" (LO 9.2.2)

   Answer: *Antibodies are generated by animal immune systems when exposed to a foreign protein. The antibodies are incredibly specific for that protein and will recognize (bind to) it under most circumstances. To generate antibodies, one must first start with a protein. In the case of the chromatin precipitation assay, that means isolating and purifying the transcription factor (tf) of interest. The tf protein is then injected into the bloodstream of (usually) a bird or mammal. It takes a few days for the animal to mount a full immune response. Then blood is drawn, and the antibodies are isolated from the blood.*

4. Repressors repress transcription in a variety of ways. Have students explain ways repressors act by creating a **table** with two columns. On the left, have them list the words "interference," "competition," and "inhibition." On the right, have them complete the sentence "A repressor can act by" for each term. (LO 9.2.3)

   Answer: *See below. More details and examples are available in the text.*

interference	interfering with the binding of other transcription factors to DNA
competition	competing with activators for binding to specific regulatory sequences
inhibition	containing specific functional domains that inhibit transcription via protein–protein interactions

5. Have students create a **sequence map** of the regulation of transcription by direct modulation of RNA polymerase activity. (LO 9.2.4)

   Answer: *See Figure 9.16.*

Clicker Questions

1. In eukaryotic gene regulation, how do promoters differ from enhancers? (LO 9.2.1)
   a. Promoters are regulatory sequences that are usually far upstream from the coding region they control, while enhancers are within a few hundred base pairs of a coding region.
   b. Promoters are often active at low levels, allowing for a minimal level of gene expression, while enhancers are utilized only to up-regulate the level of transcription.
   c. Enhancers are strictly on/off regulatory elements, while promoters determine the level of transcription at any given time.
   d. Promoters are typically able to bind only specific transcription factors, while a single enhancer may up-regulate several different genes.

2. Three techniques to isolate transcription factors: electrophoretic-mobility shift, chromatin precipitation and DNA-affinity chromatography, are based on the same principle. What is that principle and why would it be effective? (LO 9.2.2)
   a. Transcription factors must accurately recognize and bind to a very specific sequence of DNA nucleotides in order to regulate specific gene expression.
   b. Transcription factors are all small molecules, and electrophoretic-mobility shift, chromatin precipitation, and DNA-affinity chromatography all separate molecules on the basis of size.
   c. Transcription factors are present in the cell in very small quantities. Abundant proteins would not be detected with any of the techniques.
   d. Transcription factors will bind to multiple promoter regions. All three techniques use a variety of promoter sequences at the same time.

3. Coactivators act differently than activators, and corepressors act differently than repressors. Which statement correctly contrasts these differences? (LO 9.2.3)
   a. Coactivators work together with activators, and corepressors work together with repressors to regulate gene expression.
   b. Coactivators and corepressors act antagonistically with activators and repressors (respectively), meaning the activity of one activates or represses the activity of the other.

c. Coactivators and activators regulate the initiation phase of transcription, while corepressors and repressors regulate the elongation phase.
d. Activators and repressors bind to specific regulatory DNA sequences, while coactivators and corepressors chemically modify chromosome structure.

4. Recent studies have shown that most protein-coding genes in human embryonic stem cells are regulated at the level of elongation by a "poised" mechanism. How would this be advantageous? (LO 9.2.4)
   a. By poising the RNA Pol II at the start of elongation, a cell halts all gene expression and has time to develop before activating the genes needed for later steps in differentiation.
   b. Specific internal or external signals would activate a small subset of the poised genes in each cell, thus allowing for specific developmental pathway(s) to be engaged at the proper time.
   c. Only a small subset of the stem cells in an embryo ever develop. Poising allows the embryo to "decide" which cells will continue to develop and which will not.
   d. Poising is necessary to allow for the embryonic stem cells to manufacture the necessary biomolecules needed for subsequent growth and development.

5. What would happen if eukaryotic transcription were allowed to proceed in the presence of radiolabeled ATP (known as AT^{32}P)? (LO 9.2.4)
   a. P-TEFb (positive transcription-elongation factor-b) would be inactivated by the radioactivity, and transcription would be inhibited.
   b. P-TEFb (positive transcription-elongation factor-b) would be radiolabeled with ^{32}P, and transcription would not be inhibited.
   c. Multiple factors involved in the elongation phase of transcription would be inactivated by the radioactivity, and transcription would be inhibited.
   d. Multiple factors involved in the elongation phase of transcription would be radiolabeled with ^{32}P, and transcription would not be inhibited.

Answers: *1: b; 2: a; 3: d; 4: b; 5: d*

9.3 Chromatin and Epigenetics

Learning Objectives

You should be able to:

9.3.1 Describe the effects of different histone modifications on transcription.
9.3.2 Summarize the action of chromatin remodeling factors.
9.3.3 Explain epigenetic inheritance based on histone modifications and on DNA methylation.
9.3.4 Describe the action of lncRNAs in gene repression and activation.

Media Available on Companion Website oup.com/uk/cooper8e

Video 9.1 Epigenetic Mechanisms
Key Experiment The Role of Histone Modification

Active Learning Exercises

1. The amino-terminal tail domains of histones are rich in lysine and can be modified by acetylation at specific lysine residues. Have students engage in **small group discussions** about how acetylation affects gene expression. (LO 9.3.1)

   Answer: *Lysine residues are positively charged (i.e., protonated) at physiological pHs. Adding an acetyl group shields that charge, making the side group neutral. The positive charges are needed to maintain chromatin structure in a specific conformation. Therefore, the loss of positive charges changes the chromatin structure and increases the availability of the DNA template to transcription factors and RNA polymerase.*

2. Have students, in groups of 2 or 3, write a **minute paper** explaining why promoters and enhancers are DNAse hypersensitive sites. (LO 9.3.1)

   Answer: *Because they are nucleosome-free. They are nucleosome-free because promoters and enhancers have to be accessible by activators, coactivators, repressors, and corepressors.*

3. Have students draw a **sequence map** that lists the steps taken by chromatin remodeling factors. Provide a brief explanation of each step. (LO 9.3.2)

   Answer: *See Figure 9.21.*

4. Ask students, in groups of 2–4, to prepare a **T-table** that organizes the following terms (column one) with a brief description of their function (column two): promotors, enhancers, transcription factors, cohesion, activators, coactivators, repressors, corepressors, histone modification, chromatin remodeling, Polycomb proteins, DNA methylation, miRNA, lncRNA (LO 9.3.1, LO 9.3.2)

   Answer: *Definitions are found in the text. Terms can be removed from or added to the list, and the list can be customized to focus on one or two key concepts.*

5. Have students engage in a **think-pair-share** exercise to discuss how genomic imprinting is active in somatic cells but not in germ cells. (LO 9.3.3)

   Answer: *A gene in the chromosome of one parent is methylated during meiosis and inactivated. After fertilization and beyond, the methylated gene remains inactive. The methyl group is removed in germ cells, so a new pattern of methylation can be established in the new gametes.*

Clicker Questions

1. Histones are DNA-binding proteins with an amino terminal tail that sticks out of the nucleosome. What are the structure and the significance of that exposed tail? (LO 9.3.1)
   a. The amino terminal tail contains a number of amino acids that can be covalently modified by methylation, acetylation, phosphorylation, and ubiquitination.
   b. The amino terminal tails wrap around the nucleosome and prevent the binding of transcription factors and RNA polymerase II.
   c. The amino terminal tail contains only structural amino acids. Enzymatic removal of the tail allows for the binding of transcription factors and RNA polymerase II.
   d. The amino terminal tail contains a high percentage of hydrophobic amino acid residues, which help recruit activators and RNA polymerase II to the active coding regions of the DNA.

2. What is the major difference between histone modification and chromosome remodeling? (LO 9.3.2)
   a. Histone modification enzymes excise nucleosomes from the chromatin, while chromosome remodeling enzymes add phosphate, acetyl, or methyl groups to the entire nucleosome.
   b. The histone modification enzymes remove methyl and acetyl groups from nucleosomes, and chromosome remodeling enzymes replace them.
   c. Histone modification enzymes recruit repressors and activators, while chromosome remodeling enzymes recruit corepressors and coactivators.
   d. Histone modification enzymes add side groups to the nucleosome proteins, while chromosome remodeling enzymes move, alter, or remove entire nucleosomes.

3. What would happen if a cell line were unable to pass on epigenetic changes to progeny cells? (LO 9.3.3)
   a. Regulation of gene expression in the progeny cells would not be able to respond to internal or external stimuli, and mitosis would not proceed.
   b. Programs of gene expression developed by the parent cells would not be transmitted to progeny cells during mitosis.
   c. The progeny cells would be genetically identical to their parent cells, and mitosis would proceed normally.
   d. The parental cells would be unable to undergo mitosis and the cell line would die, or mitosis would be abnormal and the progeny cells would die.

4. Long noncoding RNAs (lncRNAs) are (LO 9.3.4)
   a. stretches of DNA (a.k.a. genes) that do not code for RNA; also known as noncoding regions.
   b. molecules of RNA that bind to DNA coding regions to inhibit the action of histone deacetylases, polycomb proteins, and DNA methylases.
   c. molecules of RNA that recruit DNA-modifying enzymes and associate them with their binding sites.
   d. stretches of DNA that are bound by a variety of histone deacetylases, polycomb proteins, and DNA methylases.

Answers: *1: a; 2: d; 3: b; 4: c*

CHAPTER

10

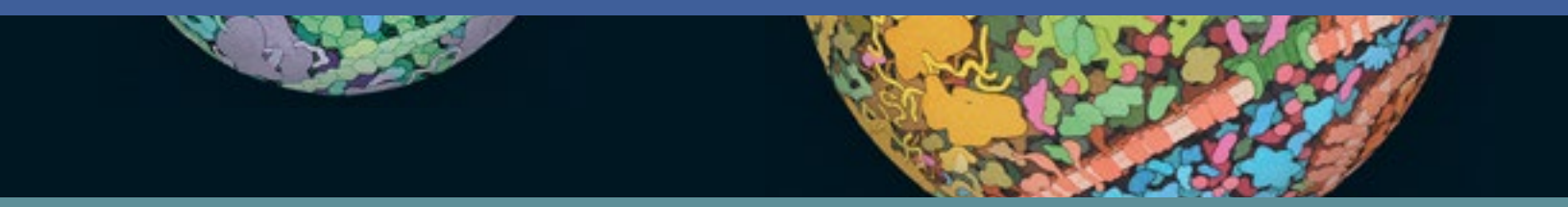
Part II **The Flow of Genetic Information**

Protein Synthesis, Processing, and Regulation

Chapter Overview

Transcription and RNA processing are followed by translation, the synthesis of proteins as directed by mRNA templates. Proteins are the active players in most cell processes, implementing the myriad tasks that are directed by the information encoded in genomic DNA. Protein synthesis is thus the final stage of gene expression. However, the translation of mRNA is only the first step in the formation of a functional protein. The polypeptide chain must then fold into the appropriate three-dimensional conformation and, frequently, undergo various processing steps before being converted to its active form. These processing steps, particularly in eukaryotes, are intimately related to the sorting and transport of different proteins to their appropriate destinations within the cell.

Gene expression is controlled not only at the level of transcription (see Chapter 9), but also at the level of translation, and this control is an important element of gene regulation. Of even broader significance, however, are the mechanisms that control the activities of proteins within cells. Once synthesized, most proteins can be regulated in response to extracellular signals either by covalent modifications or by association with other molecules. In addition, the levels of proteins within cells can be controlled by differential rates of protein degradation. These multiple controls of both the amounts and activities of intracellular proteins ultimately regulate all aspects of cell behavior.



Chapter Outline

Section Reviews

10.1 Translation of mRNA

tRNAs serve as adaptors that align amino acids on the mRNA template, where peptide bond formation is catalyzed by rRNA. A variety of nonribosomal proteins are also required for initiation, elongation, and termination of translation. Translation is initiated by the binding of initiator tRNA and mRNA to the small ribosomal subunit. The large ribosomal subunit then joins the complex, and the polypeptide chain elongates until the ribosome reaches a termination codon. Translation of specific mRNAs can be regulated by repressor proteins and miRNAs. In addition, global translational activity can be regulated by modification of initiation factors.

10.2 Protein Folding and Processing

Protein folding is facilitated by chaperones and at least two types of enzymes, protein disulfide isomerase and peptidyl prolyl isomerase. Aggregation of misfolded proteins leads to a variety of diseases, including Alzheimer's. The processing of many proteins involves proteolysis, glycosylation, and the addition of lipids.

10.3 Regulation of Protein Function and Stability

Proteins are regulated by the binding of small molecules, phosphorylation and other reversible modifications, and interactions with other proteins. Proteins can also be targeted for selective degradation by the addition of ubiquitin, followed by rapid proteolysis in the proteasome.

Key Terms

aminoacyl tRNA synthetase
amyloid
anticodon
chaperone
codon
elongation factor
glycolipid
glycoprotein
glycosylation
glycosylphosphatidylinositol (GPI) anchors
microRNAs (miRNAs)
monocistronic
peptidyl prolyl isomerase
polycistronic
polysome
prions
proteasome
protein disulfide isomerase (PDI)
protein kinase
protein misfolding disease
protein phosphatase
proteolysis
release factor
ribosome
RNA interference (RNAi)
rRNA
serine/threonine kinase
Shine-Dalgarno sequence
short interfering RNA (siRNA)
tRNA
tyrosine kinase
ubiquitin
ubiquitin-proteasome pathway
5′ untranslated regions (UTR)

Additional Media and Supplements for Use in the Classroom

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All textbook figures and tables (PowerPoint slides and JPEGs)
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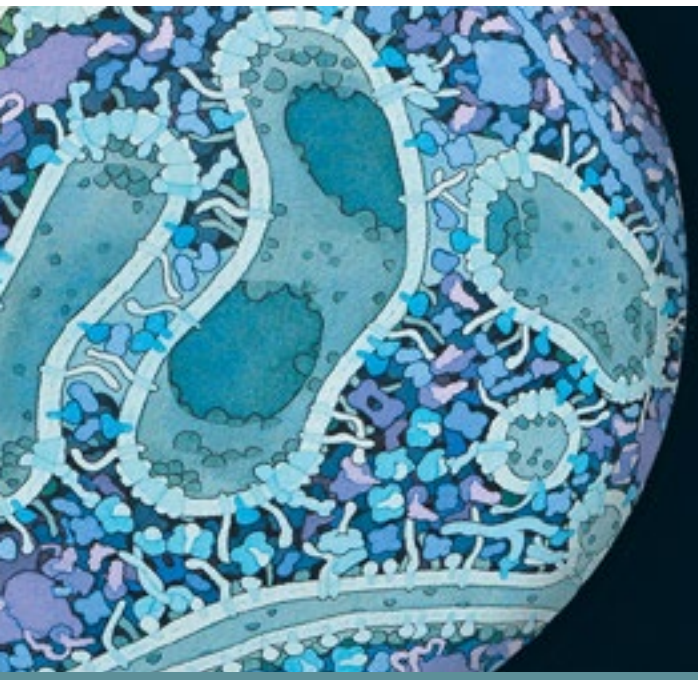

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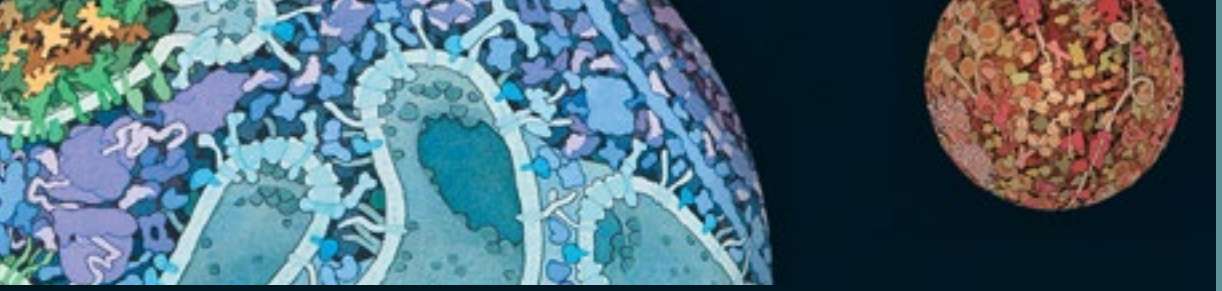

CHAPTER 10 Protein Synthesis, Processing, and Regulation

Active Learning Activities for the Classroom

10.1 Translation of mRNA

Learning Objectives

You should be able to:

10.1.1 Explain the role of tRNAs in translation.
10.1.2 Describe the structure and function of ribosomes.
10.1.3 Contrast the initiation of translation in bacterial and eukaryotic cells.
10.1.4 Outline the events of initiation, elongation, and termination of translation.
10.1.5 Summarize the mechanisms that regulate translation.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 10.1 Translation
Video 10.1 mRNA Translation
Data Analysis Problem 10.1 Protein Synthesis in Poliovirus-Infected Cells
Data Analysis Problem 10.2 The Effect of Starvation on Protein Synthesis
Data Analysis Problem 10.3 Sucrose Density Gradient Centrifugation of [3H] Leucine-Labeled Cell Extracts

Active Learning Exercises

1. Have students **in pairs** define and explain "wobble." (LO 10.1.1)

   Answer: *Wobble refers to a base pairing between two nucleotides that does not follow Watson-Crick base pair rules. Codon–anticodon base pairing is somewhat less stringent than the standard A–U and G–C base pairing described for DNA replication and transcription. Some tRNAs are able to recognize more than one codon in mRNA as a result of wobble.*

2. The two subunits of the eukaryotic ribosome are said to have rates of sedimentation of 60S (large subunit) and 40S (small subunit), yet intact ribosomes have a value of 80S. Have students use their smart devices to research "Svedberg" and write a **minute paper** explaining why Svedberg units (S) are not additive. (LO 10.1.2)

   Answer: *A Svedberg unit is a measure of the sedimentation rate of a molecule when centrifuged at high speed. Svedberg units are not additive because they are a measure of a particle's mass, density, and shape.*

3. Have students form **think-pair-share** groups to compare and contrast the initiation of translation in prokaryotes and eukaryotes. (LO 10.1.3)

   Answer: *See Figure 10.6. Prokaryotic ribosomes recognize a specific sequence (the Shine–Dalgarno sequence) that precedes the AUG initiation codon. Eukaryotic ribosomes recognize the 5′ cap on the mRNA.*

Clicker Questions

1. If all tRNAs have the same CCA nucleotide sequence at their 3′ terminus and amino acids are covalently attached to the ribose of the terminal adenosine, how can a specific tRNA recognize a specific amino acid? (LO 10.1.1)
   a. The 20 individual amino acids recognize sequences along their specific tRNA.
   b. The 20 aminoacyl tRNA synthetases are specific for each amino acid/tRNA pair.
   c. The tRNAs use complimentary base pairing to fold around the specific amino acid.

2. What do ribosomes have in common with RNase P and self-splicing introns? (LO 10.1.2)
   a. All have an innate ribozyme activity.
   b. All are composed of protein and RNA.
   c. All are found only in eukaryotes.
   d. All are regulated by protein modification.

3. Mitochondrial and chloroplast ribosomes resemble bacterial ribosomes. This is because (LO 10.1.3)
   a. both are eukaryotic organelles.
   b. both are semiautonomous organelles.
   c. both organelles arose endosymbiotically.
   d. chloroplasts arose from mitochondria.

4. Prokaryotic ribosomes initiate translation by recognizing a specific nucleotide sequence in the mRNA, whereas eukaryotic ribosomes recognize the 5′ mRNA end cap. What is the basis for this difference? (LO 10.1.3)
   a. Eukaryotic genes are monocistronic. Prokaryotic genes are polycistronic.
   b. Prokaryotic chromosomes are largely devoid of accessory proteins, like the eukaryotic histones.
   c. Being polycistronic, most prokaryotic genes lack a 5′ end cap to recognize.
   d. Eukaryotic genes are subject to varying degrees of alternative splicing.

5. What role does the ribosome "decoding center" play? (LO 10.1.4)
   a. The decoding center corrects mismatches between the codon and the anticodon.
   b. The decoding center enzymatically replaces incorrect amino acids with proper ones.
   c. The decoding center labels amino acids for later removal by editing enzymes.
   d. The decoding center helps the proper mRNA bind to the ribosomal small subunit.

6. According to the textbook, regulatory proteins that bind to the 3′ untranslated regions of mRNAs are also responsible for localizing mRNAs to specific regions of cells. This would be especially important in (LO 10.1.5)
   a. localizing rRNAs and tRNAs to the nucleus.
   b. regulating mRNA degradation and turnover.
   c. guiding the proper aminoacyl-tRNA to the ribosome.
   d. establishing cell polarity in developing embryos.

Answers: *1: b; 2: a; 3: c; 4: a, c; 5: a; 6: d*

10.2 Protein Folding and Processing

Learning Objectives

You should be able to:

10.2.1 Explain how chaperones facilitate protein folding.

10.2.2 Give examples of diseases associated with protein misfolding.

10.2.3 Describe the reactions catalyzed by protein disulfide isomerase and peptidyl prolyl isomerase.

10.2.4 Explain how proteolysis can convert an inactive precursor to an active protein.

10.2.5 Summarize the modifications of proteins by additions of carbohydrates and lipids.

Media Available on Companion Website oup.com/uk/cooper8e

Video 10.2 Protein Folding Simulation

Video 10.3 Mechanisms of Alzheimer's Disease

Molecular Medicine Alzheimer's Disease

Active Learning Exercises

1. Have students write a **minute paper** describing the key difference between a chaperone and a chaperonin. (LO 10.2.1)

   Answer: *Chaperones keep proteins in an unfolded state, whereas chaperonins help proteins fold properly.*

2. In **small discussion groups,** have students use their smart devices to research and consider how prions self-propagate. Ask for a volunteer from each group to present an answer to the class, and solicit comments. (LO 10.2.2)

   Answer: *The prion protein (PrP) is a normal product of nerve cell gene expression. Its exact function is unknown, but it is expressed in healthy cells and folded correctly (called the PrPC form). When mis-folded PrP protein (PrPSC) is introduced into the cell, it serves as a template to crystallize the normal PrPC form into large aggregates of PrPSC called amyloids.*

3. In **small discussion groups**, have students use their smart devices to research "mucins" and explain the significance of heavy glycosylation in these proteins. (LO 10.2.5)

   Answer (from Wikipedia): *"The dense 'sugar coating' of mucins gives them considerable water-holding capacity and also makes them resistant to proteolysis, which may be important in maintaining mucosal barriers."*

Clicker Questions

1. Chaperones are non-enzymatic catalysts. (LO 10.2.1)
   a. True. They help proteins fold but do not catalyze a chemical reaction.
   b. False. Any protein that is a catalyst must be an enzyme.

2. Misfolded proteins can be toxic in both soluble forms and insoluble (aggregate) forms. (LO 10.2.2)
   a. True
   b. False

3. Protein maturation is (LO 10.2.4)
   a. the secretion of proteins from a cell into the extracellular space.
   b. a range of processes that alter or modify a protein after translation.
   c. a process of combining multiple individual proteins into a larger active complex.
   d. the manner in which scaffolding proteins help nascent proteins fold correctly.

4. What would happen if an enzyme that cleaves ethanolamine were added to cells in culture that were expressing exterior proteins with a GPI anchor? (LO 10.2.5)
   a. The cells would cease growth due to the loss of membrane permeability.
   b. The phosphatidyl inositol portion of the anchor would be degraded.
   c. The process of adding lipids to proteins for export would be inhibited.
   d. The protein portion would be released from the surface of the membrane.

   Answers: *1: a; 2: a; 3: b; 4: d*

10.3 Regulation of Protein Function and Stability

Learning Objectives

You should be able to:

10.3.1 Explain how the binding of a small molecule can change the catalytic activity of an enzyme.

10.3.2 Describe the roles of kinases and phosphatases in regulating protein activity.

10.3.3 Explain how protein–protein interactions play regulatory roles.

10.3.4 Summarize protein degradation by the ubiquitin-proteasome pathway.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 10.2 The Ubiquitin-Proteasome Pathway

Key Experiment The Discovery of Tyrosine Kinases

Active Learning Exercises

1. Have students research phosphofructokinase (PFK) allosteric regulation and write a **minute paper** on how ATP and ADP regulate PFK activity. (LO 10.3.1)

   Answer: *PFK is an enzyme in the glycolytic pathway. One of the major purposes of that pathway is to break down glucose and feed that fuel the ATP-synthesizing reactions of the mitochondrion. When cytoplasmic ATP levels are high, ATP binds to PFK and slows it down, thus reducing the consumption of glucose. When ADP levels are high, ADP binds to the same site and speeds up PFK, resulting in an increase in ATP synthesis.*

2. Have students form **small discussion groups** and discuss why protein kinases target serine, threonine, and tyrosine amino acids residues. (LO 10.3.2)

   Answer: *Phosphate groups are large and bulky. They can be added only to hydrophilic (polar) amino acid side groups that extend away from the protein backbone, such as those found on serine, threonine, and tyrosine.*

3. In **small discussion groups**, have students use their smart devices to research "rubisco activase" and discover how it activates rubisco. Choose one student to provide an answer to the class. (LO 10.3.3)

   Answer: *Rubisco activase removes inhibitory substrates from the active site of rubisco.*

4. Have students prepare a **sequence map** that arranges the basic steps in initiation, elongation, and termination of translation. (LO 10.3.4)

   Answer: *See Figure 10.7 and accompanying text. This exercise can be customized by requiring more or less detail.*

5. Have students prepare a **spider map** with five legs, indicating ways in which protein activity may be regulated. Have them include a simple example or explanation of each of the following: regulation of translation (LO 10.1.5), activation by proteolysis (LO 10.2.4), small molecule binding (LO 10.3.1), kinases (LO 10.3.2), and degradation (LO 10.3.4).

   Answer: *Examples of each are given in the text.*

Clicker Questions

1. A key feature of GTP-mediated protein activation is that (LO 10.3.1)
   a. GTP is permanently bound to the protein and requires protein degradation to be inactivated.
   b. the binding of GTP initiates a dimerization and activation of the Ras proteins.
   c. the GTP will rapidly hydrolyze to GDP and Pi, providing a built-in "off switch."

2. What role does water play in the dephosphorylation of proteins? (LO 10.3.2)
   a. Water participates as a reactant in the hydrolysis reaction.
   b. Water stabilizes the dephosphorylated form until it can be reactivated by a kinase.
   c. Water stabilizes the *p*H surrounding the protein to be dephosphorylated.
   d. Water senses the environment and controls the timing of the dephosphorylation.

3. Eukaryotic proteasomes are found in both the cytoplasm and the nucleus. What would be a major role of nuclear proteasomes? (LO 10.3.4)
   a. Degrading the introns that are removed during mRNA splicing
   b. Degrading transcription factors in order to regulate gene expression
   c. Degrading the nucleolus after each round of cell division
   d. Degrading and regulating DNA and RNA polymerases

4. What happens to the amino acids that are liberated as a consequence of the ubiquitin-proteasome pathway? (LO 10.3.4)
   a. They could be reused in the synthesis of new proteins.
   b. They could be further degraded and respired.
   c. They are usually secreted to the external environment.
   d. They could be stored in the kidneys for later use.

   Answers: *1: c; 2: a; 3: b; 4: a, b*

CHAPTER

11

Part III **Cell Structure and Function**

The Nucleus

Chapter Overview

The presence of a nucleus is the principal feature that distinguishes eukaryotic from prokaryotic cells. By housing the cell's genome, the nucleus serves both as the repository of genetic information and as the cell's control center. DNA replication, transcription, and RNA processing all take place within the nucleus, with only the final stage of gene expression (translation) localized to the cytoplasm.

By separating the genome from the cytoplasm, the nuclear envelope allows gene expression to be regulated by mechanisms that are unique to eukaryotes. Whereas prokaryotic mRNAs are translated while their transcription is still in process, eukaryotic mRNAs undergo several forms of posttranscriptional processing before being transported from the nucleus to the cytoplasm. The presence of a nucleus thus allows gene expression to be regulated by posttranscriptional mechanisms, such as alternative splicing. By limiting the access of selected proteins to the genetic material, the nuclear envelope also provides novel opportunities for the control of gene expression at the level of transcription. For example, the expression of some eukaryotic genes is controlled by the regulated transport of transcription factors from the cytoplasm to the nucleus—a form of transcriptional regulation unavailable to prokaryotes. Separation of the genome from the site of mRNA translation thus plays a central role in eukaryotic gene expression.

Chapter Outline

Section Reviews

11.1 The Nuclear Envelope and Traffic between the Nucleus and the Cytoplasm

The nuclear envelope consists of the inner and outer nuclear membranes (which are joined at nuclear pore complexes) and an underlying nuclear lamina. Nuclear pore complexes are large structures that provide the only routes through which molecules can travel between the nucleus and the cytoplasm. Small molecules diffuse freely through the nuclear pore complex, but macromolecules are selectively transported. Proteins destined for import to the nucleus contain nuclear localization signals that are recognized by importins, which direct transport through the nuclear pore complex. Proteins that are transported from the nucleus to the cytoplasm contain nuclear export signals. In most cases, the small GTP-binding protein Ran determines the directionality of transport, although mRNAs are exported by a distinct mechanism. Regulation of nuclear transport provides a mechanism for controlling the activity of nuclear proteins, such as transcription factors.

11.2 The Organization of Chromatin

Individual chromosomes occupy distinct territories within the nucleus and are divided into large looped domains that function as independent units. Transcriptionally inactive heterochromatin is frequently associated with the nuclear envelope or nucleolus, whereas transcriptionally active chromatin is localized to the interior of the nucleus. DNA replication takes place within large complexes containing multiple replication forks, and transcription occurs at clustered sites that are enriched in RNA polymerases and transcription factors.

11.3 Nuclear Bodies

Several types of nuclear bodies compartmentalize the nucleus and serve to concentrate proteins and RNAs involved in a variety of aspects of gene expression. The nucleolus is associated with the genes for ribosomal RNAs and is the site of rRNA transcription, rRNA processing, and ribosome assembly. Polycomb proteins, which repress a variety of genes via histone methylation, are concentrated in clusters that repress multiple chromatin

domains. Cajal bodies are involved in snRNA modification and snRNP assembly, and nuclear speckles are storage sites of snRNPs and other components of the pre-mRNA splicing machinery.

Key Terms

Cajal body
chromosome conformation capture (3C)
euchromatin
exportin
fluorescence *in situ* hybridization (FISH)
heterochromatin
importin
karyopherin
lamina-associated domain (LAD)
lamin
nuclear body
nuclear envelope
nuclear export signal
nuclear lamina
nuclear localization signal
nuclear membrane
nuclear pore complex
nuclear transport receptor
nucleolar organizing region
nucleolus
nucleolus-associated domain (NAD)
Polycomb body
Ran
replication factory
small nucleolar RNA (snoRNA)
speckles
transcription factory

Additional Media and Supplements for Use in the Classroom

Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
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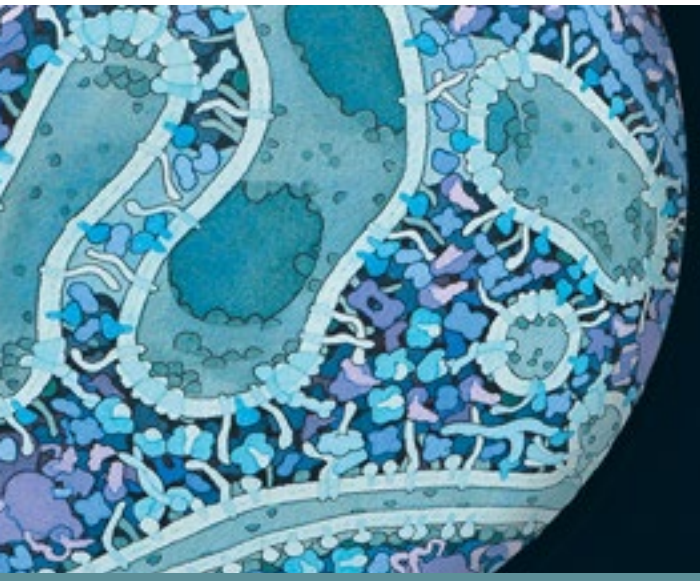
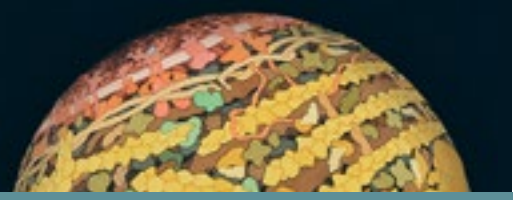
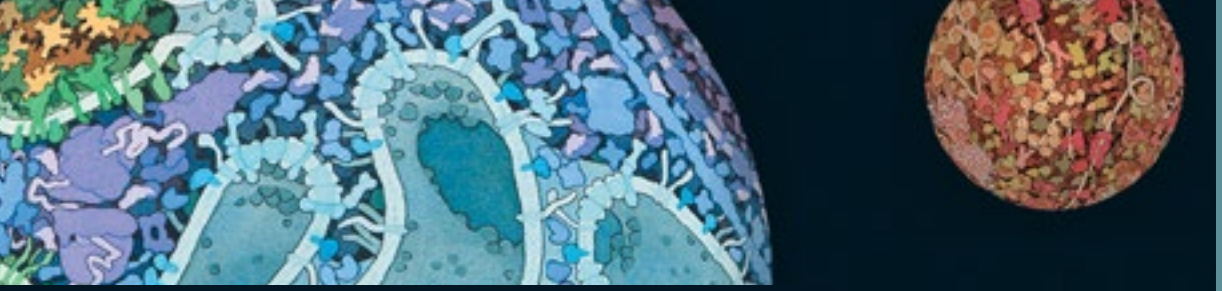
*Also available to students on the Companion Website



The **Active Learning Guide** that follows will help you create a dynamic learning environment in your classroom. It provides in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the chapter's Learning Objectives.





CHAPTER 11 Protein Synthesis, Processing and Regulation

Active Learning Activities for the Classroom

11.1 The Nuclear Envelope and Traffic between the Nucleus and the Cytoplasm

Learning Objectives

You should be able to:

11.1.1 Illustrate the structure of the nuclear envelope and nuclear pore complex.

11.1.2 Summarize how proteins and RNAs are transported into and out of the nucleus.

11.1.3 Explain how transport across the nuclear envelope can regulate gene expression.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 11.1 Nuclear Import and Export
Video 11.1 The Nuclear Pore Complex
Video 11.2 Into the Nucleus
Micrograph 11.1a The nuclear envelope I
Micrograph 11.1b The nuclear envelope II
Data Analysis Problem 11.1 Nuclear Import of a Protein
Data Analysis Problem 11.2 Fate of Wild-Type and Mutant Pre-tRNAs
Data Analysis Problem 11.3 In Situ Hybridization with Radioactive rRNA
Molecular Medicine Nuclear Lamina Diseases
Key Experiment Identification of Nuclear Localization Signals

Active Learning Exercises

1. Have students read the Molecular Medicine box (p. 359), and in **think-pair-share** groups, describe the difference between the mechanical stress hypothesis and the gene expression hypothesis as mechanisms for nuclear lamina diseases. (LO 11.1.1)

   Answer: *The mechanical stress hypothesis proposes that the nuclear envelope is weakened and more vulnerable to mechanical stress. The gene expression hypothesis posits that the association of heterochromatin with the nuclear lamina controls gene expression.*

2. Looking at Figure 11.10, have students write a **minute paper** describing the fates of the cytoplasmic Pi and the nuclear GDP. (LO 11.1.2)

   Answer: *Eventually, the pool of GTP inside the nucleus will need to be replenished or the transport cycle will stop. There must be a mechanism to export the nuclear GDP, phosphorylate it with the cytoplasmic Pi (probably by using mitochondrial-generated ATP as the energy source), and then move the resulting GTP back into the nucleus.*

3. Remind students that protein import into the nucleus relies on the energy derived from the hydrolysis of GTP by Ran (Figs. 11.10 and 11.11). Ran, however, is not involved in the export of mRNAs (Fig. 11.12). Every transport process requires energy in one form or another. Ask students to explain, in a **minute paper**, what the energy source for the export of mRNAs from the nucleus is. (Students can use their smart devices to research "helicase.") (LO 11.1.3)

   Answer: *Helicase hydrolyzes ATP and uses that energy to both remodel and transport the mRNA.*

Clicker Questions

1. Lamins are members of a class of structural cytoskeletal proteins called intermediate filaments. Microtubules and microfilaments are also components of the proteinaceous cytoskeleton. What is a major difference between lamins on the one hand and microtubules and microfilaments on the other? (LO 11.1.1)
   a. Lamins are non-force generating and structural only.
   b. Lamins are found in both animal and plant cells.
   c. Lamins are located exclusively inside the nucleus.
   d. Lamins associate with each other; the other proteins act as monomers.

2. Proteins must be transported into the nucleus through the nuclear pore complex because (LO 11.1.2)
   a. the nuclear pore complex is selective in what it transports.
   b. nuclear transport receptors are specific for an individual nuclear localization signal.
   c. the energy to drive the transport is generated by cytoplasmic mitochondria.
   d. there are no tRNAs or ribosomes inside the nucleus.

3. Both the large and small ribosomal subunits are assembled in the (LO 11.1.3)
   a. cytoplasm.
   b. nucleolus
   c. nucleus.
   d. endoplasmic reticulum.

4. Control over which proteins are imported into the nucleus relies on (LO 11.1.3)
   a. recognition of the protein by the nuclear pore complex.
   b. phosphorylation/dephosphorylation events.
   c. ubiquitination and degradation of inhibitory proteins.
   d. the hydrolysis of ATP.

Answers: *1: a, c; 2: d; 3: b; 4: a, b, c, d*

11.2 The Organization of Chromatin

Learning Objectives

You should be able to:

11.2.1 Explain chromosome territories and the methods used to study the organization of chromosomes within the nucleus.

11.2.2 Summarize the relationship between transcriptional activity and chromatin localization.

11.2.3 Describe replication and transcription factories.

Media Available on Companion Website oup.com/uk/cooper8e

Micrograph 11.18 Heterochromatin in interphase nuclei

Active Learning Exercises

1. Instruct students to use their smart devices to research "cohesin." Then have them form **small discussion groups** and speculate about why cohesin has so many roles in the nucleus. Choose a student to present conclusions to the class. (LO 11.2.2)

   Answer: *To a large extent, cohesin appears to be just a handle—a means to grab and hold onto DNA so other proteins and processes can take place.*

2. In **think-pair-share groups**, have students discuss the difference between a replication fork and a replication factory. (LO 11.2.3)

   Answer: *A replication fork is the site on a single DNA molecule where DNA is being replicated. A replication factory is a site in the nucleus where multiple molecules of DNA are being replicated at the same time.*

3. Have students prepare a **spider map** of the various levels of nuclear and chromatin organization with a definition next to each of the following terms: chromosome territories, lamina-associated domains, nucleolus-associated domains, replication factories, and translation factories. (LO 11.2.1, LO 11.2.2, LO 11.2.3)

   Answer: *Chromosome territories (regions of the nucleus occupied by a particular chromosome or portion of a chromosome), lamina-associated domains (regions of the chromosome that are associated with the lamina consisting of transcriptionally*

inactive chromatin), nucleolus-associated domains (regions of the chromosome that are associated with the lamina consisting of transcriptionally inactive chromatin), replication factories (regions of the nucleus where multiple strands of DNA are replicated), and translation factories (regions of the nucleus where multiple genes are being transcribed). When students are done, explain that no functions are ascribed to most of these levels of organization.

Clicker Questions

1. In order for the FISH technique to localize specific chromosome regions, the chromosomes must be (LO 11.2.1)
   a. separated.
   b. denatured.
   c. hybridized.
   d. replicated.

2. If a FISH probe localized a particular exon, what could you conclude about that chromosomal region if it lit up in the assay? (LO 11.2.2)
   a. The chromosomal region is made of euchromatin.
   b. The chromosomal region of made of heterochromatin.
   c. The chromosomal region should localize to the lamina.
   d. The chromosomal region is being actively transcribed.

3. Replication factories are distinct in that they contain (LO 11.2.3)
   a. areas of replication of multiple DNA molecules.
   b. multiple copies of RNA Pol I and III.
   c. high concentrations of lamin-binding proteins.
   d. transcriptionally inactive chromatin.

4. The discovery of chromosome territories required the development of powerful microscopes. (LO 11.2.1)
   a. True
   b. False

Answers: *1: b; 2: d; 3: a; 4: b*

11.3 Nuclear Bodies

Learning Objectives

You should be able to:

11.3.1 Explain the similarities and differences between nuclear bodies and cytoplasmic organelles.

11.3.2 Describe the structure and function of nucleoli.

11.3.3 Compare Polycomb bodies and transcription factories.

11.3.4 Summarize the functions of Cajal bodies and nuclear speckles.

Active Learning Exercise

1. Break students into seven **research/discussion groups**, and ask each group to use their smart devices to research the definition and function of one of the nuclear bodies shown in Table 11.2. Choose one student from each group to present that group's results to the class. (LO 11.3.1, LO 11.3.2, LO 11.3.3, LO 11.3.4)

   Answer: *Answer will vary depending on how deep students dig (i.e., Wikipedia vs. original literature) and what information is known about each (nucleolus, a lot; clastosome, less). The goal is to get students digging, thinking, and appreciating the complexity of the nucleus.*

Clicker Questions

1. What would happen if a nuclear body were treated with a protease? (LO 11.3.1)
   a. It would be exported from the nucleus.
   b. Its chromatin would condense.
   c. Its membrane would dissolve.
   d. It is likely to fall apart.

2. Because they are not bound by a membrane, nuclear bodies can freely exchange proteins and RNA molecules with the rest of the nucleus. (LO 11.3.1)
   a. True
   b. False

3. The nucleolar organizing region is an association between the (LO 11.3.2)
   a. nucleolus and nucleus.
   b. nucleolus and euchromatin.
   c. nucleolus and heterochromatin.
   d. heterochromatin and euchromatin.

4. The difference between a Polycomb body and a transcription factory is that (LO 11.3.3)
   a. transcription factories are associated with euchromatin; Polycomb bodies are associated with heterochromatin.
   b. Polycomb bodies are sites of transcriptional activation; transcription factories are sites of active repression.
   c. Polycomb bodies are sites of transcriptional repression; transcription factories are sites of active transcription.
   d. transcription factories are associated with heterochromatin; Polycomb bodies are associated with euchromatin.

5. What do the various nuclear bodies have in common with cytoplasmic organelles? (LO 11.3.1, LO 11.3.2, LO 11.3.3, LO 11.3.4)
   a. All are bounded by membranes that help them isolate and regulate specific metabolic reactions.
   b. All represent localized and isolated areas where specific metabolic reactions can take place and be controlled.
   c. They can freely exchange substrates and products with the surrounding medium in order to direct and speed up specific pathways.
   d. They each have mechanisms for membrane-based transport regulatory steps that control what gets into and out of the organelle.

Answers: *1: c; 2: a; 3: b; 4: a, c; 5: b*

CHAPTER

12

Part III **Cell Structure and Function**

Protein Sorting and Transport

Chapter Overview

In addition to the presence of a nucleus, eukaryotic cells have a variety of membrane-enclosed organelles within their cytoplasm. These organelles provide discrete compartments in which specific cellular activities take place, and the resulting subdivision of the cytoplasm allows eukaryotic cells to function efficiently in spite of their large size.

Because of the complex internal organization of eukaryotic cells, the sorting and targeting of proteins to their appropriate destinations are considerable tasks. The first step of protein sorting takes place while translation is still in progress. Proteins destined for the endoplasmic reticulum, the Golgi apparatus, lysosomes, the plasma membrane, and secretion from the cell are synthesized on ribosomes that are bound to the membrane of the endoplasmic reticulum. As translation proceeds, the polypeptide chains are transported into the endoplasmic reticulum where protein folding and processing take place. From the endoplasmic reticulum, proteins are transported in vesicles to the Golgi apparatus, where they are further processed and sorted for transport to lysosomes, the plasma membrane, or secretion from the cell. About one-third of cellular proteins are processed by this pathway, highlighting its importance in cell physiology.

Chapter Outline

Section Reviews

12.1 The Endoplasmic Reticulum

Proteins destined for secretion, lysosomes, or the plasma membrane are translated on membrane-bound ribosomes and transferred into the rough ER as their translation proceeds. Ribosomes engaged in the synthesis of secreted proteins are targeted to the ER by signal sequences at the amino terminus of the polypeptide chain. Growing polypeptide chains are then translocated into the ER through protein channels and released into the ER lumen by cleavage of the signal sequence. Integral membrane proteins are inserted into the membrane of the ER by membrane spanning α helices that stop the transfer of the polypeptide chain across the membrane. Polypeptide chains are folded into their correct three-dimensional conformations and modified by *N*-linked glycosylation and addition of GPI anchors within the ER; proteins that are not folded correctly are diverted from the secretory pathway and degraded. The ER is also the major site of lipid synthesis in eukaryotic cells, and smooth ER is abundant in cells that are active in lipid metabolism and detoxification of lipid-soluble drugs.

12.2 The Golgi Apparatus

Proteins are transported from the ER to the *cis* compartment of the Golgi. Distinct processing events take place as proteins move through the medial and *trans* compartments to the *trans*-Golgi network. The *N*-linked oligosaccharides added to proteins in the ER are modified within the Golgi, and proteins destined for lysosomes are specifically phosphorylated on mannose residues. *O*-linked glycosylation also takes place within the Golgi. In addition, the Golgi apparatus is the site of synthesis of glycolipids, sphingomyelin, and the complex polysaccharides of plant cell walls. Proteins are sorted in the *trans*-Golgi network for secretion, the plasma membrane, and lysosomes. In polarized cells, proteins are specifically targeted to the apical and basolateral domains of the plasma membrane.

12.3 The Mechanism of Vesicular Transport

The cytoplasmic surfaces of most vesicles are coated with proteins that drive vesicle budding. The specific molecules to be transported are selected by complexes of small GTP-binding proteins and adaptor proteins that associate with the coat proteins. The initial interaction between vesicles and their target membranes is mediated by the binding of tethering factors to Rab proteins. Subsequent interactions between transmembrane proteins on vesicle and target membranes lead to membrane fusion.

12.4 Lysosomes

Lysosomes contain acid hydrolases that degrade proteins, nucleic acids, polysaccharides, and lipids. These enzymes function specifically at the acidic pH maintained within lysosomes. Extracellular molecules taken up by endocytosis are transported to endosomes, and late endosomes mature to lysosomes as lysosomal acid hydrolases are delivered from the Golgi. In addition to degradation of extracellular materials, lysosomes are responsible for digestion of the cell's own components by autophagy.

Key Terms

apical domain
autophagosome
autophagy
basolateral domain
cis compartment
clathrin
clathrin-coated vesicle
COPI
COPI-coated vesicle
COPII
COPII-coated vesicle
endocytosis
endoplasmic reticulum (ER)
endosome
ER-associated degradation (ERAD)
flippase
glycosylphosphatidylinositol (GPI) anchor
Golgi apparatus
Golgi complex
lysosomal storage disease
lysosome
mannose-6-phosphate
medial compartment
protein disulfide isomerase (PDI)
Rab protein
rough ER
secretory pathway
secretory vesicle
signal peptidase
signal recognition particle (SRP)
signal sequence
smooth ER
SNAREs
SRP receptor
SRP RNA
tethering factor
trans compartment
trans-Golgi network
translocon
unfolded protein response (UPR)

Additional Media and Supplements for Use in the Classroom

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*Online Quiz**

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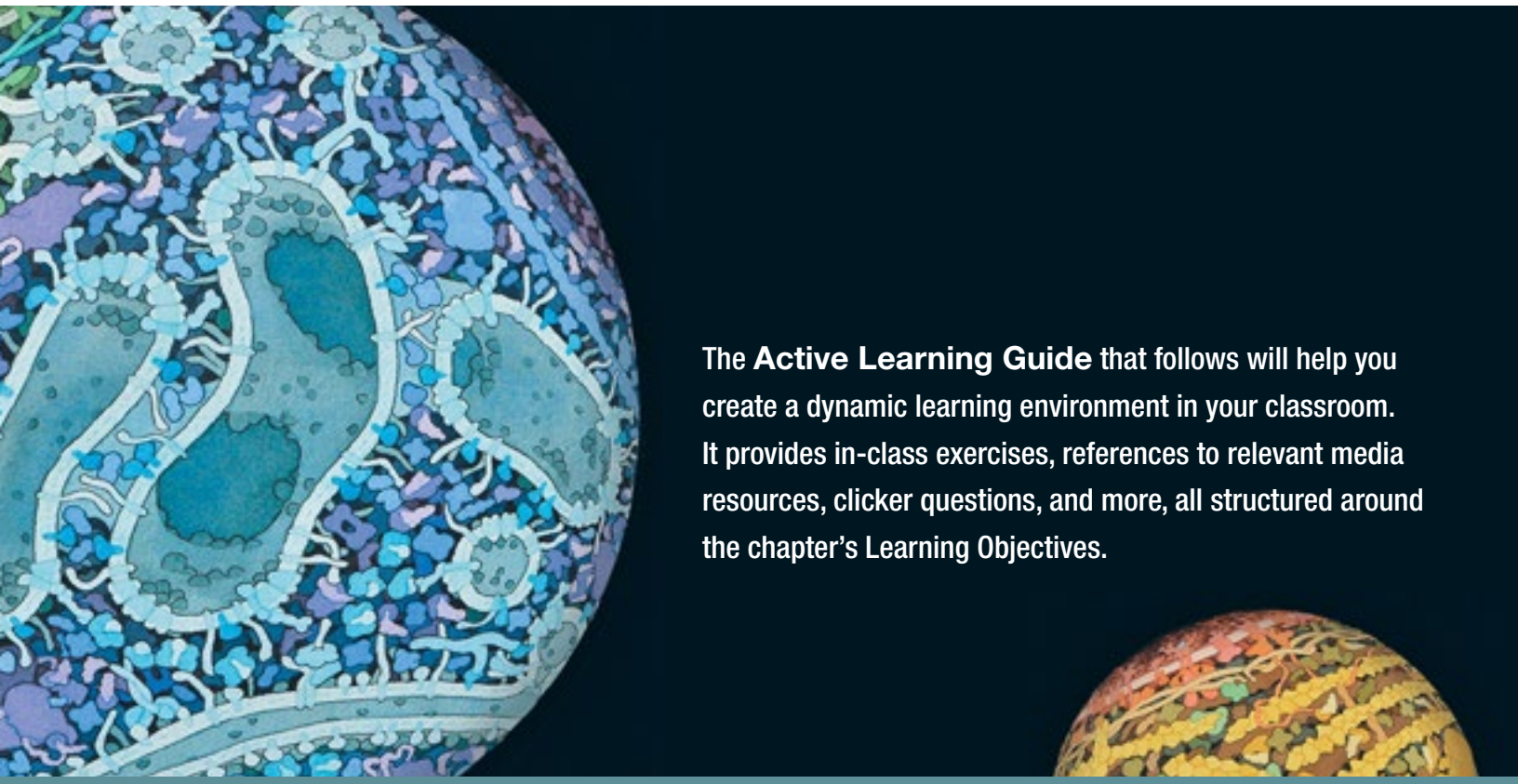

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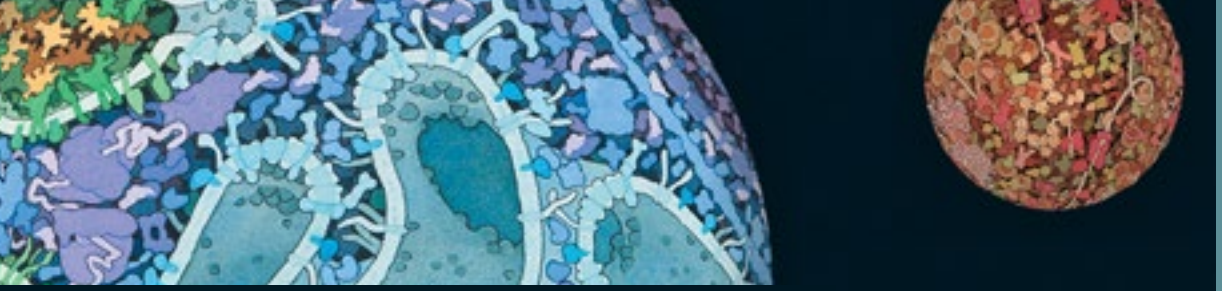


CHAPTER 12 Protein Sorting and Transport

Active Learning Activities for the Classroom

12.1 The Endoplasmic Reticulum

Learning Objectives

You should be able to:

12.1.1 Diagram the secretory pathway.
12.1.2 Summarize the mechanisms that target proteins to the ER.
12.1.3 Explain how proteins are inserted into the ER membrane.
12.1.4 Describe protein folding and quality control in the ER.
12.1.5 Distinguish the roles of smooth and rough ER.
12.1.6 Explain transport to and retrieval from the Golgi apparatus.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 12.1 Cotranslational Targeting of Secretory Proteins to the ER
Video 12.1 Transport through the Secretory Pathway
Data Analysis Problem 12.1 The Synthesis and Posttranslational Fate of a Bee Venom Protein
Data Analysis Problem 12.4 Analysis of Microsomes from Pigeon Pancreas
Data Analysis Problem 12.5 The Effect of a Chemical Chaperone on a Wild-Type and a Mutant Vasopressin Receptor
Key Experiment The Signal Hypothesis

Active Learning Exercises

1. Have students form **small discussion groups** and use their smart devices to research "sarcoplasmic reticulum." Then choose a student to describe the roles of the sarcoplasmic reticulum (SR) and calcium sparks in muscle contraction. (LO 12.1.1)

   Answer: *SR is a form of endoplasmic reticulum found in muscle cells that specialize in calcium storage. Upon the proper signal, the SR rapidly releases large amounts of calcium ions into the muscle cell cytoplasm. In skeletal and cardiac muscle cells, the increased Ca^{+2} induces muscle contraction. In smooth muscle tissue, the calcium increase induces muscle relaxation.*

2. Have students form **small discussion groups** and use their smart devices to research the TIC/TOC complex. Then have them examine the concept of a transit peptide. (LO 12.1.2)

   Answer: *The TIC/TOC complex is a series of proteins that mediate the transport of cytoplasmic proteins into the chloroplast stroma. It recognizes a short (15–30 amino acid) sequence at the N terminus of the protein. Once translocated into the stroma, the transit peptide is removed. If the protein is destined for the thylakoid lumen, a second transit peptide is needed to target the protein to that compartment.*

3. Have students prepare a **T table** of the various means by which proteins are processed in the ER, with a brief description of each. (LO 12.1.3)

   Answer:

Process	Description
Removal of signal sequence	Proteolytic enzymes in the ER lumen remove the signal sequence.
Protein folding	Chaperones mediate proper folding.
Disulfide bond formation	Oxidizing environment in the ER lumen forces S-S bond formation.
Glycosylation	Addition of sugar groups protect and direct the proteins.
Glycolipid anchoring	Hydrophobic lipids are added to anchor the protein in the membrane.

4. Have students write a **minute paper** or create a **sequence map** laying out the basics of the unfolded protein response (UPR). (LO 12.1.4)

   Answer: *Cells need to balance their rate of protein production (i.e., translation) with the rate at which the ER can correctly process those proteins. If the rate of translation exceeds the rate of processing, one of four things happens. 1) The synthesis of ER proteins is decreased. 2) The synthesis of chaperones and other protein-processing enzymes is increased. 3) The amount of ER is increased. 4) The cell is targeted for programmed cell death.*

5. In **small discussion groups** have students research the paper Lipid biosynthesis (Ohlrogge J. and J. Browse. 1995. *The Plant Cell* 7: 957–970), then discuss whether there may be some exceptions to the textbook claim: "The ER is thus responsible for synthesis of either the final products or the precursors of all the major lipids of eukaryotic membranes." (LO 12.1.5)

   Answer: *The statement only holds true for animals and fungi. Plant cells have two major lipid synthesis pathways: the prokaryotic pathway (localized in the plastid) and the eukaryotic pathway (located in the cytosol and ER). The vast majority of fatty acid synthesis in plant cells is in the plastid, not the ER.*

Clicker Questions

1. The ER/Golgi/vesicles secretory pathway is used by cells to synthesize and transport proteins to any compartment that requires crossing a membrane. (LO 12.1.1)
   a. True
   b. False

2. Signal sequences that target proteins to the ER are usually deficient in arginine, glutamine, and lysine because these amino acids have _____ side groups. (LO 12.1.2)
   a. polar
   b. bulky
   c. non-polar
   d. hydrophobic

3. What role do translocons play in inserting proteins into the ER membrane? (LO 12.1.3)
   a. They allow parallel alpha helices to be inserted from both sides of the ER membrane.
   b. They allow the insertion of alpha helices with the amino terminus on the cytoplasmic side.
   c. They allow ribosomes to cross into the ER lumen, where they can synthesize alpha helices from the inside out.
   d. They allow mRNA to cross into the ER lumen, where it can be translated by ribosomes on that side of the membrane.

4. What is often the first step in the processing of newly synthesized ER proteins? (LO 12.1.3)
   a. Chaperone-mediated protein folding
   b. The addition of sugar residues (glycosylation)
   c. Proteolytic removal of the signal sequence
   d. Disulfide bond formation

5. How does the ERAD (ER-associated degradation) system recognize misfolded proteins? (LO 12.1.6)
   a. Misfolded proteins are blocked from entering the lumen of the ER system by the cytoplasmic ribosomes.
   b. The reducing environment of the ER lumen causes misfolded proteins to aggregate.
   c. Misfolded proteins have their signal sequence buried in the protein's interior so it cannot be removed.
   d. Protein processing enzymes look for hydrophobic regions that would be shielded if the protein were folded correctly.

Answers: *1: b; 2: a; 3: b; 4: c; 5: d*

12.2 The Golgi Apparatus

Learning Objectives

You should be able to:

12.2.1 Relate the structure of the Golgi apparatus to its function.
12.2.2 Describe the types of protein glycosylation that take place in the Golgi.
12.2.3 Summarize the role of the Golgi in synthesis of membrane lipids.
12.2.4 Diagram the routes of protein export from the Golgi.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 12.2 Organization of the Golgi
Video 12.2 Budding from the Golgi Apparatus
Video 12.3 Post-Golgi Transport
Micrograph 11.24b The Golgi Apparatus

Active Learning Exercises

1. Have students form **think-pair-share** groups to discuss the mechanism by which proteins move through the Golgi system. Choose a student to present an explanation to the class. (LO 12.2.1)

   Answer: *A Golgi cisterna is formed at the cis face by the fusion of protein-containing vesicles from the ER. That individual cisterna, and the proteins within, are pushed through the Golgi stack by the formation of new cisternae behind it. Proteins are modified during the transit of the cisterna through the stack. Eventually, it reaches the trans face, where it breaks up into vesicles that feed the TGN. Golgi resident proteins are returned to younger cisternae by vesicles budding from the sides of the stack.*

2. In **small discussion groups**, have students use smart devices to determine whether Golgi activity would be low or high in each of the following: a human muscle cell, a plant cell at cytokinesis, a canine pancreas cell, and an axon terminal of a nerve fiber during neurotransmitter release. Answers should include a brief explanation. (LO 12.2.3)

   Answer: *A human muscle cell would have low activity because muscle cells are not secretory. A plant cell at cytokinesis would have high activity, as Golgi deliver polysaccharide cell wall precursors to the growing cell plate. A canine pancreas cell would have high activity, as the pancreas cells synthesize and secrete digestive enzymes, and an axon terminal of a nerve fiber during neurotransmitter release would have low activity, because neurotransmitter release is via vesicles budding with the plasma membrane, but those vesicles are not produced by Golgi.*

3. Have students create a **T table** showing functions and descriptions of various Golgi properties. (LO 12.2.2, LO 12.2.3, LO 12.2.4)

Answer:

Function	Description
Protein glycosylation	Various sugar groups are added to or removed from proteins.
Lipid synthesis	ER-derived ceramide is modified to glycolipids and sphingomyelin for incorporation into the plasma membrane.
Protein sorting and export	Proteins are trafficked according to glycosylation signals or short amino acid sequences.

4. Have students prepare a **T table** describing the three routes of protein export from the Golgi complex. (LO 12.2.4)

Answer:

Export route	Description
Direct export	Vesicles carry proteins directly from the TGN to the plasma membrane.
Endosome/lysosome	Vesicles containing digestive enzymes fuse with an endosome (usually a food particle taken up from the cell exterior) to form a lysosome.
Secretory granules	Proteins such as hormones or digestive enzymes are temporarily stored in immature granules until an external signal calls for their release.

Clicker Questions

1. What is the fate of Golgi resident proteins in the operation of the Golgi complex? (LO 12.2.1)
   a. They are transferred to the *trans* Golgi network and lost from the Golgi complex.
   b. They are recycled and returned to the Golgi complex by vesicles pinching off the sides of the stack.
   c. They are anchored within the individual Golgi cisternae, where they remain and are degraded.
   d. They remain attached to the proteins they are modifying and are secreted from the cell.

2. Many viral coat proteins are glycosylated. What would this be advantageous? (LO 12.2.2)
   a. Glycosylation of viral coat proteins would make it easier for the virus to evade the host cell's immune system.
   b. Glycosylation of viral coat proteins would aid in the trafficking of viral particles from one cell to the next.
   c. Glycosylation of viral coat proteins would allow the viral particles to remain in the cytoplasm during host cell mitosis.
   d. Glycosylation of viral coat proteins would aid in the Golgi-mediated export of mature viral particles.

3. What function of plant Golgi complexes is unique to plant cells? (LO 12.2.3)
   a. They participate in photosynthesis, which is unique to plants.
   b. They participate in maintaining proper intercellular water homeostasis.
   c. They participate in the packaging and processing of proteins for secretion.
   d. They participate in cell-wall formation, and animal cells lack cell walls.

4. What is the role of secretory granules in protein export from the Golgi? (LO 12.2.4)
   a. They transport proteins destined for export directly from the TGN to the plasma membrane.
   b. They recycle membrane and proteins from the TGN back to earlier compartments in the Golgi complex.
   c. They fuse with late endosomes to form a lysosome, which is used to digest food.
   d. They store condensed proteins until an external signal calls for their release from the cell.

5. What makes plant and animal epithelial cells unique in terms of protein trafficking? (LO 12.2.4)
   a. They are involved in the active uptake of nutrients and must have receptors over their entire surface.
   b. They are polarized so different proteins must be trafficked to different regions in the same cell.
   c. They are secretory, so all of their proteins must be trafficked to the apical surface for export.
   d. They must be able to distinguish between proteins that have been glycosylated and proteins attached to anchoring lipids

Answers: *1: b; 2: a; 3: d; 4: d; 5: b*

12.3 The Mechanism of Vesicular Transport

Learning Objectives

You should be able to:

12.3.1 Summarize the process of vesicle budding and cargo selection.

12.3.2 Explain the role of coat proteins.

12.3.3 Describe the mechanism by which vesicles fuse with the correct target membranes.

Media Available on Companion Website oup.com/uk/cooper8e

Video 12.4 Vesicle Trafficking

Data Analysis Problem 12.2 The Release of Histamine from Mast Cells

Active Learning Exercises

1. Have students form **small discussion groups** and, reviewing textbook Figures 12.16, 12.23, 12.24, 12,25, and 12.28, summarize how cargo is selected for export from the Golgi apparatus. (LO 12.3.1)

   Answer: *All of the structures described in these figures work in conjunction with receptors and, as explained on page 415, the adaptor proteins bind to sequences in the cytosolic domains of ER transmembrane proteins that signal their export from the Golgi. As discussed earlier, the transmembrane proteins include receptors for lumenal cargo proteins.*

2. Have students prepare a **sequence map** of the steps in clathrin-mediated vesicle formation. (LO 12.3.2)

   Answer: *Step 1) Arf on the cytosolic surface of the ER membrane is activated. Step 2) It recruits an adaptor protein that nucleates cargo selection and coat assembly. Step 3) Clathrin covers the surface of the budding vesicle, distorts the membrane, and initiates the bud. Step 4) Dynamin forms a contractile ring that pinches off the vesicle.*

3. Have students prepare a **sequence map** that outlines the mechanism by which vesicles fuse with the correct target membrane. (LO 12.3.3)

   Answer: *Step 1) A Rab protein on the vesicle binds to a specific tethering factor. Step 2) The tethering factor also binds to vesicle coat proteins. Step 3) SNAREs on the vesicle and target membrane bind to each other. Step 4) The SNARE binding brings the two membranes together and leads to the fusion of the two membranes.*

Clicker Questions

1. After their formation, vesicles diffuse from the TGN to the plasma membrane. (LO 12.3.1)
   a. True
   b. False

2. What would happen if a cell could *not* produce dynamin? (LO 12.3.2)
   a. COPI vesicles could form but could not move in a retrograde direction and recycle Golgi resident proteins.
   b. CPOII vesicles would move in a retrograde direction instead of an anterograde direction.
   c. Clathrin coated vesicles could form but could not be released from the surface of the ER membrane.
   d. Clathrin-coated vesicles could form and be trafficked but could not fuse with the plasma membrane.

3. COPI coat proteins are needed to (LO 12.3.2)
   a. scavenge and return Golgi resident proteins.
   b. guide vesicles to the late endosome.
   c. traffic vesicles to the plasma membrane.
   d. move vesicles from the ER to the ERGIC.

4. Vesicle fusion with the correct target membrane requires that (LO 12.3.3)
   a. clathrin binds to the target membrane and squeezes the vesicle contents to the cell exterior.
   b. a Rab protein on the vesicles binds to a specific tethering factor in the target membrane.
   c. either COPI or COPII must be present to aid in target membrane recognition.
   d. SNAREs on the vesicle and target membranes interact and drive fusion of the two membranes.

Answers: *1: b; 2: c; 3: a; 4: b, d*

12.4 Lysosomes

Learning Objectives

You should be able to:

12.4.1 Describe the function of lysosomes.
12.4.2 Explain how lysosomes are formed.
12.4.3 Summarize the process of autophagy.

Media Available on Companion Website oup.com/uk/cooper8e

Micrograph 11.38 Lysosomes and mitochondria in a mammalian cell
Data Analysis Problem 12.3 Electron Microscopic Localization of Acid Phosphatase
Molecular Medicine Gaucher Disease

Active Learning Exercises

1. In **small discussion groups**, have students use their smart devices to research whether plant cells have lysosomes, then discuss their findings. (LO 12.4.1)

   Answer: *The cell wall prevents plant cells from performing endocytosis. Also, plants have no need to seek nutrition by digesting external food particles because they make their own food. There do appear to be catabolic compartments containing hydrolytic enzymes in some plant cells that play a role analogous to animal lysosomes, so the answer is "yes." (For more, see Swanson, S. J., P. C. Bethke, and R. L. Jones. 1998. Barley aleurone cells contain two types of vacuoles: Characterization of lytic organelles by use of fluorescent probes.* The Plant Cell *10: 685–698.*

2. Have students prepare a **sequence map** of the steps in lysosome formation. (LO 12.4.2)

   Answer: *Step 1) A molecule, food particle, or cell is taken up from the cell's exterior (called an endocytic vesicle). 2) The endocytic vesicle splits into an early endosome and a recycling endosome. 3) The recycling endosome returns the receptors to the plasma membrane, while 4) material to be degraded remains in what is now called the late endosome. Subsequently, the late endosome 5) fuses with a vesicle containing acid hydrolases from the Golgi apparatus to 6) form a lysosome.*

3. Have students use their smart devices to research "autophagy" and prepare a T table that compares microautophagy, macroautophagy and chaperone-mediated autophagy. (LO 12.4.3)

   Answer:

Form of autophagy	Description
Microautophagy	An autophagosome containing material to be degraded fuses with a lysosome and the material is degraded.
Macroautophagy	A lysosome surrounds and engulfs cytoplasmic material to be degraded.
Chaperone-mediated autophagy	Individual, specific proteins are unfolded and transported into the lysosome for degradation.

Clicker Questions

1. Lysosomes contain acid hydrolases. What do hydrolases do? (LO 12.4.1)
   a. They split water into H^+ and O_2 gases.
   b. They perform a reaction that is the opposite of a dehydration synthesis reaction.
   c. They increase the permeability of the lysosomal membrane to allow for the uptake of H^+ ions.
   d. They cleave covalent bonds and add an H to one exposed bond and an OH to the other.

2. Lysosomes are unique in that they (LO 12.4.1)
   a. are derived from the Golgi apparatus.
   b. are found only in animal cells.
   c. have a low internal pH of 5.0.
   d. are formed by the fusion of two separate organelles.

3. Only macrophages are affected in type 1 Gaucher disease. Why is this? (LO 12.4.2)
   a. The main function of a macrophage is phagocytosis.
   b. Macrophages are dependent on the nutrients released by autophagy.
   c. Autophagy requires that cells be supplied with an external food source.
   d. Late endosomes must fuse with a macrophage to form a lysosome.

   Answers: *1: b, d; 2: d, 3: a*

CHAPTER

13

Part III **Cell Structure and Function**

Mitochondria, Chloroplasts, and Peroxisomes

Chapter Overview

In addition to being involved in protein sorting and transport, cytoplasmic organelles provide specialized compartments in which a variety of metabolic activities take place. The generation of metabolic energy is a major activity of all cells, and two cytoplasmic organelles are specifically devoted to energy metabolism and the production of ATP. Mitochondria are responsible for generating most of the useful energy derived from the breakdown of lipids and carbohydrates, and chloroplasts use energy captured from sunlight to generate both ATP and the reducing power needed to synthesize carbohydrates from CO_2 and H_2O. The third organelle discussed in this chapter, the peroxisome, contains enzymes involved in a variety of different metabolic pathways, including the breakdown of fatty acids.

Mitochondria, chloroplasts, and peroxisomes differ from the organelles discussed in the preceding chapter not only in their functions but also in their mechanism of assembly. Rather than being synthesized on membrane-bound ribosomes and translocated into the endoplasmic reticulum, most proteins destined for mitochondria, chloroplasts, and peroxisomes are synthesized on free ribosomes in the cytosol and imported into their target organelles as completed polypeptide chains. Mitochondria and chloroplasts also contain their own genomes, which include some genes that are transcribed and translated within the organelle.

Chapter Outline

Section Reviews

13.1 Mitochondria

Mitochondria are surrounded by a double-membrane system. The matrix contains the enzymes of the citric acid cycle; the inner membrane contains protein complexes involved in electron transport and oxidative phosphorylation. In contrast to the inner membrane, the outer membrane is freely permeable to small molecules. Mitochondria also contain their own genomes, which encode rRNAs, tRNAs, and some of the proteins involved in oxidative phosphorylation. However, most mitochondrial proteins are encoded by the nuclear genome. These proteins are translated on free ribosomes and imported into mitochondria as completed polypeptide chains. Positively charged presequences target proteins for import to the mitochondrial matrix and inner membrane, with protein import driven by the electrochemical gradient across the inner membrane. The electrochemical gradient also drives the transport of ATP, ADP, and other metabolites into and out of mitochondria.

13.2 Chloroplasts and Other Plastids

Chloroplasts are large organelles that function in photosynthesis and other metabolic activities. Like mitochondria, chloroplasts are bounded by a double-membrane envelope. In addition, chloroplasts have an internal thylakoid membrane, which is the site of electron transport and ATP generation. Chloroplast genomes contain approximately 150 genes, including proteins involved in photosynthesis and metabolism. Most chloroplast proteins are synthesized on free ribosomes in the cytosol and targeted for import to chloroplasts by amino-terminal transit peptides. Most proteins incorporated into the thylakoid lumen are first imported into the chloroplast stroma and then targeted for transport across the thylakoid membrane. Other plastids store energy sources, such as starch and lipids, and function in diverse aspects of plant metabolism.

13.3 Peroxisomes

Peroxisomes are small organelles, bounded by a single membrane, that contain enzymes involved in a variety of metabolic reactions, including fatty acid oxidation, lipid biosynthesis, the glyoxylate cycle, and photorespiration. Most transmembrane proteins are transported to peroxisomes from the ER, whereas internal peroxisomal proteins are synthesized on free ribosomes in the cytosol and imported into peroxisomes as completed and folded polypeptide chains. Peroxins can be formed both *de novo* and by growth and division of existing peroxisomes.

Key Terms

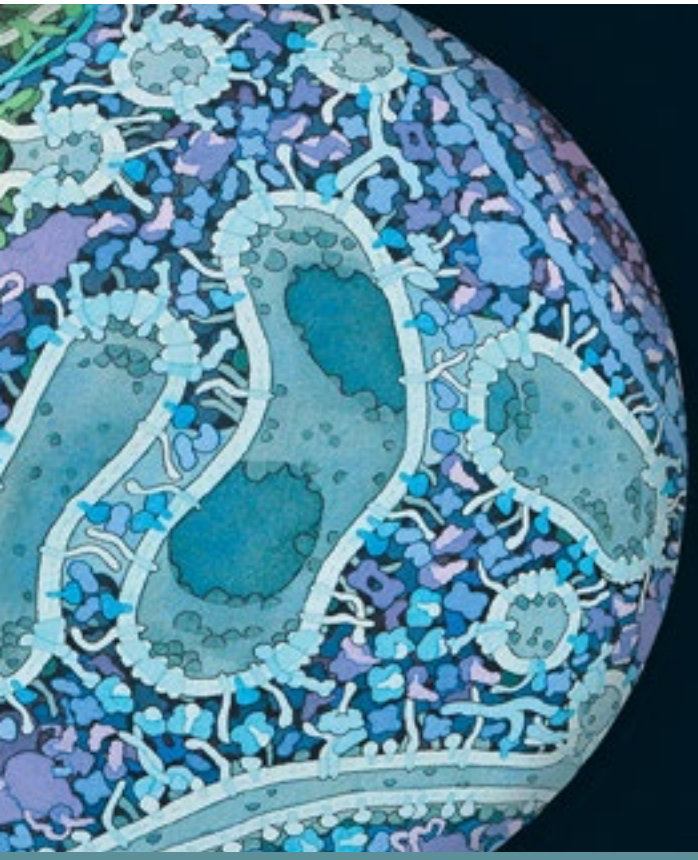
amyloplast
cardiolipin
catalase
chloroplast
chromoplast
cristae
elaioplast
endosymbiosis
leucoplast
matrix
matrix processing peptidase (MPP)
mitochondria
mitochondrial replacement therapy
peroxin
peroxisome biogenesis disorder
peroxisome
Pex protein
phospholipid transfer protein
plasmalogen
plastid
porins
presequence
proplastid
stroma
stromal processing peptidase (SPP)
thylakoid membrane
Tic complex
Tim complex
Toc complex
Tom complex
transit peptide

Additional Media and Supplements for Use in the Classroom

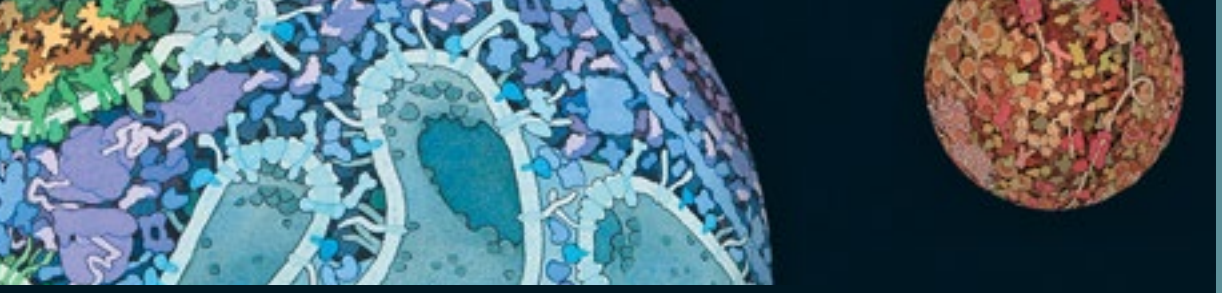
Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website



The **Active Learning Guide** that follows will help you create a dynamic learning environment in your classroom. It provides in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the chapter's Learning Objectives.



CHAPTER 13 Mitochondria, Chloroplasts, and Peroxisomes

Active Learning Activities for the Classroom

13.1 Mitochondria

Learning Objectives

You should be able to:

13.1.1 Illustrate the functional organization of mitochondria.

13.1.2 Describe mitochondrial genomes.

13.1.3 Summarize how proteins and lipids are imported into mitochondria.

13.1.4 Explain the role of the proton gradient in transport across the mitochondrial membrane.

Media Available on Companion Website oup.com/uk/cooper8e

Molecular Medicine Mitochondrial Replacement Therapy

Video 13.1 Mitochondrial Networks

Video 13.2 Mitochondrial Dynamics

Data Analysis Problem 13.1 Electron Microscopic Analysis of Mitochondrial DNA

Data Analysis Problem 13.2 Staining of Mitochondria with a Fluorescent Dye

Data Analysis Problem 13.3 Mitochondrial Protein Import

Active Learning Exercises

1. Have students prepare a **matrix** in which they compare and contrast the genomes of the following: a free-living α-proteobacterium, *Rickettsia prowazekii*, *A. thaliana* mitochondrion, and *H. sapiens* mitochondrion. (LO 13.1.2)

   Answer: *(Numbers in bold should be provided to students, as they do not appear in the textbook.)*

Genome	Genome size	Number of genes	Number of proteins coded for
α-proteobacteria	**1,000–1,500 kb**	7,000	**≈700**
Rickettsia prowazekii	**1,111 kb**	7,000	**684**
A. thaliana mitochondrion	370 kb	**57**	31
H. sapiens mitochondrion	16 kb	37	13

2. Have students write a **minute paper** to explain why the Tim complex uses an electrochemical potential, while the Tom complex does not. (LO 13.1.3)

   Answer: *The outer membrane, where the Tom complex resides, cannot generate an electrochemical potential.*

3. Ask students in **think-pair-share** groups to answer the question: "Why is the voltage component used to transport ADP/ATP across the mitochondrial inner membrane but the pH gradient used to transport pyruvate (which has a net charge of –1)?" (LO 13.1.4)

   Answer: *ADP and ATP are both charged (–3 and –4, respectively), so a one-for-one swap results in a net loss of membrane potential, which must be replaced by pumping (electrically charged) protons. However, swapping pyruvate (–1) with a hydroxyl (–1) is electrically neutral but reduces the pH gradient.*

Clicker Questions

1. Respiration takes place in the mitochondrion. (LO 13.1.1)
   a. True
   b. False

2. The majority of the genes in the human mitochondrial genome code for (LO 13.1.2)
   a. tRNAs and rRNAs needed for translation.
   b. proteins needed for mitochondrial electron transport.
   c. proteins needed for export of ATP from the matrix.
   d. proteins of the citric acid cycle.

3. Where are the genes for the human mitochondrial RNA polymerase? (LO 13.1.3)
   a. in the nuclear genome
   b. in the mitochondrial genome

4. The electrical component and the chemical component of the energy stored by the mitochondrial inner membrane are both established by the movement of (LO 13.1.4)
   a. electrons through the membrane.
   b. ATP across the membrane.
   c. pyruvate across the membrane.
   d. protons across the membrane.

5. The electrochemical gradient across the mitochondrial inner membrane captures energy that ultimately came from (LO 13.1.4)
   a. mitochondrial electron transport.
   b. photosynthesis.
   c. glycolysis.
   d. the sun.

   Answers: *1: b; 2: a, 3: a; 4: d; 5: d*

13.2 Chloroplasts and Other Plastids

Learning Objectives

You should be able to:

13.2.1 Compare the structural and functional organization of chloroplasts with mitochondria.

13.2.2 Contrast chloroplast and mitochondrial genomes.

13.2.3 Summarize the mechanisms of protein import into chloroplasts.

13.2.4 Describe the roles of other plastids.

Media Available on Companion Website oup.com/uk/cooper8e

Video 13.3 Chloroplasts in *Elodea*

Animation 13.1 From Proplastid to Chloroplast

Active Learning Exercises

1. Have students **sketch** a mitochondrion and a chloroplast, labeling all components and indicating which membrane is responsible for energy transduction in each organelle. (LO 13.2.2)

   Answer: *See Figures 13.2, 13.11, and 13.12.*

2. Have students form **small discussion groups** and determine why a presequence would *not* work in moving chloroplast proteins through the Toc/Tic complex. (LO 13.2.3)

   Answer: *The presequence on mitochondrial proteins is composed of positively charged amino acids. This allows the electric potential across the mitochondrial inner membrane to drive translocation of the positively charged presequence. The inner membrane of the chloroplast envelope does not establish a membrane voltage.*

3. Have students use their smart devices to research plastids, then write a **minute paper** on the structure and function of one of the plastid types (chloroplast is excluded). (LO 13.2.4)

   Answer: *(Any plastid type can be chosen.)*

Plastid type	Function(s)	Distinctive features
Proplastid	Source of other plastids	Found in egg, meristematic, and embryonic cells; source of all other plastids in the plant
Etioplast	Transitionary stage	Develops in tissue grown in darkness; site of gibberellin synthesis; converts to chloroplast in light
Amyloplast	Starch synthesis and storage	Also functions in gravisensing (sensing and reacting to gravitational force)
Elaioplast	Oil synthesis and storage	Supplies lipids and oils to outer layer upon pollen grain maturation
Chromoplast	Fruit and flower coloration	Rich in carotenoids; used to attract pollinators and seed/fruit-dispersing animals
Gerontoplast	Catabolism	Controls the dismantling of the photosynthetic apparatus during senescence
C_3	Photosynthesis, *etc*.	Also functions in fatty acid, lipid, amino acid and protein synthesis, N and S assimilation
C_4	Photosynthesis, *etc*.	Dimorphic chloroplasts provide a CO_2-rich, O_2-poor environment for enhanced Rubisco activity (enzyme for early carbon fixation)
Sun/Shade	Photosynthesis, *etc*.	Dimorphic forms develop under different light conditions in order to optimize photosynthesis
Guard cell	Stomatal functioning	Senses light and CO_2; signals and metabolically drives opening and closing of stomata

Clicker Questions

1. The mitochondrion has _____ membrane systems and _____ energy-transducing membrane(s) whereas the chloroplast has _____ and _____ . (LO 13.2.1)
   a. 1-2-1-3
   b. 2-1-3-1
   c. 3-1-2-1
   d. 4-3-2-1

2. Ribulose bisphosphate carboxylase/oxygenase has two subunits: large (LSU) and small (SSU). The holoenzyme is composed of eight subunits of each. Hence, it is a 16-mer. The LSU is synthesized in the stroma and the SSU is synthesized in the cytosol and imported to the stroma. In order to efficiently synthesize a functional 16-mer holoenzyme, there must be (LO 13.2.2)
   a. an effective means of signaling between the chloroplast genome and the nuclear genome.
   b. a significant amount of LSU protein imported into the chloroplast.
   c. chaperones to correctly assemble the 16 subunits into an active enzyme.
   d. export of the LSU mRNA from the chloroplast for translation on cytoplasmic ribosomes.

3. For a protein synthesized in the cytosol to be imported to the thylakoid lumen, it must have (LO 13.2.3)
   a. a presequence.
   b. a signal sequence.
   c. a presequence and a signal sequence.
   d. two signal sequences.

4. All plastids begin as proplastids with their mature form dictated by environmental signals and cell differentiation. (LO 13.2.4)
   a. True
   b. False

Answers: *1: b; 2: a , c; 3: d; 4: a*

13.3 Peroxisomes

Learning Objectives

You should be able to:

13.3.1 Summarize the roles of peroxisomes in animal and plant cells.

13.3.2 Describe the pathways responsible for peroxisome biogenesis.

Media Available on Companion Website oup.com/uk/cooper8e

Molecular Medicine: Peroxisome Biogenesis Disorders

Active Learning Exercises

1. Have students prepare a **spider map** for peroxisomes. Place "Peroxisomal Functions" in the middle and the following terms as legs. Include (where possible) the location. (LO 13.3.1)

   Answer: *Functions include: oxidizing organic compounds for detoxification (uric acid, amino acids, purines, methanol), fatty acid catabolism, lipid biosynthesis (animals), synthesis of bile acids (liver), synthesis of plasmalogens (liver), mobilizing stored fatty acids (seeds), photorespiration.*

2. Have students form **small discussion groups** and consider the unique aspects of peroxisome biogenesis. (LO 13.3.2)

   Answer: *Two pre-peroxisomes bud off of the ER, each containing distinct components of a transmembrane protein import complex. New peroxisomes are "empty," and their internal proteins must be synthesized on cytosolic ribosomes and imported. Peroxisomes may arise de novo or by division of existing peroxisomes.*

Clicker Questions

1. In plants, one would expect to find peroxisomes in the (LO 13.3.1)
   a. seed.
   b. stem.
   c. root.
   d. leaf.

2. Peroxisome biogenesis requires the fusion of two distinct ER-derived vesicles, V_1 and V_2, because (LO 13.3.2)
   a. both V_1 and V_2 vesicles contain a portion of the importomer.
   b. both V_1 and V_2 vesicles contain a unique set of proteins imported from the cytoplasm.
   c. the V_1 and V_2 vesicles are derived from separate regions of the ER.
   d. the V_1 and V_2 vesicles must be trafficked from the *trans* Golgi network.

Answers: *1: a, d; 2: a*

Instructor's Manual: **Resources**

CHAPTER

14

Part III **Cell Structure and Function**

The Cytoskeleton and Cell Movement

Chapter Overview

The membrane-enclosed organelles discussed in the preceding chapters constitute one level of the organizational substructure of eukaryotic cells. A further level of organization is provided by the cytoskeleton, which consists of a network of protein filaments extending throughout the cytoplasm. The cytoskeleton provides a structural framework for the cell, serving as a scaffold that determines cell shape and the positions of organelles. In addition to this structural role, the cytoskeleton is responsible for cell movement and the transport of organelles and other structures (such as mitotic chromosomes) through the cytoplasm. Importantly, the cytoskeleton is much less rigid and permanent than its name implies. Rather, it is a dynamic structure that is continually reorganized as cells move and change shape—for example, during mitosis and cell division.

The cytoskeleton is composed of three principal types of protein filaments: actin filaments, microtubules, and intermediate filaments (Figure 14.1), which are held together and linked to subcellular organelles and the plasma membrane by a variety of accessory proteins. This chapter discusses the structure and organization of each of these three major components of the cytoskeleton as well as the roles of actin filaments and microtubules in cell motility, organelle transport, and cell division.

Chapter Outline

Section Reviews

14.1 Structure and Organization of Actin Filaments

Actin filaments are formed by the polymerization of monomers into a helix with distinct plus and minus ends. A variety of actin-binding proteins regulate the assembly and disassembly of actin filaments within the cell, as well as the organization of filaments into bundles and networks. A network of actin filaments and associated proteins underlies the plasma membrane and determines cell shape. Actin bundles attached to the plasma membrane anchor the cell at regions of cell–cell and cell–substratum contact. Bundles of actin filaments also support protrusions of the cell surface, such as microvilli. Transient protrusions of the plasma membrane, driven by growth of actin filaments at the leading edge of the cell, are responsible for phagocytosis and cell locomotion.

14.2 Myosin Motors

Studies of muscle established the role of myosin as a motor protein that uses the energy derived from ATP hydrolysis to generate force and movement. Muscle contraction results from the sliding of actin and myosin filaments past each another. ATP hydrolysis drives repeated cycles of interaction between myosin and actin during which conformational changes result in movement of the myosin head group along actin filaments. Assemblies of actin and myosin II are responsible for a variety of movements of nonmuscle cells, including cytokinesis. Other types of myosin that do not function in contraction transport membrane vesicles and organelles along actin filaments.

14.3 Microtubules

Microtubules are formed by the reversible polymerization of tubulin. They display dynamic instability and undergo continual cycles of assembly and disassembly as a result of GTP hydrolysis following tubulin polymerization. The microtubules in most animal cells

extend outward from a centrosome, located near the center of the cell. The centrosome usually contains a pair of centrioles surrounded by pericentriolar material. The growth of microtubules is initiated in the pericentriolar material, which then serves to anchor their minus ends. Selective stabilization of microtubules by posttranslational modification of tubulin and binding of microtubule associated proteins can determine their organization within the cell.

14.4 Microtubule Motors and Movement

Two families of motor proteins, the kinesins and the dyneins, are responsible for movement along microtubules. Most kinesins move in the plus-end direction, whereas the dyneins and some members of the kinesin family move toward microtubule minus ends. Movement along microtubules transports macromolecules, membrane vesicles, and organelles through the cytoplasm, as well as positioning cytoplasmic organelles. Cilia and flagella are microtubule-based extensions of the plasma membrane that act as sensors as well as being responsible for cell motility. Their movements result from the sliding of microtubules driven by the action of dynein motors. Microtubules reorganize at the beginning of mitosis to form the mitotic spindle, which is responsible for chromosome separation.

14.5 Intermediate Filaments

Intermediate filaments are polymers of more than 70 different proteins that are expressed in various types of cells. They are not involved in cell movement but provide mechanical support to cells and tissues. Intermediate filaments are formed from dimers of two polypeptide chains wound around each other in a coiled-coil structure. The dimers then associate to form tetramers, which assemble into protofilaments and filaments. Intermediate filaments form a network extending from a ring surrounding the nucleus to the plasma membrane of most cell types. In epithelial cells, intermediate filaments are anchored to the plasma membrane at regions of specialized cell contacts (desmosomes and hemidesmosomes). Intermediate filaments also play specialized roles in muscle and nerve cells.

Key Terms

actin
actin-binding protein
actin bundle
actin network
adherens junction
adhesion belt
anaphase A
anaphase B
ankyrin
Arp2/3 complex
astral microtubule
axonemal dynein
axoneme
basal body
cadherin
calmodulin
catenin
cell cortex
centriole
centrosome
cilia
cofilin
colcemid
colchicine
contractile ring
cytokinesis
cytoplasmic dynein
desmin
desmosome
dynamic instability
dynein
dystrophin
filamentous [F] actin
filopodia
flagella
focal adhesion

Key Terms (*Continued*)

formin
globular [G] actin
hemidesmosome
integrin
intermediate filament
interpolar microtubule
keratin
kinesin
kinetochore microtubule
lamellipodia
microfilament
microtubule
microtubule-associated protein (MAP)
microtubule-organizing center
microvilli
mitotic spindle
molecular motor
motile cilia
muscle fiber
myofibril
myosin
myosin light-chain kinase
myosin I
myosin II
neurofilament (NF) protein
nexin
pericentriolar material
plakin
primary cilia
profilin
pseudopodia
Rho
sarcomere
sarcoplasmic reticulum
sliding filament model
spectrin
stereocilia
stress fiber
talin
taxol
treadmilling
tropomyosin
troponin
tubulin
γ-tubulin ring complex
unconventional myosin
villin
vimentin
vinblastine
vincristine
vinculin

Additional Media and Supplements for Use in the Classroom

Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
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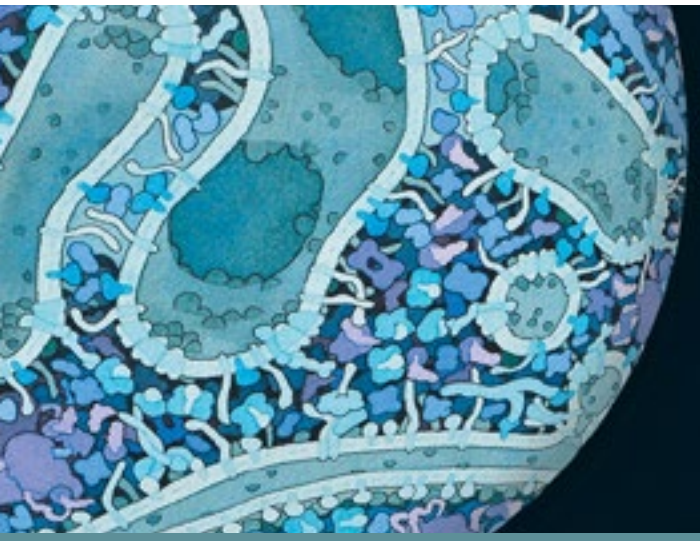
*Also available to students on the Companion Website



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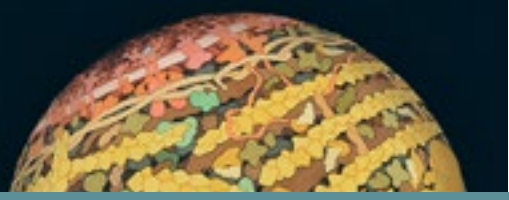

CHAPTER 14 The Cytoskeleton and Cell Movement

Active Learning Activities for the Classroom

14.1 Structure and Organization of Actin Filaments

Learning Objectives

You should be able to:

14.1.1 Summarize the dynamics of actin filaments and the roles of actin-binding proteins.

14.1.2 Illustrate the organization of actin filaments underlying the plasma membrane.

14.1.3 Describe the structure and function of microvilli.

14.1.4 Explain how remodeling of actin filaments is responsible for cell motility.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 14.1 Assembly of an Actin Filament

Video 14.1 Lamellipodia

Video 14.2 Cell Movement

Video 14.3 Actin Filament Induced Movement

Micrograph 14.14 Microvilli

Micrograph 14.15 Cell Surface Projections

Data Analysis Problem 14.1 Effect of Ionomycin on the Cytoskeleton of Fibroblasts

Data Analysis Problem 14.3 Cytoskeleton Elements of Cultured Kidney Cells

Data Analysis Problem 14.4 Electron Microscopic Analysis of Actin Filaments

Active Learning Exercises

1. Have students prepare a **T table** of the actin-binding proteins and their functions, described in the textbook on pages 456 through 462. Provide the list of proteins, shown in Column 1 below, if time is short. (LO 14.1.1)

   Answer:

Actin-binding protein	Function
α-Actinin	Cross-links actin filaments and mediates the binding of actin filaments to integrins
Ankyrin	Mediates the binding of the spectrin-actin network to transmembrane protein Band 3
Arp2/3 complex	Initiates growth of branched actin filaments
Catenin	Mediates the binding of actin filaments to cadherin
Cofillin	Severs actin filaments
Dystrophin	Mediates the binding of actin filaments to transmembrane proteins of the muscle cell plasma membrane
Fimbrin	Cross-links microfilaments within microvilli
Formin	Binds ATP-actin and nucleate the initial polymerization of actin monomers
Profillin	Binds actin monomers and stimulates the exchange of bound ADP for ATP
Protein 4.1	Mediates the binding of the spectrin-actin junction to glycophorin
Spectrin	Binds actin and organizes it against the erythrocyte membrane
Talin	Mediates the binding of actin filaments to integrins
Tropomyosin	Stabilizes microfilaments
Vinculin	Mediates the binding of actin to talin
Villin	Cross-links microfilaments within microvilli

2. Have students in pairs complete a **table** to compare the descriptions and main functions of pseudopodia, lamellipodia, filipodia, and microvilli, then quiz each other on the details. (LO 14.1.3, LO 14.1.4)

   Answer:

Structure	Description	Main function
Pseudopodia	Large, moderate width, dynamic projections of the plasma membrane	Phagocytosis and amoeboid movement
Lamellipodia	Broad, sheet-like, dynamic projections of the plasma membrane	Cell motility
Filipodia	Thin, dynamic projections from the lamellipodia	Cell motility
Microvilli	Static, finger-like projections from the plasma membrane	Nutrient absorption

Clicker Questions

1. Actin filament stability is dependent on (LO 14.1.1)
   a. the ratio of ATP to ADP.
   b. proteins like tropomyosin.
   c. proteins like cofilin.
   d. capping proteins.

2. Red blood cells need an extensive network of spectrin to be associated with the plasma membrane because they (LO 14.1.2)
   a. are subjected to significant stress as they are forced through the vascular system.
   b. carry hemoglobin, the main oxygen-binding protein in mammals.
   c. lack a nucleus and are incapable of dividing.
   d. lack microtubules, intermediate filaments, and internal organelles.

3. Spectrin is found only in red bold cells. (LO 14.1.3)
   a. True; erythrocytes have an extensive spectrin network.
   b. False; spectrin is also a component of the terminal web.

4. Microvilli differ from pseudopodia in that (LO 14.1.3, LO 14.1.4)
   a. microvillus structure is maintained by actin-binding proteins; this is not the case in pseudopodia.
   b. the actin bundles in microvilli are attached to the plasma membrane; this is not the case in pseudopodia.
   c. microvilli contain actin and myosin, whereas pseudopodia do not.
   d. microvilli are static, whereas pseudopodia are dynamic.

5. Arp2/3 plays a role in cell migration by (LO 14.1.4)
   a. catalyzing branch point formation in the developing actin network at the leading edge.
   b. severing branch points in the actin network at the trailing edge.
   c. polymerizing f-actin and generating the force needed to extend the leading edge.
   d. severing the adhesins needed to attach the migrating cell to the extracellular matrix.

Answers: *1: b, d; 2: a; 3: b; 4: d; 5: a*

14.2 Myosin Motors

Learning Objectives

You should be able to:

14.2.1 Explain the molecular basis of muscle contraction.

14.2.2 Summarize the roles of contractile actin–myosin filaments in nonmuscle cells.

14.2.3 Describe the functions of unconventional myosins

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Animation 14.2 A Thin Filament

Micrograph 14.19 Structure of the sarcomere

Active Learning Exercises

1. Have students form **small discussion groups** to research and discuss what makes myosin different from most other proteins. (LO 14.2.1)

   Answer: *Unlike most proteins, myosin is not defined by an amino acid sequence or a gene sequence. A myosin protein is defined by activity: actin binding, ATP hydrolysis, and force generation. The different classes are probably monophyletic, but evolution has led to tremendous diversity in the protein/gene families.*

2. Have students prepare a **sequence map** of the steps in the molecular model of muscle contraction. (LO 14.2.1)

   Answer: *Sequence maps should include the following: A nerve signal induces the sarcoplasmic reticulum to release a large amount of calcium ions. Ca^{+2} binds to troponin C, which allows myosin head groups to bind to myosin. In the absence of ATP, myosin is tightly bound to actin. ATP binds to the complex, it falls apart, the ATP is hydrolyzed, and myosin undergoes a conformational change by bending at the neck region. The head group rebinds to another actin on the filament. The Pi is released, which triggers the power stroke. The subsequent release of ADP causes the myosin head to return to its initial position.*

Clicker Questions

1. In muscle contraction, the protein titin (LO 14.2.1)
   a. releases large quantities of Ca^{+2} ions.
   b. generates the force needed to contract.
   c. acts as a centering spring.
   d. undergoes a conformation change.

2. Both calcium ions and ATP are needed for muscle contraction because (LO 14.2.1)
   a. calcium induces the production of ATP.
   b. calcium provides the access for myosin action, ATP provides the power.
   c. ATP promotes release of calcium from the sarcoplasmic reticulum.
   d. ATP needs to be activated by calcium to bind to myosin.

3. For a cell to be motile it must contain both actin and myosin because (LO 14.2.2)
   a. actin filaments can only push, whereas actin/myosin complexes can pull.
   b. myosin molecules form a gel-like matrix upon which the actin molecules slide.
   c. actin polymerizes into filaments that trap myosin molecules in a scaffolding structure.
   d. actin-binding proteins are positioned and removed by the action of myosins.

4. The key difference between conventional and unconventional myosins is that (LO 14.2.3)
   a. conventional myosins are responsible for transport and unconventional myosins, for cell division.
   b. conventional myosins are responsible for transport and unconventional myosins, for contraction.
   c. conventional myosins are responsible for contraction and unconventional myosins, for transport.
   d. conventional myosins are responsible for cell division and unconventional myosins, for transport.

Answers: *1: c; 2: b; 3: a; 4: c*

14.3 Microtubules

Learning Objectives

You should be able to:

14.3.1 Describe the structure and dynamic instability of microtubules.

14.3.2 Summarize how the growth of microtubules is initiated within cells.

14.3.3 Explain how microtubule-associated proteins regulate the organization of microtubules

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Animation 14.3 Microtubule Assembly

Micrograph 14.34 Structure of centrosomes

Data Analysis Problem 14.2 Microinjection of Fibroblasts with Biotin-Labeled Tubulin

Data Analysis Problem 14.4 Electron Microscopic Analysis of Isolated Microtubules

Data Analysis Problem 14.5 Purification of Bovine Brain Tubulins

Active Learning Exercises

1. Microtubules are dynamic structures. Have students prepare a **spider map** with four legs to show the mechanisms by which microtubules can be stabilized or destabilized. Each leg will have one to four sub-legs. (This exercise ignores the MAPs discussed in the textbook under "MAPs and the organization of microtubules," but those can be added.) (LO 14.3.1)

   Answer:

Growth	1. GTP cap forms at plus end. 2. GTP-bound tubulin dimers are added more rapidly than GTP is hydrolyzed at plus end. 3. Polymerases bind to plus end. 4. CLASP proteins promote growth at plus end.
Shrinkage	1. GTP bound to β-tubulin is hydrolyzed to GDP at minus end. 2. GTP cap is lost at plus end. 3. Depolymerases accelerate dissociation of GTP-tubulin from plus end.
Inhibit assembly	1. vincristine 2. vinblastine 3. colchicine 4. colcemid
Stabilize microtubules	1. taxol

2. Have students form **think-pair-share** groups to research and discuss the role of tau proteins in nerve cell axons. (LO 14.3.3)

   Answer: *Tau proteins appear to control the unidirectional organization of the axon microtubules.*

Clicker Questions

1. The polarity of microfilaments and microtubules (LO 14.3.1)
   a. allows them to bind to each other in an antiparallel orientation.
   b. determines the direction of molecular motor movement along the cytoskeletal element.
   c. is a consequence of the polarity of the monomers or dimers.
   d. restricts the movement of motor proteins to one direction only.

2. Why are microtubule organizing centers (MTOCs) needed? (LO 14.3.2)
   a. MTOCs create an initiation site and serve to stabilize the minus end.
   b. MTOCs regulate the rate and direction of MT polymerization.
   c. MTOCs control the rate of polymerization versus depolymerization.
   d. MTOCs are needed to accelerate the rate of polymerization.

3. Plant cells lack microtubule organizing centers. (LO 14.3.2)
   a. True; in the absence of centrosomes, plant cells cannot form microtubules.
   b. False; they lack centrosomes but have other proteins that serve as MTOCs.

4. Posttranslational modification of tubulin regulates (LO 14.3.3)
   a. the rate and direction of microtubule polymerization.
   b. the cross-linking of multiple microtubules into bundles.
   c. both the severing and the branching of microtubules.
   d. the binding of specific microtubule-associated proteins.

Answers: *1: b, c; 2: a; 3: b; 4: d*

14.4 Microtubule Motors and Movement

Learning Objectives

You should be able to:

14.4.1 Summarize the properties of kinesins and dyneins.
14.4.2 Explain how organelles and other cargo are transported on microtubules.
14.4.3 Contrast the structures and functions of primary and motile cilia.
14.4.4 Diagram the mitotic spindle.
14.4.5 Explain how different types of microtubules act during mitosis.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 14.4 Kinesin
Micrograph 14.42 The Mitotic Spindle
Video 14.4 Vesicle Movement along Microtubules
Video 14.5 Mitochondrial Movement
Video 14.6 Ciliate Movement
Video 14.7 Flagellum in *Euglena*
Key Experiment The Isolation of Kinesin

Active Learning Exercises

1. Have students prepare a **sequence map** showing how Vale, Reese, and Sheetz (Key Experiment, p. 480) were able to isolate and identify kinesin as a microtubule-associated motor protein. (LO 14.4.1)

   Answer: *Sequence maps should include the following: Isolate tubulin from source and get it to form stable microtubules in solution. Homogenize squid giant axons to generate a preparation that contains all the cell's cytoplasmic (soluble) proteins. Add those soluble proteins to the MTs in the presence of AMP-PNP (any MT-binding protein that needs ATP to be released will bind to the MTs). Wash away all non-bound proteins. Add ATP to force release of the kinesin.*

2. Have students write a **minute paper** explaining how and where lysosomes are positioned in the cell. The phrase "carboxy terminus tail" should be included in their answers. (LO 14.4.2)

   Answer: *Microtubules run from the centrosome (minus end) toward the periphery of the cell (plus end). A kinesin motor protein with a lysosome-specific carboxy terminus tail binds to receptors on the exterior of the lysosome and traffics the organelle to the cell periphery.*

3. Have students prepare a **matrix** comparing the structures and functions of primary cilia, motile cilia, eukaryotic flagella, and bacterial flagella. (LO 14.4.3)

   Answer:

Organelle	Structure	Function
primary cilia	Anchored in basal bodies made of nine triplets of microtubules. Two of the microtubules in each triplet extend to form the axoneme.	sensory
motile cilia	Anchored in basal bodies made of nine triplets of microtubules. Two of the microtubules in each triplet extend to form the axoneme, which contains an additional central pair of microtubules. The nine outer microtubule doublets consist of a complete A tubule, containing 13 protofilaments and an incomplete B tubule, containing 10 or 11 protofilaments. The outer doublets are joined to each other by nexin links and to the central pair of microtubules by radial spokes. Each outer microtubule doublet is associated with inner and outer dynein arms.	motility
eukaryotic flagella	Same as motile cilia	motility
bacterial flagella	Protein filaments projecting from the cell surface	motility

4. Have students form **small discussion groups** to compare the role of microtubules during Anaphase A and Anaphase B. (LO 14.4.5)

   Answer: *In Anaphase A, kinetochore microtubules pull the chromosomes towards the two spindle poles by the depolymerizing action of kinesin at the kinetochore. In Anaphase B, interpolar microtubules push the spindle poles apart by sliding past each other (mediated by kinesin), and astral microtubules pull the spindle poles toward the cell periphery by the tractor action of a dynein anchored to the cell cortex.*

Clicker Questions

1. What would happen if squid giant axons were treated with a drug that inhibited kinesin? (LO 14.4.1)
   a. Cargo vesicle transport in both directions would be unaffected.
   b. Anterograde transport of cargo vesicles would be inhibited.
   c. Retrograde transport of cargo vesicles would be inhibited.
   d. Both anterograde and retrograde transport of cargo vesicles would be inhibited.

2. In animal cells, primary cilia are responsible for sensing and flagella are responsible for movement. (LO 14.4.3)
   a. True
   b. False

3. Kinetochore microtubules _____, interpolar microtubules _____, and astral microtubules _____ . (LO15)
   a. span between the spindle poles; connect spindle poles to the cell cortex; connect chromosomes to the spindle poles
   b. connect spindle poles to the cell cortex; connect chromosomes to the spindle poles; span between the spindle poles
   c. connect chromosomes to the spindle poles; connect spindle poles to the chromosomes; span from the chromosomes to the cell cortex
   d. connect chromosomes to the spindle poles; span between the spindle poles; connect spindle poles to the cell cortex

Answers: *1: b; 2: a; 3: d*

14.5 Intermediate Filaments

Learning Objectives

You should be able to:

14.5.1 Summarize the types of intermediate filament proteins.
14.5.2 Diagram the structure of intermediate filaments.
14.5.3 Describe the organization and function of intermediate filaments within cells.

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Key Experiment Function of Intermediate Filaments
Micrograph 14.48a Desmosomes
Micrograph 14.49 Plectin Bridges

Active Learning Exercises

1. Project Figure 14.46 for the class and have students prepare a **sequence map** of the steps in intermediate filament assembly. (LO 14.5.2)

   Answer: *Sequence maps should include the following: Intermediate filament proteins contain central α-helical rod domains, N-terminal head domains, and C-terminal tail domains. The central rod domains of two polypeptides wind around each other in a coiled-coil structure to form dimers. Dimers then associate in a staggered antiparallel fashion to form tetramers. Tetramers associate end-to-end to form protofilaments and laterally to form filaments. Each filament contains approximately eight protofilaments wound around one another in a ropelike structure.*

2. Have students prepare a **T table** displaying the roles of the various proteins in a desmosome. (LO 14.5.3)

Answer:

Protein	Role
desmoglein	A transmembrane cadherin that links to desmocollin in the intercellular space and plakophilin and plakoglobein in the cytoplasm
desmocollin	A transmembrane cadherin that links to desmoglein in the intercellular space and plakophilin and plakoglobein in the cytoplasm
plakoglobin	A cytoplasmic plakin that links desmoglein and desmocolin to desmoplakin
plakophilin	A cytoplasmic plakin that links desmoglein and desmocolin to desmoplakin
desmoplakin	A cytoplasmic plakin that links plakoglobin and plakophilin to intermediate filaments

Clicker Questions

1. Plant cells contain a number of proteins that cross-react with antibodies to animal intermediate filaments. These proteins are the same size as animal intermediate filaments and appear to have similar functions. However, there are many fewer intermediate filaments in plant cells than in animal cells. Why is this? (LO 14.5.1)
   a. In animals, intermediate filaments provide cell structure and cell-to-cell attachment, roles that are fulfilled in plants by the plant cell wall.
   b. Plant cells do not need to perform any of the basic functions that animal cells perform.
   c. Plant cells are capable of photosynthesis and therefore do not need intermediate filaments.
   d. Animal cells control cell structure by changing cell turgor via osmoregulation.

2. Neurofilaments are the major intermediate filaments in most mature neurons. They play a role in (LO 14.5.3)
   a. trafficking of synaptic vesicles through the axon in an anterograde fashion.
   b. ensuring plus/minus directionality for vesicle traffic in the dendron.
   c. providing cell-to-cell attachments from one axon to another.
   d. providing mechanical support for the axon and the microtubule networks.

3. Networks of intermediate filaments may be crosslinked to both microfilament and microtubule networks. (LO 14.5.3)
   a. True
   b. False

Answers: *1: a; 2: d; 3: a*

Instructor's Manual: **Resources**

CHAPTER

15

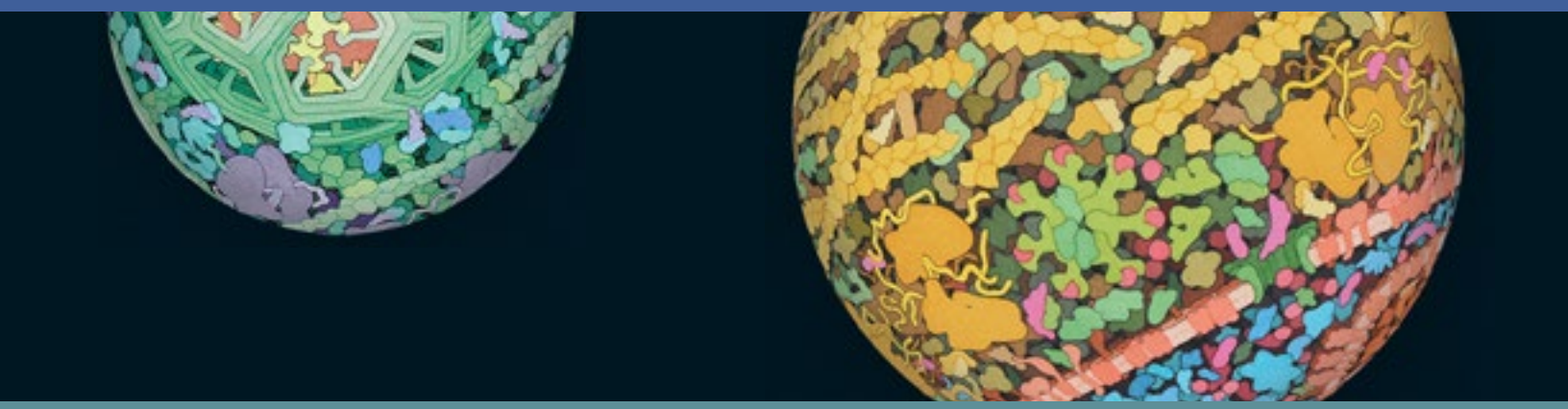
Part III **Cell Structure and Function**

The Plasma Membrane

Chapter Overview

All cells—both prokaryotic and eukaryotic—are surrounded by a plasma membrane, which defines the boundary of the cell and separates its internal contents from the environment. By serving as a selective barrier to the passage of molecules, the plasma membrane determines the composition of the cytoplasm. This ultimately defines the very identity of the cell, so the plasma membrane is one of the most fundamental structures of cellular evolution. Indeed, as discussed in Chapter 1, the first cell is thought to have arisen by the enclosure of self-replicating RNA in a membrane of phospholipids.

The basic structure of the plasma membrane of present-day cells is the phospholipid bilayer, which is impermeable to most water-soluble molecules. The passage of ions and most organic molecules across the plasma membrane is therefore mediated by proteins, which are responsible for the selective traffic of molecules into and out of the cell. Other proteins of the plasma membrane control the interactions between cells of multicellular organisms and serve as sensors through which the cell receives signals from its environment. The plasma membrane thus plays a dual role: It both isolates the cytoplasm and mediates interactions between the cell and its environment.



Chapter Outline

Section Reviews

15.1 Structure of the Plasma Membrane

The fundamental structure of the plasma membrane is a phospholipid bilayer, which also contains glycolipids and cholesterol. Associated proteins are responsible for carrying out specific membrane functions. Membranes are viewed as fluid mosaics in which proteins are inserted into phospholipid bilayers. Although proteins are free to diffuse through the phospholipid bilayer, the mobility of many proteins is restricted, and plasma membranes are composed of distinct domains. Plasma membranes of epithelial cells are divided into apical and basolateral domains with different functions. The mobility of plasma membrane proteins is also restricted by their associations with the cytoskeleton and discrete domains consisting of lipids and other proteins.

15.2 Transport of Small Molecules

The passage of most biological molecules is mediated by carrier or channel proteins that allow polar and charged molecules to cross the plasma membrane without interacting with its hydrophobic interior. Ion channels mediate the rapid passage of selected ions across the plasma membrane. They are particularly well characterized in nerve and muscle cells, where they are responsible for the transmission of electric signals. Energy derived from ATP hydrolysis can drive the active transport of molecules against their electrochemical gradients. Ion gradients are also used as a source of energy to drive the active transport of other molecules.

15.3 Endocytosis

Cells ingest large particles, such as bacteria and cell debris, by phagocytosis, which is driven by actin remodeling. Macromolecules are internalized by clathrin-mediated endocytosis, which provides a mechanism for the selective uptake of specific molecules into clathrin-coated vesicles. Clathrin-coated vesicles are transported to early endosomes, from which receptors are recycled to the plasma membrane and cargo is transported to late endosomes and lysosomes for degradation.

Key Terms

ABC transporter
action potential
active transport
apical domain
aquaporin
basolateral domain
carrier protein
caveolae
channel protein
cholesterol
clathrin-coated pits
clathrin-coated vesicle
clathrin-independent endocytosis
clathrin-mediated endocytosis
dynamin
endocytosis
facilitated diffusion
fluid mosaic model
glycosylphosphatidylinositol (GPI) anchor
glycocalyx
glycolipid
integral membrane protein
ion channel
ion pump
ligand-gated channel
lipid raft
low-density lipoprotein (LDL)
macropinocytosis
Na^+-K^+ pump
Na^+-K^+ ATPase
Nernst equation
peripheral membrane protein
phagocytosis
phagolysosome
phagosome
phosphatidylcholine
phosphatidylethanolamine
phosphatidylinositol
phosphatidylserine
sphingomyelin
transmembrane protein
voltage-gated channel

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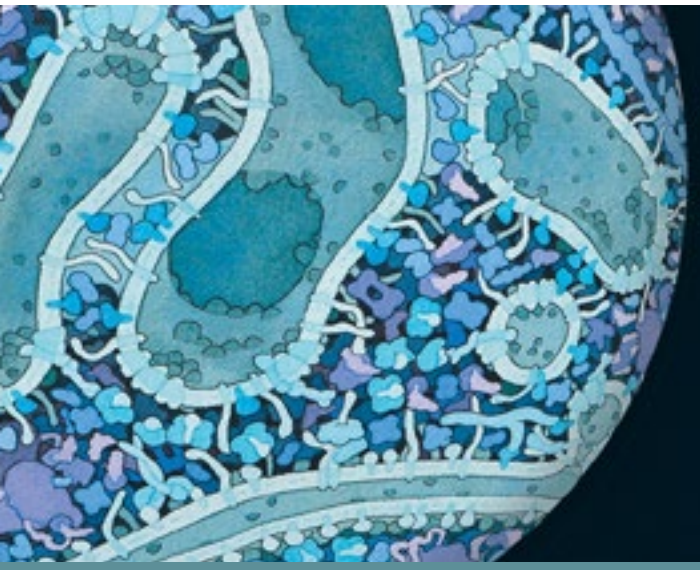

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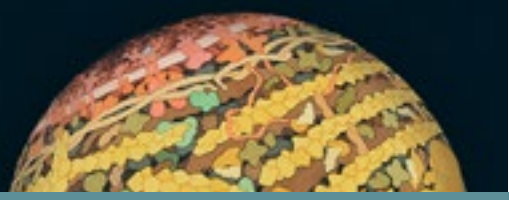
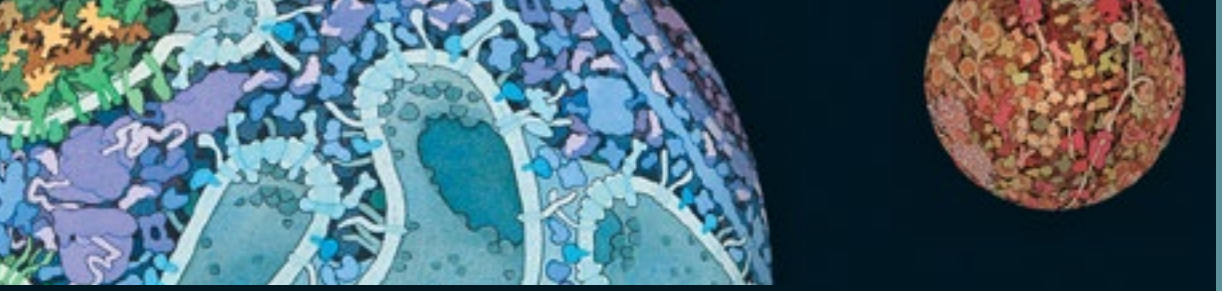




CHAPTER 15 The Plasma Membrane

Active Learning Activities for the Classroom

15.1 Structure of the Plasma Membrane

Learning Objectives

You should be able to:

15.1.1 Summarize the lipid composition of plasma membranes.
15.1.2 Illustrate how proteins are associated with the plasma membrane.
15.1.3 Explain the significance of plasma membrane domains.

Media Available on Companion Website oup.com/uk/cooper8e

Video 15.1 Membrane Fluidity
Video 15.2 Lipid Raft Turnover
Micrograph 15.1 Structure of the plasma membrane
Micrograph 15.9 The glycocalyx
Micrograph 15.13a Caveolae I
Micrograph 15.13b Caveolae II
Data Analysis Problem 15.3 Freeze-Fracture Image of the Cell Membrane

Active Learning Exercises

1. Instruct students to prepare a **spider map** with three legs and label the legs "inner leaflet," "outer leaflet," and "both leaflets." Then, have students place each of the following lipids on the appropriate leg or legs: cholesterol, glycolipids, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and sphingomyelin. (LO 15.1.1)

   Answer: *Cholesterol (both), glycolipids (outer), phosphatidylcholine (outer), phosphatidylethanolamine (inner), phosphatidylserine (inner), and sphingomyelin (outer)*

2. Separate students into **small discussion groups**. With their smart devices, ask them to research "Davson–Danielli model," then answer the question "What aspects of membrane structure did the D-D model get right and what aspects did it get wrong?" (LO 15.1.2)

   Answer: *Right: the membrane is made of protein and lipid. Wrong: protein coated both surfaces of the membrane.*

3. Have students form **think-pair-share** groups to solve this problem: If the average molecular mass of an amino acid is 110 Da, and glycophorin has 131 amino acids and a mass of 30kDa, what is the mass of the carbohydrate portion, in kDa? (LO 15.1.2)

   Answer: *110 Da x 131 amino acids = 14,410 Da.*
   30,000 Da – 14,410 Da = 15.59 kDa

Clicker Questions

1. Of the lipid classes shown in Figure 15.2, only cholesterol is located in both leaflets of the plasma membrane. Why might that be the case? (LO 15.1.1)
   a. Cholesterol is synthesized on both sides of the membrane and is deposited at the site of synthesis.
   b. Membrane lipids, such as cholesterol, lack the bipolar nature needed to be sequestered to one leaflet or the other.
   c. Cholesterol is "surface neutral" because it is embedded entirely in the plasma membrane and not exposed to the surface.
   d. Phosphatidylcholine and phosphatidylethanolamine force the cholesterol into both leaflets of the plasma membrane.

2. If the average molecular mass of an amino acid is 110 Da, and glycophorin has 131 amino acids and a mass of 30kDa, what is the approximate mass of the carbohydrate portion? (LO 15.1.2)
   a. 15.6 kDa
   b. 30 kDa
   c. 110 kDa
   d. 131 kDa

3. The glycocalyx is composed of both glycolipids and glycoproteins. (LO 15.1.2)
   a. True
   b. False

4. What aspect of plasma membrane structure did the Singer–Nicholson model *not* address? (LO 15.1.3)
   a. Membrane lipids have their fatty acid tails exposed to the cytoplasmic fluid.
   b. The proteins and lipids in a membrane are able to diffuse laterally.
   c. Membranes are composed of three layers: protein/lipid/protein.
   d. Membranes can have specialized lipid domains.

5. Why are plasma membrane domains common in epithelial cells? (LO 15.1.3)
   a. Epithelial cells are polarized when organized into tissues.
   b. Plasma membrane domains are polarized when isolated.
   c. Different parts of epithelial cells must perform different functions.
   d. Lipid rafts can move from one end of the cell to the other.

6. The polarity of epithelial cell plasma membrane lipid domains is maintained by (LO 15.1.3)
   a. lipid rafts.
   b. tight junctions.
   c. gap junctions.
   d. caveolae.

Answers: *1: c; 2: a; 3: a; 4: d; 5: a, c; 6: b*

15.2 Transport of Small Molecules

Learning Objectives

You should be able to:

15.2.1 Describe the transport of small molecules by carrier proteins.
15.2.2 Contrast ion channels and carrier proteins.
15.2.3 Summarize the role of ion channels in transmission of nerve impulses.
15.2.4 Describe the action of the sodium/potassium pump.
15.2.5 Explain how ion gradients across the plasma membrane can drive active transport.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 15.1 A Chemical Synapse
Animation 15.2 The Na^+-K^+ Pump
Data Analysis Problem 15.1 The Effect of Antidiuretic Hormone on the Localization of Aquaporin in Kidney Cells
Data Analysis Problem 15.2 Localization of Wild-Type and Mutant CFTR Proteins
Molecular Medicine Cystic Fibrosis

Active Learning Exercises

1. Have students form **think-pair-share** groups and consider the question "What do passive transport and facilitated diffusion have in common, and how do they differ?" (LO 15.2.1)

   Answer: *Both are driven by a concentration gradient across a membrane, and solutes move from an area of higher concentration to an area of lower concentration. Passive transport is the movement of a molecule (solute) directly through a membrane by dissolving in and passing through the lipid portion of the membrane. It is non-specific. In facilitated diffusion, a transmembrane protein is needed to facilitate the diffusion. It is quite specific.*

2. Have students write a **minute paper** in which they contrast two forms of facilitated diffusion: ion channels and carrier proteins. (LO 15.2.2)

   Answer: *Ion channels, while specific, do not bind the diffusing molecule (solute) and do not undergo a conformation change upon transport. Carrier proteins are just as specific but bind the solute and undergo a conformational change upon transport.*

3. Have students form **small discussion groups** and consider the question "How can the carbonyl oxygens that form the filter of the K^+ channel dehydrate K^+-H_2O?" (LO 15.2.4)

   Answer: *Carbonyl oxygens carry a slightly negative charge. Because there are multiple carbonyl oxygens exposed to the channel, and the potassium ion is positively charged, the carbonyls can "pull" the K^+ away from water, thus effecting dehydration.*

4. Have students form **small discussion groups** and discuss the relationship between the chloroplast ATP synthase and the gastric H^+ pump. (LO 15.2.5)

   Answer: *They run in opposite directions. The ATP synthase takes the energy in a transmembrane pH gradient and uses that to synthesize ATP. The gastric proton pump uses the energy in ATP to generate a transmembrane pH gradient.*

Clicker Questions

1. What happens to most of the glucose that is transported into a mammalian cell by the glucose transporter? (LO 15.2.1)
   a. It is metabolized by the citric acid cycle.
   b. It is polymerized into starch.
   c. It is immediately excreted as uric acid.
   d. It is metabolized by the glycolytic pathway.

2. Carrier proteins are similar to enzymes in that both (LO 15.2.2)
   a. span the plasma membrane.
   b. are involved in solute transport.
   c. have substrate binding sites.
   d. catalyze chemical reactions.

3. A major difference between the sodium channel and the potassium channel is that (LO 15.2.3)
   a. Na^+ can pass through in the hydrated form.
   b. K^+ can pass through in the hydrated form.
   c. the water that accompanies Na^+ transport changes the pH across the membrane.
   d. the water that accompanies K^+ transport changes the voltage across the membrane.

4. The sodium/potassium pump is also called the sodium-potassium ATPase because (LO 15.2.4)
   a. the sodium and potassium movements are bidirectional.
   b. three sodium ions are exchanged for three potassium ions.
   c. ATP movement across the membrane drives the sodium and potassium exchange.
   d. ATP is hydrolyzed to provide the energy to drive transport.

5. Active transport requires that ATP be hydrolyzed by the transporter protein. (LO 15.2.5)
   a. True
   b. False

Answers: *1: d; 2: c; 3: a; 4: d; 5: b*

15.3 Endocytosis

Learning Objectives

You should be able to

15.3.1 Describe the mechanism of particle uptake by phagocytosis.
15.3.2 Summarize the pathway of clathrin-mediated endocytosis.
15.3.3 Explain recycling of cell surface receptors.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 15.3 Endocytosis
Animation 15.4 Clathrin-Coated Pits and Vesicles
Video 15.3 Clathrin-Mediated Endocytosis
Micrograph 15.30 Phagocytic cells
Micrograph 15.31a Clathrin-coated vesicle formation
Micrograph 15.31b Clathrin-coated pit
Key Experiment The LDL Receptor

Active Learning Exercises

1. Instruct students to prepare a **sequence map** that shows the steps in phagocytosis. Have them include the RER, Golgi apparatus, and actin cytoskeleton. (LO 15.3.1)

   Answer: *This is a combination of Figures 12.9, 12.27, and 15.29. Ribosomes bound to the RER synthesize hydrolytic enzymes that are injected into the ER lumen. Vesicles containing those enzymes bud off the ER and are trafficked to the Golgi and ultimately to a lysosome. The cell senses a particle for uptake and remodels its actin cytoskeleton to extend pseudopodia, which surround and engulf the particle to form a phagosome. The phagosome and the lysosome fuse to form a phagolysosome, and the particle is digested.*

2. Without allowing them to look at Figure 15.33, have students **draw a diagram** of the process of LDL uptake and release. All of these terms must be used: coated vesicle, release of cholesterol, recycling endosome, late endosome, coated pit, LDL receptor, early endosome, lysosome, dissociation of LDL. (LO 15.3.3)

   Answer: *See Figure 15.33.*

Clicker Questions

1. Plant cells do not engage in phagocytosis because (LO 15.3.1)
   a. plant cells produce all their own food and have no need for phagocytosis.
   b. the plant cell central vacuole is too small to accommodate phagocytosed food particles.
   c. the plant cell wall prevents direct contact of plant cells with external material.
   d. plant cells engage in external digestion of food particles.

2. A cell's ability to perform phagocytosis relies on its ability to (LO 15.3.1)
   a. process and package hydrolytic enzymes in the Golgi apparatus.
   b. utilize the actin cytoskeleton to form pseudopodia.
   c. activate the genes that code for integrin proteins.
   d. engage ATP-driven plasma lemma proton pumps.

3. Hypercholesterolemia is generally characterized by an inability to make the LDL receptor protein. (LO 15.3.2)
   a. True
   b. False

4. How is cholesterol released from the cholesterol receptor? (LO 15.3.3)
   a. The enzyme cholesterolase hydrolyzes the cholesterol-to-receptor bond.
   b. The receptor remains in the membrane while the cholesterol is allowed to cross into the cell.
   c. Water molecules bind to the cholesterol and force it to dissociate from the receptor.
   d. The low pH of the early endosome forces the dissociation.

   Answers: *1: a, c; 2: a, b; 3: a; 4: d*

Instructor's Manual: **Resources**

CHAPTER

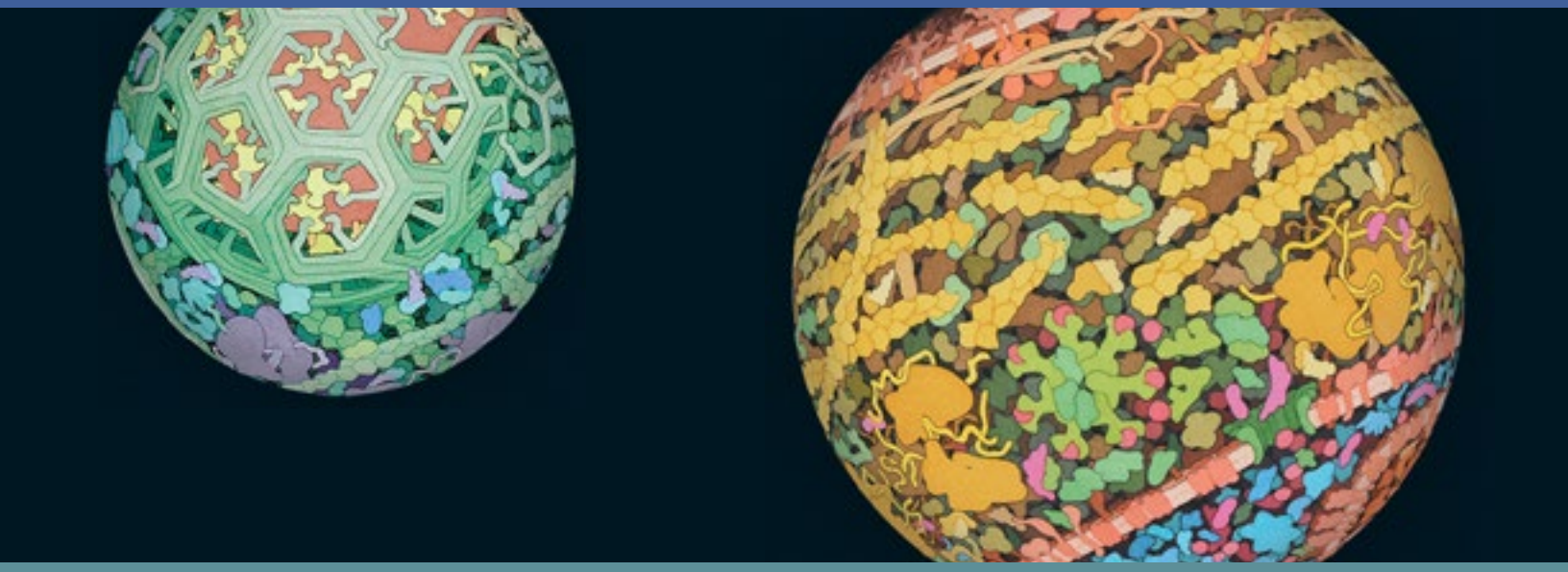
16

Part III **Cell Structure and Function**

Cell Walls, the Extracellular Matrix, and Cell Interactions

Chapter Overview

Although cell boundaries are defined by the plasma membrane, many cells are surrounded by an insoluble array of secreted macromolecules. Cells of bacteria, fungi, algae, and higher plants are surrounded by rigid cell walls, which are an integral part of the cell. Although animal cells are not surrounded by cell walls, most of the cells in animal tissues are embedded in an extracellular matrix consisting of secreted proteins and polysaccharides. The extracellular matrix not only provides structural support to cells and tissues but also plays important roles in regulating cell behavior. Interactions of cells with the extracellular matrix anchor the cytoskeleton and regulate cell shape and movement. Likewise, direct interactions between cells are key to the organization of cells in tissues, as well as providing channels through which cells can communicate with their neighbors.



Chapter Outline

Section Reviews

16.1 Cell Walls

The principal component of bacterial cell walls is a peptidoglycan consisting of polysaccharide chains cross-linked by short peptides. The cell walls of algae and higher plants are composed of fibrous polysaccharides (e.g., cellulose) embedded in a gel-like matrix of polysaccharides and proteins. Their rigid cell walls allow plant cells to expand rapidly by the uptake of water.

16.2 The Extracellular Matrix and Cell–Matrix Interactions

The major structural proteins of the extracellular matrix are members of the collagen family. Collagens form the fibrils that characterize the extracellular matrix of connective tissues, as well as forming networks in basal laminae. Polysaccharides in the form of glycosaminoglycans and proteoglycans make up the bulk of the extracellular matrix. They bind to collagen fibrils and interact with other matrix molecules. Adhesion proteins link the components of the extracellular matrix to one another and to cells. Integrins are the major cell surface receptors that attach cells to the extracellular matrix. At focal adhesions and hemidesmosomes, integrins provide stable links between the extracellular matrix and the cytoskeleton.

16.3 Cell–Cell Interactions

Selective cell–cell interactions are mediated by four major groups of cell adhesion proteins: selectins, integrins, immunoglobulin (Ig) superfamily members, and cadherins. The cadherins link the cytoskeletons of adjacent cells at stable cell–cell junctions. Tight junctions prevent the free passage of molecules between epithelial cells and separate the apical and basolateral domains of the plasma membranes. Gap junctions are regulated channels connecting the cytosols of adjacent animal cells. Adjacent plant cells are linked by cytoplasmic connections called plasmodesmata.

Key Terms

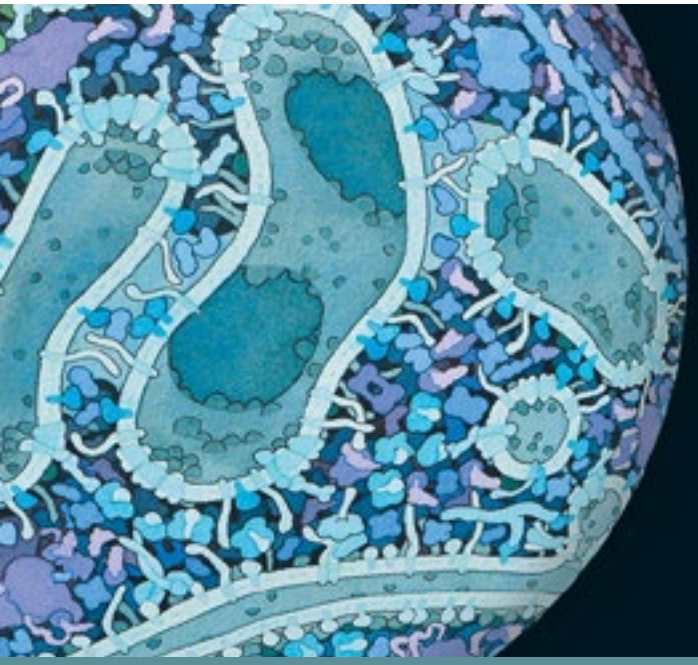
adherens junction
auxin
basal laminae
cadherin
cell adhesion molecule
cellulose
cellulose synthase
chitin
collagen
collagen fibril
connexin
connexon
desmosome
elastic fiber
elastin
electrical synapse
extracellular matrix
fibronectin
focal adhesion
gap junction
glycosaminoglycan (GAG)
hemicellulose
hemidesmosome
heterophilic interaction
homophilic interaction
immunoglobulin (Ig) superfamily
integrin
laminin
middle lamella
nidogen
pectin
peptidoglycan
plasmodesmata
procollagen
proteoglycan
selectin
tight junction
turgor pressure

Additional Media and Supplements for Use in the Classroom

Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website



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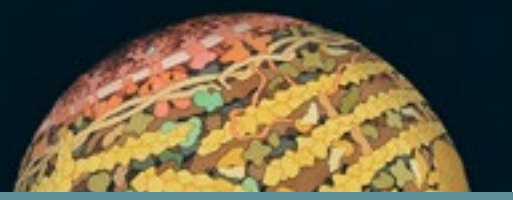
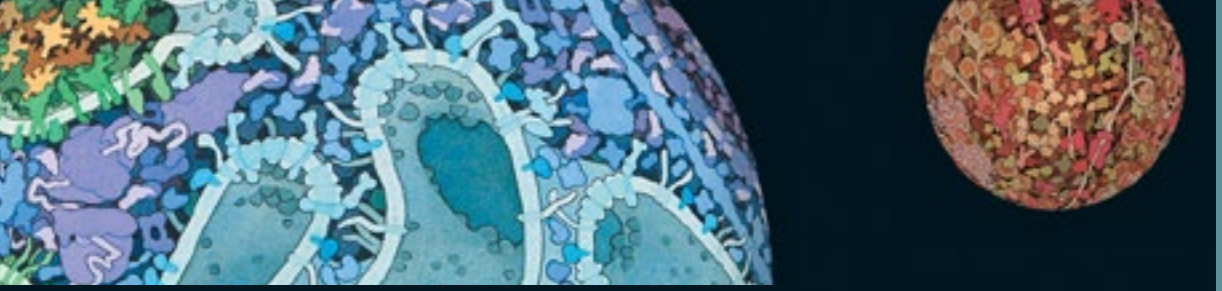




CHAPTER 16 Cell Walls, the Extracellular Matrix, and Cell Interactions

Active Learning Activities for the Classroom

16.1 Cell Walls

Learning Objectives

You should be able to:

16.1.1 Describe the structure of bacterial cell walls.
16.1.2 Distinguish the organization of yeast and plant cell walls.
16.1.3 Explain the role of the cell wall in plant cell growth.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 16.1 Cellulose Synthesis during Elongation

Active Learning Exercises

1. Cell walls independently evolved three times (bacterial, fungal, and plant), yet all three are analogous structures that share common traits. Have students write a **minute paper** in which they compare the structures and functions of the three cell-wall types. (LO 16.1.1, LO 16.1.2)

   Answer: *The basic structure of all three cell walls is based on strong polymeric fibers. The monomers in bacterial cell walls are NAG and NAM. Chitin (fungi) is a polymer of N-acetylglucosamine, and cellulose (plants) is a polymer of glucose.*

2. Plant cell walls have been called a "marvel of flexible packaging." Have students form **think-pair-share** groups to consider the meaning of this, and choose one group to present an answer to the class. (LO 16.1.3)

   Answer: *Plant cell walls can be rigid at times, and they can grow and expand at other times. Hormonal signals activate proteins that break some of the bonds between the structural components of the cell wall. The positive turgor pressure of the cytoplasm pushes against the weakened cell wall, and the cell expands. The cell wall is then re-strengthened and new cell wall layers are deposited. By controlling where the cell wall is loosened, the plant can control the timing, rate, and direction of cell expansion.*

Clicker Questions

1. Individual bacterial cell shape, whether it is spherical, rod, or spiral, is maintained by (LO 16.1.1)
   a. side groups on the *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) residues.
   b. the tetrapeptides that crosslink the *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) residues.
   c. the linear polysaccharide chains that form the basis of the peptidoglycan cell wall.
   d. the bacterial tubulin, actin, and intermediate filament cytoskeletal homologs.

2. Fungi have cell walls made of chitin. Why is this an advantage to wood-rotting fungi? (LO 16.1.2)
   a. It allows them to penetrate more deeply into the wood.
   b. Chitin-based cell walls are stronger and can overcome the cellulose-based cell walls of the wood.
   c. Fungal cell walls are resistant to the cellulases the fungi secrete to digest wood.
   d. Chitin can bind to the peptidoglycans in the wood.

3. β-1,4 linkages result in a straight chain polymer of glucose. β-1,6 linkages result in (LO 16.1.2)
   a. branch points.
   b. end caps.
   c. antiparallel chains.
   d. short segments.

4. Because they have stiff cell walls, plant cells do not need to osmoregulate. (LO 16.1.3)
   a. True; Unlike animal cells, plant cells will not burst.
   b. False; Turgor pressure is needed for cell expansion.

5. Plant cells establish an osmotic imbalance between their cytosol and extracellular fluids to prevent wilting and drive cell expansion. (LO 16.1.3)
   a. True
   b. False

Answers: *1: d; 2: c; 3: a; 4: b; 5: a*

16.2 The Extracellular Matrix and Cell–Matrix Interactions

Learning Objectives

You should be able to:

16.2.1 Describe the types of collagen in extracellular matrix.
16.2.2 Summarize the properties of proteoglycans.
16.2.3 Explain the functions of adhesion proteins.
16.2.4 Describe the roles of integrins in cell–matrix junctions.

Media Available on Companion Website oup.com/uk/cooper8e

Video 16.1 Focal Adhesions
Data Analysis Problem 16.1 The Pericellular Coat of Chondrocytes
Data Analysis Problem 16.2 Synthesis and Secretion of Fibronectin
Data Analysis Problem 16.3 Analysis of the Pathomechanism of Pemphigus, a Human Skin Disorder
Data Analysis Problem 16.4 A Cell Culture Model to Analyze Collagen Synthesis
Data Analysis Problem 16.5 Analysis of Cell-Adhesion Structures in Cultured Cells
Key Experiment The Characterization of Integrin

Active Learning Exercises

1. Instruct students to sketch an extracellular matrix using structural proteins, structural polysaccharides, and adhesion proteins. (LO 16.2.1, LO 16.2.2, LO 16.2.3)

   Answer: *Student sketches will vary.*

2. Have students form **small discussion groups** and use their smart devices to research and discuss hemidesmosome diseases. (LO 16.2.4)

   Answer: *There are several forms of inherited hemidesmosome diseases, and students will find good information at Wikipedia. The point of the exercise it to take the detailed cell biology and translate that into an actual medical condition.*

Clicker Questions

1. The major component of the extracellular matrix of most animal cells is _____, while the primary component of the extracellular matrix of most plant cells is _____. (LO 16.2.1)
   a. hemicellulose; glycosaminoglycans
   b. collagen; cellulose
   c. collagen; hemicellulose
   d. glycosaminoglycans; cellulose

2. Cellulose (plants), chitin (fungi), and hyaluronan (animals) must be synthesized by a transmembrane complex because (LO 16.2.2)
   a. the final form is composed of short repeats cross-linked by sugar groups.
   b. the monomers are covered by highly negative surface charges.
   c. the final form must be bound to the inside of the plasma membrane.
   d. the monomers are produced in the cytoplasm, but the final form is an extracellular cable.

3. Many matric polysaccharides are rich in sulfate groups. What role does the sulfate play in extracellular matrix stability? (LO 16.2.2)
   a. Sulfates are negatively charged and bind water.
   b. Sulfates are negatively charged and bind to collagen.
   c. Sulfates are negatively charged and bind divalent cations.
   d. Sulfates are negatively charged and bind to each other

4. Fibronectin is an adhesion protein that can bind to (LO 16.2.3)
   a. collagen only.
   b. proteoglycans only.
   c. collagen, proteoglycans, and integrin.
   d. both collagen and integrin, but not proteoglycans.

5. Pectinase breaks down the plant cell wall, releasing juice from the cells. What is the equivalent enzyme in the process of tadpole metamorphosis? (LO 16.2.4)
   a. Tadpolase
   b. Integrins
   c. Hemidesmosomes
   d. Collagenase

Answers: *1: b; 2: d; 3: c; 4: c; 5: d*

16.3 Cell–Cell Interactions

Learning Objectives

You should be able to:

16.3.1 Summarize the major types of selective cell–cell adhesion.
16.3.2 Describe the role of tight junctions in epithelial sheets.
16.3.3 Compare and contrast gap junctions and plasmodesmata.

Media Available on Companion Website oup.com/uk/cooper8e

Video 16.3 Cadherins
Micrograph 16.20a A junctional complex
Micrograph 16.21a Gap junctions

Micrograph 16.22 Plasmodesmata
Molecular Medicine Gap Junction Diseases

Active Learning Exercises

1. Have students in **small discussion groups** describe the differences between the selectin/carbohydrate interactions and the integrin/ICAM interactions in the adhesion of leukocytes to endothelial cells. (LO 16.3.1)

   Answer: *The weaker selectin/carbohydrate interactions occur first and are transient. The integrin/ICAM interactions follow. They are stronger and more stable.*

2. Instruct students to write a **minute paper** comparing a tight junction with an adherens junction. (LO 16.3.2)

   Answer: *A tight junction forms a seal between adjacent cells that prevents extracellular fluids from passing between the cells of an epithelial sheet and separates the plasma membrane into apical and basal domains. Adherens junctions act as "rivets" to hold the two cells together.*

3. Have students in **small discussion groups** use their smart devices to research viral movement proteins and discuss the mechanism by which viruses move through a plant. (LO 16.3.3)

   Answer: *Viral movement proteins make it possible for viruses to move between plant cells. These proteins modify the plasmodesmata either by forming a transport tubule within the plasmodesmata pore or by associating with and coating the genome of the virus. The latter leads to the ribonucleoprotein complexes, but not the viral coat proteins, being transported through the plasmodesmata.*

Clicker Questions

1. Figure 16.18 shows the steps in the adhesion of a leukocyte to endothelial cells. It also shows a change in the shape of the leukocyte. What process must take place for leukocytes to change shape? (LO 16.3.1)
   a. Total rearrangement of the cytoskeleton
   b. Release of calcium ions from the cytoplasm
   c. Uptake of integrins from the extracellular matrix
   d. Polar movement of the nucleus to the leading edge

2. Tight junctions involve the fusion of the outer membrane leaflets of adjacent cells. (LO 16.3.2)
   a. True
   b. False

3. Gap junctions allow molecules smaller than 1 kDa to diffuse between neighboring cells. Would an amino acid be able to pass through a gap junction? (LO 16.3.3)
   a. Yes
   b. No

   Answers: *1: a; 2: b; 3: a*

CHAPTER

17

Part IV **Cell Regulation**

Cell Signaling

Chapter Overview

All cells respond to signals from their environment. Even the simplest bacteria sense and swim toward high concentrations of nutrients, such as glucose or amino acids. Many bacteria and unicellular eukaryotes also respond to signaling molecules secreted by other cells, allowing for cell–cell communication. It is in multicellular organisms, however, that cell–cell communication reaches its highest level of sophistication, with the behavior of each individual cell carefully regulated to meet the needs of the whole organism. This is accomplished by a variety of signaling molecules that are secreted or expressed on the surface of one cell and bind to receptors expressed by other cells.

The binding of most signaling molecules to their receptors initiates a series of intracellular reactions that regulate virtually all aspects of cell behavior, including metabolism, movement, proliferation, survival, and differentiation. Interest in this area is heightened by the fact that many cancers arise as a result of a breakdown in the signaling pathways that control normal cell proliferation and survival. In fact, many of our current insights into cell signaling have come from the study of cancer cells—a striking example of the interplay between medicine and basic research.

Cells use a large and complex array of signaling pathways. A select few of these pathways are discussed in this chapter, with the goal of introducing the principles of cell signaling.

Chapter Outline

Section Reviews

17.1 Signaling Molecules and Their Receptors

Most signaling molecules are secreted by one cell and bind to receptors expressed by a target cell. Cell–cell signaling can occur by direct cell contact or by endocrine, paracrine, and autocrine signaling. The steroid hormones, thyroid hormone, vitamin D_3, and retinoic acid are small hydrophobic molecules that cross the plasma membrane of their target cells and bind to intracellular transcription factors. Other small signaling molecules include nitric oxide, neurotransmitters, and plant hormones. The widest variety of signaling molecules in animals are peptides, ranging from only a few to more than 100 amino acids. This group of molecules includes the growth factors that regulate animal cell growth and development.

17.2 G Proteins and Cyclic AMP

The largest family of cell surface receptors, including the receptors for many hormones and neurotransmitters, transmit signals to intracellular targets via the intermediary action of G proteins, which are regulated by GTP binding. Cyclic AMP is an important second messenger in the response of animal cells to a variety of hormones and odorants. Most actions of cAMP are mediated by protein kinase A, which phosphorylates both metabolic enzymes and the transcription factor CREB.

17.3 Tyrosine Kinases and Signaling by the MAP Kinase and PI 3-Kinase Pathways

The receptors for most growth factors are tyrosine kinases. Other receptors act in association with nonreceptor tyrosine kinases, including members of the JAK family, which phosphorylate and activate STAT transcription factors, and members of the Src family, which function downstream of a variety of growth factor receptors as well as

integrins and other cell adhesion molecules. The MAP kinase pathway is coupled to tyrosine kinase receptors by the small GTP-binding protein Ras, which initiates a protein kinase cascade leading to MAP kinase (ERK) activation. ERK then phosphorylates a variety of cytosolic and nuclear proteins, including transcription factors that mediate immediate early gene induction. Other MAP kinase pathways mediate responses of mammalian cells to inflammation and stress. Another major pathway downstream of tyrosine kinases is initiated by phosphorylation of the plasma membrane phospholipid PIP_2 by PI 3-kinase. This leads to activation of the serine/threonine kinase Akt, which plays a key role in cell proliferation and survival. One of the targets of Akt is the protein kinase mTOR, which is a central regulator of cell growth and couples protein synthesis and autophagy to the availability of growth factors, nutrients, and cellular energy.

17.4 Receptors Coupled to Transcription Factors

Members of the TGF-β receptor family are serine/threonine kinases that directly phosphorylate and activate Smad transcription factors. NF-κB transcription factors are activated in response to cytokines, growth factors, and a variety of other stimuli. Their activation is mediated by phosphorylation and degradation of inhibitory IκB subunits. The Wnt and Notch pathways play key roles in determination of cell fate during animal development. Wnt signaling acts by preventing degradation of β-catenin, which serves as a transcriptional activator. Notch signaling is mediated by direct cell–cell interactions, which induce proteolytic cleavage of Notch, followed by translocation of the Notch intracellular domain to the nucleus, where it activates a transcription factor.

17.5 Signaling Dynamics and Networks

The activity of signaling pathways within the cell is regulated by feedback loops that control the extent and duration of signaling. Quantitative differences in activity can be critical to the biological outcome of signaling pathways. Different signaling pathways interact by crosstalk to regulate each other's activity. The extensive crosstalk between individual pathways leads to the formation of complex signaling networks. A full understanding of signaling within the cell will require the development of quantitative network models.

Key Terms

abscisic acid
adenylyl cyclase
Akt
autocrine signaling
autophosphorylation
cAMP phosphodiesterase
cAMP response element (CRE)
cAMP-dependent protein kinase
corticosteroids
CREB (CRE-binding protein)
crosstalk
cyclic AMP (cAMP)
cyclic GMP
cytokine receptor superfamily
cytokines
cytokinins
Elk-1
endocrine signaling
endorphins
enkephalins
epidermal growth factor (EGF)
ERK (extracellular signal-regulated kinase)
estrogen
ethylene
FAK (focal adhesion kinase)
feedback loops
G protein-coupled receptors
G proteins
gibberelins
glucocorticoids
growth factors
GTPase-activating proteins (GAPs)
guanine nucleotide exchange factors (GEFs)
guanylyl cyclase

Key Terms (*Continued*)

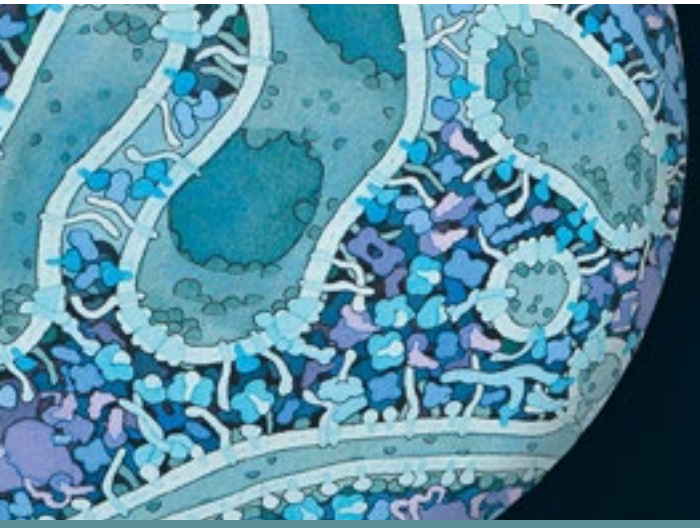
heterotrimeric G proteins
hormones
IκB
immediate early genes
Janus kinase (JAK)
MAP kinases
MEK (MAP kinase/ERK kinase)
membrane-anchored growth factors
mTOR
nerve growth factor (NGF)
neuropeptides
neurotransmitters
NF-κB
nonreceptor tyrosine kinases
Notch
nuclear receptor superfamily
paracrine signaling
peptide hormones
phosphatidylinositide (PI) 3-kinase
phosphatidylinositol 3,4,5-trisphosphate (PIP_3)
phosphatidylinositol 4,5-bisphosphate (PIP_2)
platelet-derived growth factor (PDGF)
progesterone
protein kinase A
Raf
Ras
receptor tyrosine kinases
retinoic acid
retinoids
scaffold proteins
second messenger
secondary response genes
serum response element (SRE)
serum response factor (SRF)
SH2 domains
signal transduction
signaling networks
Smad
Src
STAT proteins
steroid hormones
testosterone
thyroid hormone
Toll-like receptors
transforming growth factor β (TGF-β)
tumor necrosis factor (TNF)
tyrosine kinases
vitamin D_3
Wnt

Additional Media and Supplements for Use in the Classroom

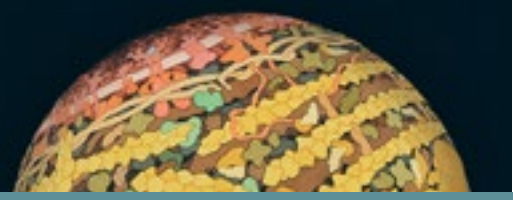
Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

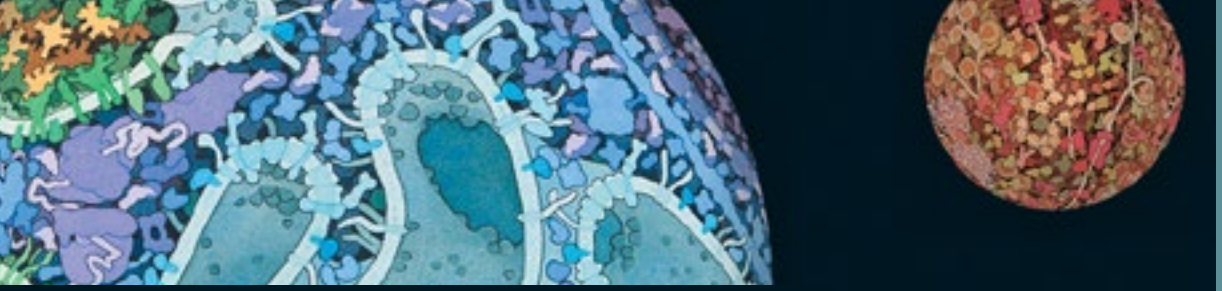
All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website



The **Active Learning Guide** that follows will help you create a dynamic learning environment in your classroom. It provides in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the chapter's Learning Objectives.





CHAPTER 17 Cell Signaling

Active Learning Activities for the Classroom

17.1 Signaling Molecules and Their Receptors

Learning Objectives

You should be able to:

17.1.1 Describe the principal modes of cell signaling.
17.1.2 Explain how steroid hormones regulate gene expression.
17.1.3 Compare the actions of different types of small signaling molecules.
17.1.4 Give examples of polypeptide growth factors.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 17.1 Signaling by Secreted Molecules
Data Analysis Problem 17.1 The Effect of Cholera Toxin on the Transcription Factor CREB

Active Learning Exercises

1. Have students create a **matrix** with three columns and three rows, labeling the columns "Mode of cell-to-cell signaling," "Description," and "Example." Put the words "endocrine," "paracrine," and "autocrine" in the cells in the left column. Fill in the middle column with a description of the term and the right cells with an example. (LO 17.1.1)

   Answer: *See table below.*

Mode of cell-to-cell signaling	Description	Example
Endocrine	signaling molecules are secreted by specialized endocrine cells and carried through the circulation to act on target cells at distant body sites	estrogen
Paracrine	a molecule released by one cell acts on neighboring target cells	neurotransmitters
Autocrine	signaling molecules are secreted by cells and act on the same cell	T lymphocyte growth factors

2. Proteins in the nuclear receptor superfamily are transcription factors that contain domains for ligand binding, DNA binding, and transcriptional activation. Have students **sketch a figure** that shows how a steroid hormone regulates gene expression. (LO 17.1.2)

   Answer: *Figure 17.3 shows an example of one such system: glucocorticoid action. The students' responses would look like that figure, except the specific labels would be replaced with the generic terms steroid hormone, ligand binding, DNA binding, and transcriptional activation.*

3. Have students use their smart devices to **research** the ways angina, nitroglycerin, and Viagra are interrelated. (LO 17.1.3)

   Answer: *Angina is heart pain caused by a restriction of blood flow to the muscles of the heart. Nitroglycerin, when ingested, causes the release of nitric oxide (NO) into the bloodstream. NO travels to the heart, where it dilates the blood vessels, increasing the flow of blood to the heart and relieving angina. Upon sexual arousal, the body produces NO, which dilates blood vessels in the penis, increasing blood flow and causing an erection. An enzyme, cGMP-specific phosphodiesterase type 5 (or PDE5), actively breaks down the NO. Viagra is a specific inhibitor of PDE5, so NO levels remain high for a longer period of time.*

4. Have students draw a **spider map**. Place "Peptide hormones and growth factors" at the center and have the "legs" be peptide hormones, neuropeptides, and growth factors. Each leg will then branch out to include the two to five examples given in the book for each type. (LO 17.1.4)

   Answer: *The answer is embodied in the assignment.*

Clicker Questions

1. What would happen if a cell's autocrine system were constantly producing growth factors? (LO 17.1.1)
   a. Mitosis would proceed unchecked, and a mass of cells would be produced, resulting in a tumor or cancer.
   b. The cells would literally "grow themselves to death" and lead to a necrotic lesion.
   c. Nothing would happen because in autocrine signaling the target cells are some distance away.
   d. Mitosis would be halted because growth factors are negative regulators of the cell cycle.

2. Among the modes of cell-to-cell signaling, what is unique about steroid signaling? (LO 17.1.2)
   a. Steroid receptors are on the cell surface, embedded in the plasma membrane.
   b. Steroid receptors can bind multiple types of molecules, including non-steroids.
   c. Steroid receptors are in the cytosol or nucleus.
   d. Steroid receptors are the main component in autocrine signaling.

3. Farmers who produce table grapes will often spray the developing clusters of grapes with gibberellic acid (GA), resulting in larger grapes. How does GA work to achieve this result? (LO 17.1.3)
   a. GA stimulates fruit ripening. Therefore, a GA application will increase grape production.
   b. GA stimulates cell division. More cell division results in larger grapes.
   c. GA induces the onset of dormancy. The sooner grapes enter dormancy, the larger they can grow.
   d. GA induces stem elongation. By having longer stems, the grapes in a cluster have more room to develop and can grow to a larger size.

4. Activating a ligand-gating ion channel can have significant effects on cell physiology because (LO 17.1.3)
   a. when they're activated, ligand-gating ion channels allow for a large flux of signaling molecules into the target cell.
   b. the ligand is specific for the receptor, meaning non-specific activation is prohibited.
   c. as ions exit the target cell they bind to and inactivate the signaling molecule, thus allowing for an "off" switch in the pathway.
   d. opening ion channels allows for a large change in membrane voltage, as ions leave or enter the target cell.

5. Why do you think the World Anti-Doping Agency (WADA) includes human growth hormone (hGH – a small polypeptide hormone) on its Prohibited List? (LO 17.1.4)
   a. hGH is available in only a few countries. It would be unfair to allow its use, given that very few athletes have access to it.
   b. hGH can give endurance athletes a competitive edge by increasing muscle strength, reducing fat, and increasing resistance to and recovery from injury.
   c. Overuse of hGH can lead to increased insulin resistance, swelling in the arms and legs (edema), joint and muscle pain and, for men, enlargement of breast tissue.
   d. Because hGH cannot be synthesized in the laboratory, it must be isolated from porcine pituitary glands and therefore has many undesirable side effects.

Answers: *1: a; 2: c; 3: d; 4: b, d; 5: b*

17.2 G Proteins and Cyclic AMP

Learning Objectives

You should be able to:

17.2.1 Diagram the structure of a G protein-coupled receptor.
17.2.2 Explain how G proteins carry signals to their target enzymes.
17.2.3 Summarize the role of cAMP.
17.2.4 Describe gene regulation by cAMP-dependent protein kinase.

Media Available on Companion Website oup.com/uk/cooper8e

Key Experiment G Protein-Coupled Receptors and Odor Detection

Animation 17.2 Signal Transduction

Animation 17.3 Signal Amplification

Data Analysis Problem 17.2 The Effect of Neurofibromin 1 on Wild-Type and Mutant Ras Proteins

Active Learning Exercises

1. Have a student draw the structure of a G protein-coupled receptor on the board, using Figure 17.7 as a guide. Initiate a brief **class discussion** on the role of each component. (LO 17.2.1)

   Answer: *The extracellular domain binds the receptor molecule, which induces a conformational change in the seven membrane-spanning helices, allowing the cytosolic domain of the receptor to activate a G protein associated with the inner face of the plasma membrane.*

2. Approximately 34 percent of all Food and Drug Administration-approved drugs in the United States target G proteins. Have students form **think-pair-share** groups and discuss why this is the case. (LO 17.2.2)

   Answer: *More than 1,000 G protein-coupled receptors have been identified, including the receptors for many hormones and neurotransmitters. They play a significant role in the physiology of fungi, plants, and animals.*

3. Have students construct a **sequence map** of the steps in the activity cycle of a G protein. (LO 17.2.2)

   Answer: *Use Figure 17.9 and the accompanying text as a guide.*

4. Have students, in groups of 2–3 write a **minute paper** that summarizes the role of cAMP in signaling. (LO 17.2.2)

   Answer: *cAMP is a second messenger. In a typical signal transduction pathway, a G protein activates adenylyl cyclase, which converts ATP to cAMP. cAMP then goes on to activate a variety of kinases, which phosphorylate and activate downstream elements. The cAMP is eventually degraded to AMP, and the signal pathway is stopped.*

5. Have students prepare a **sequence map** of the steps in cyclic AMP-inducible gene expression. (LO 17.2.3)

   Answer: *Use Figure 17.12 and the accompanying text as a guide.*

Clicker Questions

1. G protein-coupled receptors typically have carbohydrate groups attached to the extracellular portion of the protein. Why might be the role of those carbohydrates? (LO 17.2.1)
   a. Ligand recognition
   b. Cell surface binding
   c. Stabilization of the receptor/G protein complex
   d. Binding of the complex to plant cell walls

2. G proteins are composed of three subunits: α, β, and γ. There are only 21 genes in the human genome for the α subunit, six for the β, and 12 for the γ. How can that few gene products lead to over 1,000 G protein complexes? (LO 17.2.2)
   a. The diversity of G protein complexes comes from the G protein-coupled receptor, not the G protein itself.
   b. 21 x 6 x 12 = 1,512 possible combinations, more than enough to account for the actual number of G protein complexes observed in humans.
   c. The diversity of G protein complexes comes from the diversity of activating hormones, not the G protein itself.
   d. Each gene is capable of generating up to seven unique transcripts through the process of transcript editing.

3. If a cell line were mutated so that it could *not* produce cAMP phosphodiesterase, most G protein signaling pathways (LO 17.2.2)
   a. would be in the constant "off" mode because they could not be activated, due to loss of function of the adenylyl cyclase enzyme.
   b. would be in the constant "off" mode because their receptor proteins could no longer bind the proper hormone.
   c. would be in the constant "off" mode because cAMP could not activate the proper protein kinases.
   d. would be in the constant "on" mode because there would not be a way to remove the cAMP.

4. Which best explains the statement "Every kinase needs a phosphatase"? (LO 17.2.3)
   a. Kinases activate pathways by attaching a phosphate group to target proteins. Phosphatases remove the phosphate groups and terminate the response.
   b. Phosphatases are necessary for signal pathway activation, while kinases are responsible for terminating the response.
   c. Both kinases and phosphatases are key components of every signaling pathway in that they both attach phosphate groups to target proteins.
   d. Kinases directly phosphorylate phosphatases, which then go on to activate downstream elements in the signaling pathway.

Answers: *1: a, d; 2: b; 3: d; 4: a*

17.3 Tyrosine Kinases and Signaling by the MAP Kinase and PI 3-Kinase Pathways

Learning Objectives

You should be able to:

17.3.1 Describe signaling by receptor tyrosine kinases.
17.3.2 Compare and contrast the activities of receptor and nonreceptor kinases.
17.3.3 Explain how Ras and Raf are activated downstream of tyrosine kinases.
17.3.4 Give an example of transcriptional regulation by MAP kinase signaling.
17.3.5 Summarize signaling by PI 3-kinase and mTOR.

Media Available on Companion Website oup.com/uk/cooper8e

Video 17.1 Receptor Tyrosine Kinases
Video 17.2 The Molecular Interactions of the MAPK Pathway
Data Analysis Problem 17.3 Analysis of Erythropoietin Binding to Cultured Cells

Active Learning Exercises

1. Have students form think-pair-share groups and discuss how receptor tyrosine kinases got their name. (LO 17.3.1)

   Answer: *Receptor tyrosine kinases are transmembrane sensing, phosphorylating enzymes. Upon binding a signaling molecule, a hormone, on the exterior of the cell, the receptor, they add a phosphate group from ATP- kinase to a tyrosine group on a target enzyme, sometimes called autophosphorylation. Recognizing that many components in signaling pathways are named for their function can help students with the deciphering/learning process.*

2. Have students form discussion groups to compare and contrast the features and activities of receptor and nonreceptor kinases. Have one group go to the board and write a summary of their discussion. (LO 17.3.2)

   Answer: *Refer to Figures 17.14 and 17.16.*

3. Show students Figure 17.20 (either in a handout or projected on a screen). Then have singly or in small groups create a sequence map that outlines the steps in Ras and Raf activation downstream of tyrosine kinases. Have one group write their answer on the board, leaving enough space between steps for the class to add details. (LO 17.3.3)

   Answer: *Refer to the legend in Figure 17.20.*

4. Have students form discussion groups and consider the question "Why is phosphorylation/dephosphorylation such a common feature in signal transduction pathways?" (LO 17.3.4)

   Answer: *This question is not directly addressed in Chapter 17, but students may be able to figure it out on their own. The answer comes down to three features of*

phosphate groups. First, they are big and charged, so adding (or removing) one from a protein can have a significant effect on protein conformation and therefore, activity. Second, the bond to the phosphate group is a high-energy bond. It takes 7.6 kcals/mol to add PO4 groups, and that much energy is released when they are removed. So adding or removing a PO4 group is energetically possible, has a large impact on the energy of the phosphorylated molecules, and fits with how a cell manages its energy resources. Third, phosphate groups are readily available in the form of phosphorylated nucleotides ATP, GTP, CTP, and TTP. Again, this is in line with how a cell manages and processes energy.

5. Have students make a sequence map of growth factor-mediated inactivation of FOXO-induced genes. Have one or more students draw the map on the board. (LO 17.3.5)

   Answer: *This is a combination of Figures 17.24 and 17.25. There could be a lot of steps here, depending on how detailed the maps are.*

Clicker Questions

1. The steps in receptor tyrosine kinase activation are 1) ligand binding, 2) receptor dimerization, and 3) autophosphorylation. What is the result of these steps? (LO 17.3.1)
   a. Specific binding sites are created for additional proteins that transmit intracellular signals downstream of the activated receptors.
   b. Signaling activity is greatly reduced, due to steric hindrance caused by binding of the large, charged phosphate groups.
   c. Phosphorylation of tyrosine residues within the catalytic domain increases protein kinase activity of the receptor tyrosine kinase, itself.
   d. The phosphorylated amino acid residues are enzymatically removed in order to terminate the signaling pathway.

2. What is the main difference between receptor tyrosine kinases and nonreceptor tyrosine kinases? (LO 17.3.2)
   a. Receptor tyrosine kinases contain an intrinsic kinase activity, whereas nonreceptor tyrosine kinases recruit separate kinase enzymes.
   b. Receptor tyrosine kinases can be phosphorylated and nonreceptor tyrosine kinases cannot.
   c. Receptor tyrosine kinases undergo ligand-induced dimerization and nonreceptor tyrosine kinases do not.
   d. Receptor tyrosine kinases must be activated by the binding of a ligand (hormone), whereas nonreceptor tyrosine kinases do not need to be activated.

3. What would happen if a Ras protein were unable to interact with its proper GAP (GTPase-activating protein)? (LO 17.3.3)
   a. Ras could not be activated, and cell growth would continue unchecked.
   b. Ras would be irreversibly inactivated, and cell growth would cease.
   c. Ras would remain in an active state, and cell growth would continue unchecked.
   d. Ras would not be able to bind GTP, and cell growth would cease.

4. MAP kinase pathways operate via cascades of protein kinases. An advantage of using a cascade as an intermediary between a signal and an outcome is that it would allow (LO 17.3.4)
   a. the amplification of a single signal to multiple pathways.
   b. different signal pathways to utilize the same downstream kinases.
   c. the activation of multiple genes from a single signal.
   d. different signaling molecules to activate the same downstream kinases.

5. Mammalian target of rapamycin (mTOR) inhibitors, such as rapamycin and its analogues, have recently attracted broad clinical interest among researchers. What could explain this? (LO 17.3.5)
   a. The activation or inactivation of the mTOR pathway underlies multiple human pathologies.
   b. mTORs are key transcription factors that regulate genes involved in cancer, autophagy, and maintaining nutrient levels.
   c. The mTOR pathway is a central regulator of cell growth and is involved in virtually all aspects of cellular function.
   d. mTOR1 and mTOR2 are protein kinases that are regulated by multiple signals and can phosphorylate multiple target proteins.

Answers: *1: a, c; 2: a; 3: c; 4: a, b, c, d; 5: a, c, d*

17.4 Receptors Coupled to Transcription Factors

Learning Objectives

You should be able to:

17.4.1 Compare and contrast TGF-β/Smad and JAK/STAT signaling.

17.4.2 Describe the NF-κB pathway.

17.4.3 Explain the roles of proteolysis in the Wnt and Notch pathways.

Media Available on Companion Website oup.com/uk/cooper8e

Data Analysis Problem 17.4 The Effect of an Intracellular Antibody on Interleukin-6 Signaling

Active Learning Exercises

1. Have students prepare a **T table** in which they compare and contrast TGF-β/Smad and JAK/STAT signaling. (LO 17.4.1)

   Answer: *Similarities: both are protein kinases associated with a receptor that directly phosphorylates and activates a transcription factor. Differences: TGF-β/Smad uses a receptor kinase and phosphorylates either a threonine or a serine residue. The JAK/STAT uses a nonreceptor kinase and phosphorylates a tyrosine residue.*

2. Have students form **think-pair-share** groups and discuss the question "What role does protein degradation play in the NF-κB, Wnt, and Notch pathways?" (LO 17.4.1 and LO 17.4.2)

   Answer: *In NF-κB, an inhibitory protein is degraded, which allows the pathway to continue; In Wnt, a protein in the pathway is protected from degradation, which allows the pathway to continue; In Notch, the Notch receptor is cleaved upon ligand binding and the intercellular degradation product activates transcription.*

Clicker Questions

1. What feature(s) of the TGF-β/Smad and JAK/STAT signaling pathways act as a disadvantage from the standpoint of regulation? (LO 17.4.1)
   a. Their signaling pathways are long and complex, making regulatory control difficult.
   b. Their signaling pathways are short and direct, meaning there are fewer opportunities for regulatory control.
   c. Their signaling pathways are quite long and complex, involving multiple intermediary proteins.
   d. Their signaling pathways require the use of ATP, which is often a limiting component of signaling pathways.

2. Activation of the NF-κB pathway leads to what main step? (LO 17.4.2)
   a. A protein is phosphorylated, which inactivates the pathway.
   b. A protein is degraded, which inactivates the pathway.
   c. An inhibitory protein is phosphorylated and marked for degradation.
   d. A kinase is activated, which phosphorylates a target protein.

3. Lactacystin is an inhibitor of proteasomes produced by some *Streptomyces* bacteria. What would happen to regulation of the Wnt pathway if lactacystin were added to developing embryos? (LO 17.4.3)
   a. The destruction complex would not form and b-catenin would still be able to stimulate gene expression.
   b. β-catenin would not be degraded and the pathway would still be able to respond to Wnt stimulation.
   c. The destruction complex would form but would be unable to phosphorylate β-catenin and the Wnt pathway would remain active.
   d. β-catenin would still be phosphorylated and ubiquitinated. This "extra baggage" would probably inhibit its ability to enter the nucleus and bind to the proper transcription factor.

   Answers: *1: b; 2: c, d; 3: d*

17.5 Signaling Dynamics and Networks

Learning Objectives

You should be able to:

17.5.1 Diagram a feedback loop.

17.5.2 Explain how the dynamics of signaling can alter biological response.

17.5.3 Summarize the role of crosstalk in integrating cellular response to extracellular stimuli.

Active Learning Exercises

1. Figure 17.31 shows a negative feedback loop. Have students form **small discussion** groups and use their smart devices to research and discuss the role of positive feedback loops in cell biology. (LO 17.5.1)

   Answer: *Positive feedback loops often occur in developing cells and tissues, where they serve to amplify a pathway.*

2. Have students locate this paper on the Internet: Basson, M.A. (2012, Signaling in cell differentiation and morphogenesis. Cold Spring Harbor Perspectives in Biology. 4(6) a008151. doi: 10.1101/cshperspect.a008151). Direct their attention to the first paragraph of Section 5: Signal Strength and Duration: Interpretation and Regulation. Have students, in groups of 2–4, write a **sequence map** of the steps that enable cells to distinguish between short-lived and sustained RTK signals. In their groups, using the example in the text of the ERK signaling pathway, ask students to explain how the dynamics of signaling can alter a biological response. (LO 17.5.2)

   Answer: *This would basically be a distillation of Figure 1 and its caption. Instructors can specify more or less detail, depending on class needs.*

3. Have students engage in a **class discussion** in which they identify sites of both positive and negative crosstalk. (LO 17.5.3)

   Answer: *Positive: receptor activates Ras and Raf, Ras activates PI 3-kinase, PI 3-kinase activates Akt, Ras activates MEK, MEK activates ERK, ERK activates mTORC1; Negative: Akt inhibits RAF, Akt inhibits TSC, ERK inhibits TSC, TSC inhibits mTORC1.*

Clicker Questions

1. Metabolic pathways (see Chapter 2) and signaling pathways can both be under the control of (LO 17.5.1)
   a. positive feedback loops.
   b. negative feedback loops.
   c. repressors and corepressors.
   d. activators and coactivators.

2. ERK signaling can result in completely different cellular outcomes based on how long the pathway is activated. (LO 17.5.2)
   a. True
   b. False

3. Referring to Figure 17.32, which of the following statements is true? (LO 17.5.3)
   a. A signal transmitted from the growth factor receptor through Ras to PI 3-kinase and Akt to inhibit TSC represents positive control.
   b. A signal transmitted from the growth factor receptor through Ras, to PI 3-kinase and Akt to inhibit Raf represents negative control.
   c. A signal transmitted from the growth factor receptor through Ras, Raf, MEK and ERK to activate mTORC1 represents positive control.
   d. A signal transmitted to ERK inhibits TSC, which allows mTORC1 to be activated, represents negative control.

Answers: *1: a, b; 2: a; 3: b, c, d*

CHAPTER

18

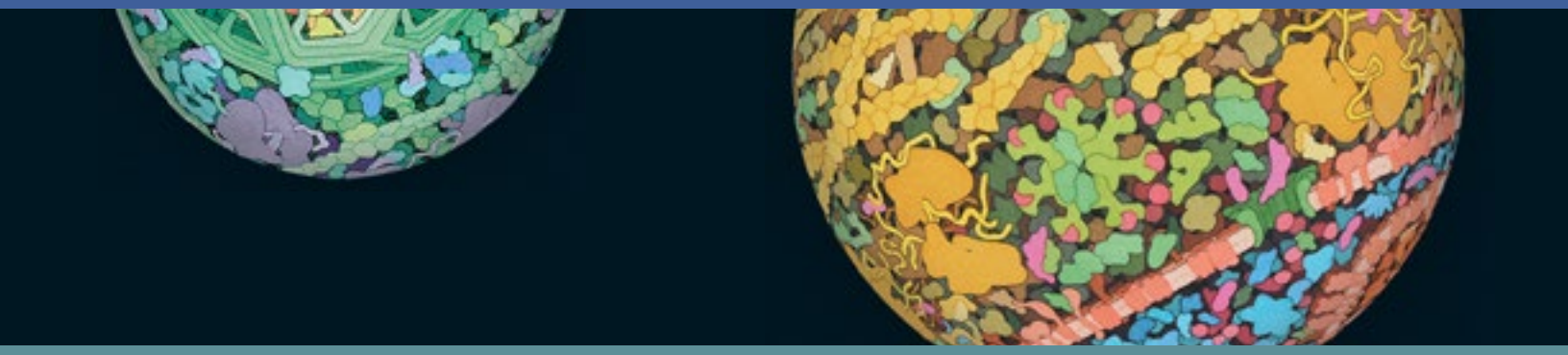
Part IV **Cell Regulation**

The Cell Cycle

Chapter Overview

Self-reproduction is perhaps the most fundamental characteristic of cells. All cells reproduce by dividing in two, with each parental cell giving rise to two daughter cells on completion of each cycle of cell division. These newly formed daughter cells can themselves grow and divide, giving rise to a new cell population formed by the growth and division of a single parental cell and its progeny. In the most complex case, repeated cycles of cell growth and division result in the development of a single fertilized egg into the approximately 10^{14} cells that make up the human body.

The division of all cells must be carefully regulated and coordinated with both cell growth and DNA replication in order to ensure the formation of progeny cells containing intact genomes. In eukaryotic cells, progression through the cell cycle is controlled by a series of conserved protein kinases. This cell cycle machinery is itself regulated by the growth factors that control cell proliferation, allowing the division of individual cells to be coordinated with the needs of the organism as a whole. Not surprisingly, defects in cell cycle regulation are a common cause of the abnormal proliferation of cancer cells, so studies of the cell cycle and cancer have become closely interconnected, similar to the relationship between studies of cancer and the cell signaling pathways discussed in Chapter 17.



Chapter Outline

Section Reviews

18.1 The Eukaryotic Cell Cycle

Eukaryotic cell cycles are divided into four discrete phases: M, G_1, S, and G_2. M phase consists of mitosis, which is usually followed by cytokinesis. S phase is the period of DNA replication. Progression through the cell cycle is regulated by extracellular signals, such as growth factors. Checkpoints and feedback controls coordinate the events that take place during different phases of the cell cycle and arrest cell cycle progression if DNA is damaged.

18.2 Regulators of Cell Cycle Progression

MPF, the key molecule responsible for regulating the G_2 to M transition, is a dimer of the Cdk1 protein kinase and cyclin B. Distinct pairs of cyclins and Cdk1-related protein kinases regulate progression through different stages of the cell cycle. The activity of Cdk's is regulated by association with cyclins, phosphorylation, and Cdk inhibitors. Growth factors stimulate animal cell proliferation by inducing synthesis of the D-type cyclins, which associate with Cdk4 and Cdk6 in G_1. A key substrate of Cdk4, 6/cyclin D complexes is the tumor suppressor protein Rb, which regulates transcription of genes required for cell cycle progression, including cyclin E. Activation of Cdk2/cyclin E complexes and inhibition of the APC/C ubiquitin ligase is then responsible for entry into S phase. Cdk2/cyclin E initiates DNA replication by activating the MCM helicase at origins of replication. Arrest of the cell cycle in response to DNA damage is mediated by protein kinases that inhibit Cdc25 phosphatases, which are required for Cdk activation. In mammalian cells, arrest at the G_1 checkpoint is also mediated by p53, which induces synthesis of the Cdk inhibitor p21.

18.3 The Events of M Phase

M phase is initiated by activation of Cdk1/cyclin B, Aurora, and Polo-like kinases, which are responsible for chromatin condensation, nuclear envelope breakdown, fragmentation

of the Golgi apparatus, and reorganization of microtubules to form the mitotic spindle. The attachment of spindle microtubules to the kinetochores of sister chromatids then leads to their alignment on the metaphase plate. Activation of the APC/C ubiquitin ligase leads to the metaphase to anaphase transition. The activity of APC/C is inhibited by the spindle assembly checkpoint until all chromosomes are properly aligned on the spindle. Ubiquitin-mediated proteolysis initiated by the APC/C then leads to the degradation of cohesin, breaking the link between sister chromatids at the onset of anaphase. The APC/C also ubiquitylates cyclin B, leading to inactivation of Cdk1, exit from mitosis, and cytokinesis.

Key Terms

anaphase
anaphase-promoting complex/ cyclosome (APC/C)
ATM
ATR
Aurora kinase
Cdk inhibitor (CKI)
Cdk's
Cdk1
cell cycle checkpoint
centromere
centrosome
checkpoint kinase
cohesins
condensins
contractile ring
cyclins
cytokinesis
DNA damage checkpoints
E2F
flow cytometer
fluorescence-activated cell sorter
G_0
G_1 cyclins (Cln's)
G_1 phase
G_2 phase
interphase
kinetochore
M phase
maturation promoting factor (MPF)
metaphase
mitosis
mitotic checkpoint complex (MCC)
mitotic spindle
p53
Polo-like kinase
prometaphase
prophase
Rb
restriction point
S phase
spindle assembly checkpoint
START
telophase
tumor suppressor gene

Additional Media and Supplements for Use in the Classroom

Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

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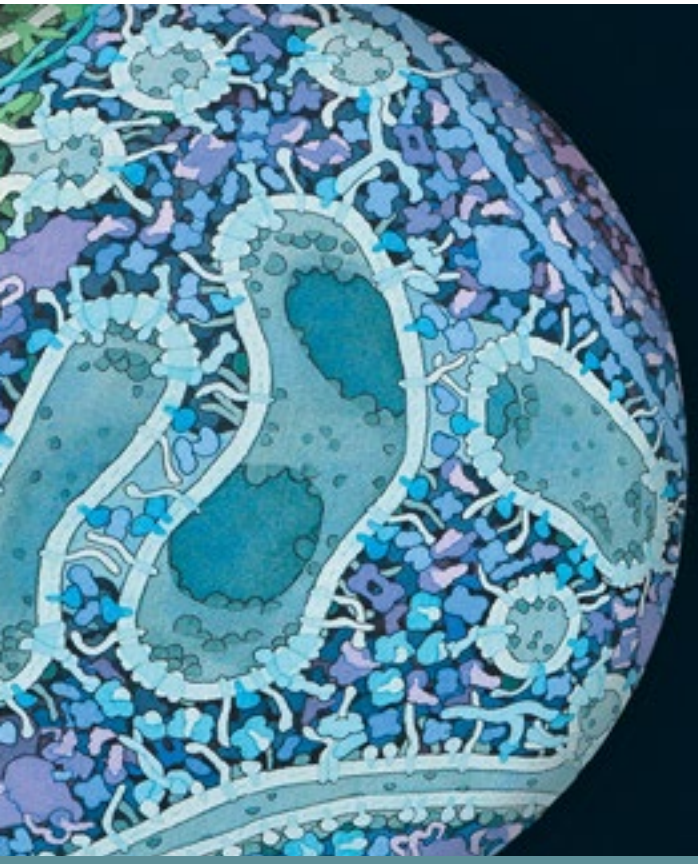
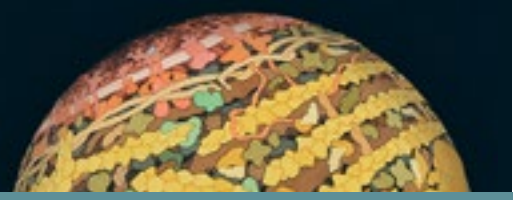
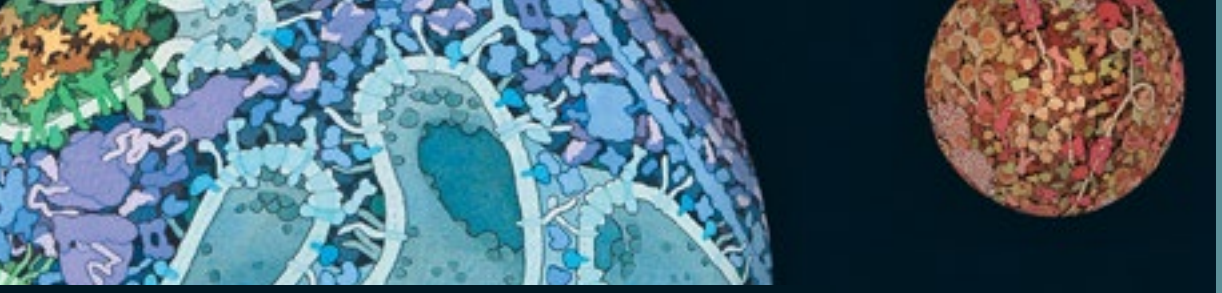


The **Active Learning Guide** that follows will help you create a dynamic learning environment in your classroom. It provides in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the chapter's Learning Objectives.





CHAPTER 18 The Cell Cycle

Active Learning Activities for the Classroom

18.1 The Eukaryotic Cell Cycle

Learning Objectives

You should be able to:

18.1.1 Summarize the phases of the cell cycle.
18.1.2 Describe growth factor regulation of cell cycle progression.
18.1.3 Explain the significance of cell cycle checkpoints.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 18.1 Phases of the Cell Cycle
Animation 18.2 Embryonic Cell Cycles
Animation 18.3 Checkpoints in the Cell Cycle
Video 18.1 Mitosis in Real Time
Video 18.2 Fission Yeast Division

Active Learning Exercises

1. Have students prepare a **sequence map** of the stages in the prokaryotic cell cycle. (LO 18.1.1)

   Answer: *1) cell elongation/enlargement, 2) replication of the chromosome, 3) fission of the single cell into two daughter cells. Note: Students may need to do some online research to find an answer. The level of detail required is at the instructor's discretion.*

2. Instruct students to write a **minute paper** explaining why yeast cell division is controlled by cues (such as nutrient availability), while animal cell division is controlled by extracellular growth factors. (LO 18.1.2)

   Answer: *Yeasts are unicellular, whereas mammalian cells are part of a tissue in which millions of cells work together.*

3. Have students form **small discussion groups** to talk about the significance of cell cycle checkpoints. Choose a student to share an answer with the class. (LO 18.1.3)

   Answer: *Checkpoints largely serve to ensure that the genome is properly replicated and ready for mitosis.*

Clicker Questions

1. Most of the cell biology discussed in the textbook happens during the (LO 18.1.1)
   a. M phase.
   b. G_1 phase.
   c. S phase.
   d. G_2 phase.

2. Rapidly dividing embryonic cells lack the (LO 18.1.1)
   a. M phase.
   b. G_1 phase.
   c. S phase.
   d. G_2 phase.

3. A major cell cycle regulatory point is in the (LO 18.1.2)
   a. M phase.
   b. G_1 phase.
   c. S phase.
   d. G_2 phase.

4. Cell cycle arrest precedes the (LO 18.1.2)
   a. M phase.
   b. G_0 phase.
   c. S phase.
   d. G_2 phase.

5. Cell cycle checkpoints serve to ensure that (LO 18.1.3)
   a. the S phase is completed before M phase initiation.
   b. damaged DNA is not passed on to daughter cells.
   c. cytokinesis has adequate time to advance fully.
   d. the spindle apparatus is properly assembled.

   Answers: *1: b; 2: b, d; 3: b; 4: b; 5: a, b, d*

18.2 Regulators of Cell Cycle Progression

Learning Objectives

You should be able to:

18.2.1 Summarize the experiments that led to the discovery of MPF.

18.2.2 Explain the role of cyclins.

18.2.3 Describe the mechanism by which growth factors regulate cell cycle progression.

18.2.4 Explain how the initiation of DNA replication is controlled.

18.2.5 Summarize the operation of DNA damage checkpoints.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 18.4 Cyclins, Cdk's, and the Cell Cycle

Key Experiment The Discovery of MPF

Key Experiment The Identification of Cyclin

Data Analysis Problem 18.1 Cyclin D1 and Cell Cycle Progression

Data Analysis Problem 18.4 Autoradiographic Tracking of Histone H1 in Cancer Cells

Active Learning Exercises

1. Provide students with Figure 18.12 (without the caption) and have them prepare a **sequence map** of the steps in MPF regulation of mitosis. (LO 18.2.2)

   Answer: *Cdk1 forms complexes with cyclin B during G_2. Cdk1 is then phosphorylated on threonine-161 (Thr161), which is required for Cdk1 activity, as well as on tyrosine-15 (Tyr15)—and threonine-14 (Thr14) in vertebrate cells—which inhibits Cdk1 activity. Dephosphorylation of Tyr15 and Thr14 activates MPF at the G_2 to M transition. MPF activity is then terminated toward the end of mitosis by proteolytic degradation of cyclin B, which is followed by dephosphorylation of Cdk1.*

2. Have students write a **minute paper** in which they describe the activation and role of the anaphase promoting complex/cyclosome (APC/C) in the regulation of the cell cycle. (LO 18.2.3)

   Answer: *The APC/C is phosphorylated and activated by Cdk1/Cyclin B. APC/C then ubiquitinates Cyclin B, which labels it for proteolytic destruction. Thus, activating the Cdk1/Cyclin B complex soon leads to its destruction, but not before it has signaled the cell to enter mitosis.*

3. Present students with the table below and have them **match** the cyclin type in the left column with the correct point of cell cycle control in the right column. (LO 18.2.3)

   Answer: *B-type cyclins regulate transition from G_2 to M phase; D-type cyclins regulate progression through G_1 to S; E-type cyclins initiate the S phase; G-type cyclins regulate progression through the S phase.*

B-type cyclins	regulate progression through G_1 to S
D-type cyclins	regulate progression through the S phase
E-type cyclins	regulate transition from G_2 to M
G-type cyclins	initiate the S phase

4. Once an origin becomes active during S phase, replication at that origin cannot initiate again until the cell passes through mitosis. Have students write a **minute paper** explaining what prevents reinitiation. (LO 18.2.4)

   Answer: *The highly charged phosphate groups on the MMC helicase proteins are repelled by the origin recognition complex (ORC), which prevents the MMC from reassociating with the ORC.*

Clicker Questions

1. MPF was discovered by a series of elegant experiments that involved injecting recipient eggs with (LO 18.2.1)
   a. extracts of progesterone taken from eggs that were undergoing mitosis.
   b. the cytoplasm of eggs that had been treated with progesterone.
   c. nuclei that were extracted from eggs that had already completed mitosis.
   d. a homogenate of mouse egg cells that were stimulated to enter mitosis.

2. The main technique used in the discovery of cyclins was (LO 18.2.2)
   a. mass spectrometry.
   b. molecular cloning.
   c. gel chromatography.
   d. gel electrophoresis.

3. The expected life span of cyclins is about (LO 18.2.3)
   a. one hour.
   b. one day.
   c. one week.
   d. one month.

4. DNA replication is restricted to the S phase of the cell cycle because (LO 18.2.4)
   a. DNA polymerase activity is inhibited during the S phase.
   b. kinase activity in S, G_2, and M prevents the initiation of DNA replication complexes.
   c. kinase activity in S, G_2, and M prevents the reinitiation of DNA replication complexes.
   d. the origin recognition complex (ORC) is phosphorylated by kinase activity in the S phase.

5. How would a mutated *p53* gene lead to cancer? (LO 18.2.5)
   a. The mutated p53 protein would activate cell cycle proliferation.
   b. The enzymes responsible for DNA damage would be activated.
   c. The loss of p53 activity would prevent cell cycle arrest due to DNA damage.
   d. p53 activity would be enhanced and lead to increased levels of DNA damage.

Answers: *1: b; 2: d; 3: a; 4: c; 5: c*

18.3 The Events of M Phase

Learning Objectives

You should be able to:

18.3.1 Describe the stages of mitosis.
18.3.2 Summarize the targets of mitotic kinases.
18.3.3 Explain the mechanism of chromosome condensation.
18.3.4 Illustrate operation of the spindle assembly checkpoint.
18.3.5 Contrast cytokinesis in animal and plant cells.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 18.5 Mitosis in an Animal Cell
Animation 18.6 Cytokinesis in Higher Plants
Video 18.3 Mitosis with Fluorescent Proteins
Video 18.5 Spindle Assembly Checkpoint
Video 18.6 Metaphase and Anaphase
Micrograph 18.25 Microtubules attached to the kinetochore of a chromosome
Data Analysis Problem 18.2 Regulation of the Nuclear Lamina by Phosphorylation
Data Analysis Problem 18.3 The Effect of Taxol on Fibroblasts

Active Learning Exercises

1. Have students prepare a **T table** with the stages of mitosis in the left column and a description of the characteristic events for each stage. (LO 18.3.2)

   Answer: *An example is given below. The level of detail required is at the instructor's discretion. Note: interphase and cytokinesis are stages of the cell cycle but not stages of mitosis.*

Stage	Characteristic events
Prophase	Duplicated chromosomes condense into two sister chromatids, which are held together at the centromere.
Prometaphase	The nuclear envelope breaks down, and microtubules of the mitotic spindle attach to the kinetochores of condensed chromosomes.
Metaphase	Chromosomes shuffle back and forth until they eventually align on the metaphase plate in the center of the spindle.
Anaphase	The link between sister chromatids breaks, after which they separate and move to opposite poles of the spindle.
Telophase	Nuclei reform and the chromosomes decondense.

2. Have students write a **minute paper** in which they compare cohesins and condensins, then share their answers with the class. (LO 18.3.3)

   Answer: *Cohesins keep the two sister chromatids together during S phase. During prophase, most of the cohesins are replaced by condensins, which drive chromosome condensation. Only the cohesins at the centromere remain. Both cohesins and condensins are activated by kinases.*

3. Instruct students to prepare a **matrix** that arranges the kinases given below in the proper sequence and provides the consequence of each kinase activity. (LO 18.3.3)

   Cdk1 phosphorylates nuclear pore proteins

   Cdk1 and Aurora B kinase phosphorylate condensins

   Cdk1, Aurora A, and Polo-like kinases phosphorylate microtubule-associated proteins (MAPs)

   Cdk1 and cyclin B phosphorylate lamins

   Aurora B and Polo-like kinases phosphorylate cohesins

   Cdk1 and Polo-like kinase phosphorylate Golgi matrix proteins

   Answer: *See matrix below.*

Kinase and action	Consequence
Cdk1 and Aurora B kinase phosphorylate condensins	condensins drive chromosome condensation
Aurora B and Polo-like kinases phosphorylate cohesins	cohesins keep sister chromatids associated
Cdk1 and cyclin B phosphorylate lamins	nuclear lamina depolymerize and nuclear envelope disintegrates
Cdk1 phosphorylates nuclear pore proteins	nuclear pore complexes disassemble
Cdk1 and Polo-like kinase phosphorylate Golgi matrix proteins	Golgi body breaks up into vesicles
Cdk1, Aurora A, and Polo-like kinases phosphorylate microtubule-associated proteins (MAPs)	interphase microtubules depolymerize

4. Have students prepare a **sequence map** of the steps in the spindle assembly checkpoint. (LO 18.3.4)

   Answer: *The steps are given in the Figure 18.27 caption. The level of detail required is at the instructor's discretion. A simple sequence would be: 1) APC/C is activated by Cdc20. 2) APC/C ubiquitylates cyclin B, leading to degradation and inactivation of Cdk1. 3) APC/C also ubiquitylates securin, leading to 4) activation of separase. 5) Separase degrades cohesin, breaking the link between sister chromatids and allowing the entry into anaphase.*

5. In **small discussion groups**, have students research "oogenesis cytokinesis" and discuss the value of unequal cytokinesis during oogenesis. Choose representatives from one group to share findings with the class. (LO 18.3.5)

   Answer: *Unequal divisions in the primary oocyte lead to three small polar bodies and one large ovum that contains the bulk of the cytoplasm. The fertilized ovum (now called a zygote) needs the food reserves that come with that cytoplasm.*

Clicker Questions

1. Cytokinesis follows telophase. (LO 18.3.1)
   a. True
   b. False

2. The nuclear envelope breaks down during prometaphase. What happens to the lipid and protein components of the nuclear envelope? (LO 18.3.2)
   a. They are hydrolyzed into simple monomers and reassembled into functional lipids and proteins during telophase.
   b. They form numerous membrane vesicles that are incorporated into the Golgi apparatus during anaphase.
   c. They are exported to neighboring cells, which use the components when they undergo mitosis.
   d. They are incorporated into the endoplasmic reticulum and used to make new nuclear envelopes during telophase.

3. Condensins work by (LO 18.3.3)
   a. forming DNA loops.
   b. complexing with cohesins.
   c. stabilizing the centromere.
   d. phosphorylating microtubulin.

4. Movement through prophase and metaphase is controlled by multiple phosphorylation events. However, progression from metaphase to anaphase requires (LO 18.3.4)
   a. activation of lamin-binding proteins.
   b. activation of APC/C ubiquitin ligase.
   c. proteolytic removal of key regulatory proteins.
   d. removal of inhibitory phosphate groups from the kinetochore.

5. Plant cells form a cell plate during cytokinesis because (LO 18.3.5)
   a. the cell plate has the microtubule binding sites needed for cytokinesis.
   b. the Golgi vesicles cannot deliver material fast enough to the new cell wall.
   c. the plasma membranes of the two daughter cells must be kept apart.
   d. the stiff cell wall cannot be pinched in two.

Answers: *1: b; 2: d; 3: a; 4: b, c; 5: d*

CHAPTER

19

Part IV **Cell Regulation**

Cell Renewal and Cell Death

Chapter Overview

Cell proliferation and cell death occur throughout the life of multicellular organisms. Animal development begins with the rapid proliferation of embryonic cells, which then differentiate to produce the specialized cells that make up adult tissues and organs. Cell proliferation is needed throughout life to replace cells that have died. Many adult tissues contain stem cells that are able to proliferate and differentiate as required for tissue maintenance. The ability of stem cells to differentiate into a wide variety of cell types has generated enormous interest in the potential clinical applications of using these cells to replace damaged tissues.

Although cells can die as a result of unpredictable traumatic events, such as exposure to toxic chemicals, most cell deaths in multicellular organisms occur by a normal physiological process of programmed cell death, which plays a key role both in embryonic development and in adult tissues. Abnormalities of cell death are associated with a wide variety of illnesses, including cancer, autoimmune disease, and neurodegenerative disorders, such as Parkinson's and Alzheimer's disease. The mechanisms and regulation of cell death as well as cell renewal have therefore become areas of research at the forefront of biology and medicine.

Chapter Outline

Section Reviews

19.1 Stem Cells and the Maintenance of Adult Tissues

Most cells in adult animals are arrested in the G_0 stage of the cell cycle. A few types of differentiated cells, including skin fibroblasts, endothelial cells, smooth muscle cells, and liver cells, are able to resume proliferation as required to replace cells that have been lost because of injury or cell death. However, most differentiated cells do not themselves proliferate but can be replaced via the proliferation of stem cells, which divide to produce one daughter cell that remains a stem cell and another that divides and differentiates. Adult stem cells are used clinically in hematopoietic stem cell transplantation. However, clinical applications of adult stem cells are limited by difficulties in isolating and culturing these cells.

19.2 Pluripotent Stem Cells, Cellular Reprogramming, and Regenerative Medicine

Embryonic stem cells can be grown in the undifferentiated state while retaining the ability to differentiate into all of the cell types in an organism. Mammals have been cloned by somatic cell nuclear transfer, in which the nucleus of an adult somatic cell is transplanted into an enucleated egg. This opens the possibility of therapeutic cloning in which embryonic stem cells derived from a cloned embryo could be used for transplantation therapy. Alternatively, adult somatic cells can be converted to pluripotent stem cells in culture by four key transcription factors, bypassing the use of embryonic stem cells for transplantation therapy. Somatic cells can also be converted directly into other differentiated cell types by appropriate combinations of transcription factors.

19.3 Programmed Cell Death

Programmed cell death plays a key role in both the maintenance of adult tissues and embryonic development. In contrast with the accidental death of cells from an acute injury, most programmed cell death takes place by the active process of apoptosis.

Apoptotic cells and cell fragments are then efficiently removed by phagocytosis. The effectors of apoptosis are a family of proteases called caspases, which cleave more than 100 cellular proteins. Members of the Bcl-2 family are central regulators of apoptosis, which either inhibit or promote caspase activation. In mammalian cells, proapoptotic Bcl-2 family members act at mitochondria, where they promote the release of cytochrome *c*, leading to caspase activation. A variety of signaling pathways regulate apoptosis by controlling the expression or activity of members of the Bcl-2 family.

Key Terms

Akt
apoptosis
apoptosome
autophagy
Bcl-2
caspase
embryonic stem cell
hematopoietic stem cell transplantation (bone marrow transplantation)
induced pluripotent stem cell
necroptosis
necrosis
niche
p53
PI 3-kinase
pluripotency
programmed cell death
reproductive cloning
somatic cell nuclear transfer
stem cells
therapeutic cloning
transdifferentiation
tumor necrosis factor (TNF)

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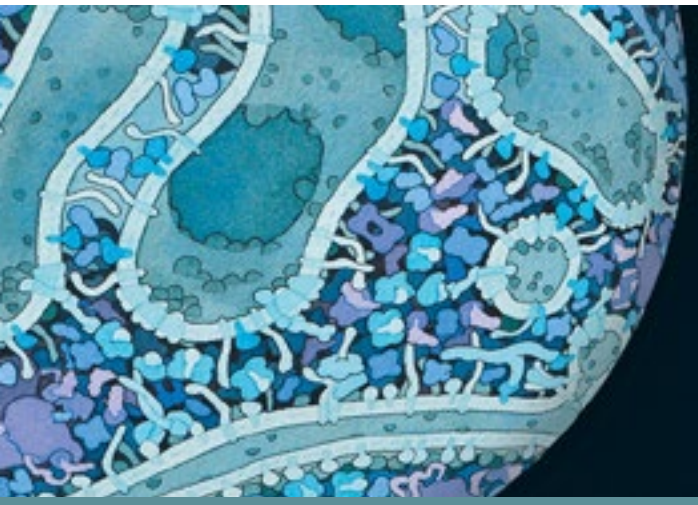

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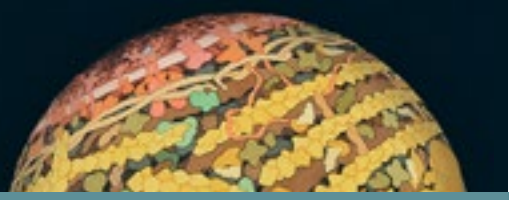
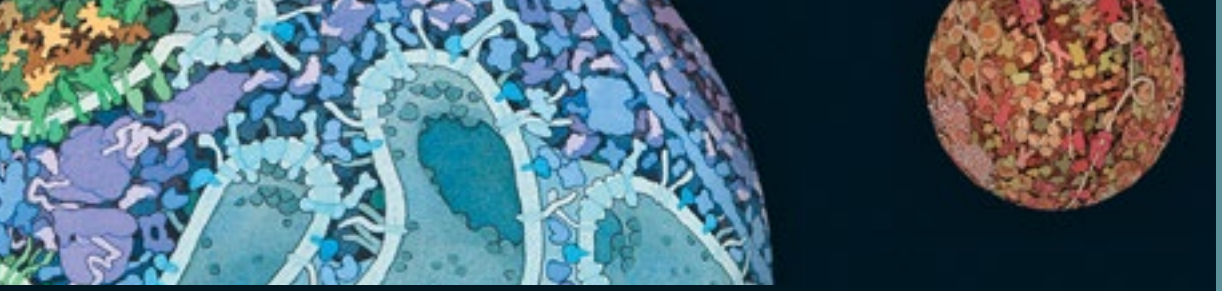




CHAPTER 19: Cell Renewal and Cell Death

Active Learning Activities for the Classroom

19.1 Stem Cells and the Maintenance of Adult Tissues

Learning Objectives

You should be able to:

19.1.1 Give examples of tissue maintenance by the proliferation of differentiated cells.

19.1.2 Summarize the key properties of stem cells.

19.1.3 Explain the role of stem cells in bone marrow transplantation.

Media Available on Companion Website oup.com/uk/cooper8e

Micrograph 19.2 Endothelial cells

Micrograph 19.12b Muscle satellite cells

Key Experiment Culture of Embryonic Stem Cells

Active Learning Exercises

1. Have students use their smart devices to research "plant stem cell" and "meristem," then form **think-pair-share** groups to discuss how plant stem cells are arranged into tissue. Choose a student to present an answer to the class, and solicit comments. (LO 19.1.2)

   Answer: *Plant stem cells are found in meristems, of which there are three types: apical (shoot and root), lateral, and intercalary. Cell division in the apical meristems increases the length of the shoot or root. Lateral meristems increase the girth of the shoot or root. Intercalary meristems are found primarily at the base of grass leaves. This basal growth, as opposed to tip growth, is a response to animal grazing and fires, which remove the tip of the leaf but leave the base.*

2. Have students use their smart devices to research how stem cells are being used in the treatment of Parkinson's disease. Then have them write a **minute paper** on the topic. (LO 19.1.3)

   Answer: *Dopamine is a neurotransmitter produced by certain cells in the brain and involved in the regulation of movement and emotional responses. Parkinson' patients suffer a gradual loss of the dopamine-producing cells. Medical researchers are focusing on reprogramming human stem cells to produce dopamine.*

Clicker Questions

1. The World Anti-Doping Agency (WADA) is an international organization whose mission is to "promote, coordinate and monitor the fight against drugs in sports." WADA has placed vascular endothelial growth factor (VEGF) on its banned list. What type of athlete would probably gain the most from using VEGF? (LO 19.1.1)
   a. A sprinter
   b. A marathon runner
   c. A weight lifter
   d. An equestrian

2. Most adult cells in animals are capable of further cell division and differentiation. (LO 19.1.2)
   a. True
   b. False

3. Transit-amplifying cells are (LO 19.1.2)
   a. undifferentiated cells that multiply rapidly.
   b. undifferentiated cells that divide to form stem cells.
   c. differentiated cells that rarely divide.
   d. differentiated cells that become part of the surface epithelium.

4. At the end of the cell cycle, a stem cell has produced (LO 19.1.2)
   a. two stem cells.
   b. two cells that subsequently differentiate.
   c. one stem cell and one derivative.
   d. two hematopoietic stem cells.

5. As a cancer treatment, chemotherapy is toxic to (LO 19.1.3)
   a. cancer cells.
   b. nerve cells.
   c. muscle cells.
   d. hematopoietic stem cells.

Answers: *1: b; 2: b; 3: a; 4: c; 5: a, d*

19.2 Pluripotent Stem Cells, Cellular Reprogramming, and Regenerative Medicine

Learning Objectives

You should be able to:

19.2.1 Explain the utility of embryonic stem cells in regenerative medicine.
19.2.2 Describe somatic cell nuclear transfer and therapeutic cloning.
19.2.3 Summarize the derivation of induced pluripotent stem cells.
19.2.4 Define transdifferentiation.

Media Available on Companion Website oup.com/uk/cooper8e

Video 19.1 Differentiated Cardiac Beating Cells
Video 19.2 Controlling Stem Cells with Light
Video 19.3 Somatic Cell Nuclear Transfer

Active Learning Exercises

1. Have students research and take notes on the current uses of embryonic stem cells. Then organize the class into "pro" and "con" groups to prepare for a **class discussion** about whether federal funding should be available to support embryonic stem-cell research. Choose a student to facilitate between representatives of the two groups. (LO 19.2.1)

   Answer: *There is no right or wrong answer; the goal is to get students thinking about some of the important implications of cutting-edge cell research.*

2. Have students use their smart devices to research somatic cell nuclear transfer (SCNT), then write a **minute paper** describing epigenetic memory and how it affects SCNT. (LO 19.2.2)

   Answer: *Epigenetic changes are covalent modifications of DNA that may be passed on to progeny. They can "pre-program" a nucleus such that the desired SCNT outcome is not achieved.*

3. Have students prepare a **sequence map** that outlines the steps in the derivation of pluripotent stem cells, including the generation of the genetically engineered retrovirus. (LO 19.2.3)

   Answer: *Sequence maps should reflect a compilation of the information in the captions for Figures 4.26 and 19.16.*

4. Have students use their smart devices to research and write a **minute paper** explaining the key difference between dedifferentiation and transdifferentiation. (LO 19.2.4)

   Answer: *Dedifferentiation is when a mature cell differentiates to a stem cell-like stage. Transdifferentiation is when a mature cell differentiates into a mature cell type without going through the stem cell stage.*

Clicker Questions

1. The most important element in manipulating embryonic stem cells in culture is (LO 19.2.1)
   a. selecting the proper embryo from which to extract the stem cells.
   b. using a growth medium that contains adequate amounts of glucose.
   c. growing the cells under the proper light/dark cycle.
   d. using the appropriate growth factors in the medium.

2. The goal of therapeutic cloning is to (LO 19.2.2)
   a. generate embryonic stem cells for transplant into a suitable recipient.
   b. produce mature cells that can be used to produce antibiotics.
   c. convert adult cells into differentiated cells.
   d. create embryos for transplant into a foster mother.

3. A major advantage of using induced pluripotent stem cells for research and therapeutic applications is that (LO 19.2.3)
   a. it avoids many of the ethical and moral issues that accompany the use of embryonic stem cells.
   b. pluripotent stem cells can be used for many more applications than embryonic stem cells.
   c. pluripotent stem cells can be programmed to "self-destruct" after only a few generations.
   d. it allows researchers to generate immortal lines of self-replicating cells.

4. The process that produces induced pluripotent stem cells is similar to (LO 19.2.3)
   a. dedifferentiation.
   b. transdifferentiation.
   c. epigenetic differentiation.
   d. embryonic stem cell transfer.

Answers: *1: d; 2: c; 3: a; 4: a*

19.3 Programmed Cell Death

Learning Objectives

You should be able to:

19.3.1 Describe the events that characterize apoptosis.
19.3.2 Explain the role of caspases in programmed cell death.
19.3.3 Summarize the activities of Bcl-2 family members.
19.3.4 Describe signaling pathways that prevent and induce apoptosis.
19.3.5 Contrast cell death by autophagy or necroptosis with apoptosis.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 19.1 Apoptosis
Animation 19.2 The Mitochondrial Pathway of Apoptosis
Video 19.4 Apoptosis
Video 19.5 Apoptosis Induced by Fas Activation
Data Analysis Problem 19.1 The Role of Ras in the Prevention of Apoptosis by Growth Factors
Data Analysis Problem 19.2 The Effect of Etoposide on Human Leukemia Cells

Data Analysis Problem 19.3 The Effect of a Metastasis Suppressor Protein on the Response of Cancer Cells to Gamma Irradiation

Data Analysis Problem 19.4 The Role of Apaf-1 Protein in Hyperosmotic Stress

Key Experiment Identification of Genes Required for Programmed Cell Death

Active Learning Exercises

1. Instruct students to prepare a **spider map** with five legs with "caspases" at the center and each leg as one of the targets of caspase action and the result of that action. (LO 19.3.2)

   Answer: *Legs should be labeled: 1) degrade DNase inhibitor (activates DNase); 2) cleave nuclear lamins (destabilizes nuclear envelope); 3) cleave cytoskeletal proteins (disrupts the cytoskeleton, causes blebbing of plasma membrane, and causes cell fragmentation; 4) cleave Golgi matrix proteins (causes fragmentation of the Golgi apparatus; 5) cleave and activate a "scramblase" (translocates phosphatidylserine from the inner to the outer leaflet of the plasma membrane).*

2. Have students prepare a **sequence map** of the steps in mitochondrial-driven activation of apoptosis. (LO 19.3.3)

   Answer: *The answer is found in the caption for Figure 19.23: 1) Bcl-2 is inactivated, which activates the proapoptotic proteins Bax and Bak. Bax and Bak form pores in the mitochondrial membrane, which allows cytochrome c to exit the mitochondrion. Cytochrome c forms an apoptosome with Apf-1 and caspase-9. The apoptosome cleaves and activates downstream effector caspases.*

3. Have students in **small discussion groups** discuss how apoptosis relates to the cell cycle. (LO 19.3.4)

   Answer: *The cell cycle has several checkpoints that look for DNA damage. If DNA damage is found and cannot be repaired, the intrinsic pathway of apoptosis is activated and the cell is destroyed.*

4. Have students write a **minute paper** that compares cell death by autophagy or necroptosis with apoptosis. Allow use of smart devices to research the concepts. Choose a student to present the answer to the class. (LO 19.3.5)

   Answer: *Apoptosis is programmed cell death that does not result in the release of cellular components; thus, there is no inflammation. Autophagy is the degradation and recycling of cell components. It generally does not result in death of the cell. Necroptosis is a "suicide" response in which the cell ruptures and releases its contents, often resulting in tissue inflammation.*

Clicker Questions

1. Apoptosis and necrosis differ in that (LO 19.3.1)
   a. apoptosis is programmed and planned.
   b. apoptosis results from acute injury to cells.
   c. necrosis is under genetic control.
   d. cells that die by necrosis swell, rather than breaking up.

2. Caspases are activated by (LO 19.3.2)
   a. gene activation of relevant transcription factors.
   b. changes in cell pH.
   c. proteolytic cleavage by another caspase.
   d. loss of plasma membrane permeability.

3. A cell that was unable to undergo apoptosis would (LO 19.3.3)
   a. undergo necrosis, instead.
   b. likely become cancerous.
   c. enter the G_0 phase of the cell cycle.
   d. fragment and be removed by a phagocytic cell.

4. In the cell cycle and apoptosis, p53 acts as (LO 19.3.4)
   a. an inhibitor of cyclins, which halts the cell cycle.
   b. an antiapoptotic regulatory protein, which inhibits apoptosis.
   c. an activator of Bax and Bak, which initiates apoptosis.
   d. a growth factor, which stimulates the cell cycle.

5. Autophagy, necroptosis, and apoptosis result in the death of the cell. (LO 19.3.5)
   a. True
   b. False

Answers: *1: a, d; 2: c; 3: b; 4: a, c; 5: b*

Part IV **Cell Regulation**

Cancer

Chapter Overview

Cancer is a particularly appropriate topic for the concluding chapter of this book because it results from a breakdown of the regulatory mechanisms that govern normal cell behavior. As discussed in preceding chapters, the proliferation, differentiation, and survival of individual cells in multicellular organisms are carefully regulated to meet the needs of the organism as a whole. This regulation is lost in cancer cells, which grow and divide in an uncontrolled manner, ultimately spreading throughout the body and interfering with the function of normal tissues and organs.

Because cancer results from defects in fundamental cell regulatory mechanisms, it is a disease that ultimately has to be understood at the molecular and cellular levels. Indeed, understanding cancer has been an objective of molecular and cellular biologists for many years. Importantly, studies of cancer cells have also illuminated the mechanisms that regulate normal cell behavior. In fact, many of the proteins that play key roles in cell signaling, regulation of the cell cycle, and control of programmed cell death were first identified because abnormalities in their activities led to the uncontrolled proliferation of cancer cells. The study of cancer has thus contributed significantly to our understanding of normal cell regulation, as well as vice versa.

Chapter Outline

Section Reviews

20.1 The Development and Causes of Cancer

Cancer can result from the abnormal proliferation of any type of cell. The most important distinction is between benign tumors, which remain confined to their site of origin, and malignant tumors, which can invade normal tissues and spread throughout the body. Tumors develop from single cells that begin to proliferate abnormally. Additional mutations lead to the selection of cells with progressively increasing capacities for proliferation and metastasis. The uncontrolled proliferation of cancer cells is reflected in reduced requirements for growth factors and lack of inhibition by cell–cell contact. The characteristic failure of cancer cells to undergo apoptosis also contributes substantially to tumor development. Radiation and most chemical carcinogens act by damaging DNA and inducing mutations. Viruses also cause cancer in both humans and other species.

20.2 Oncogenes

The first oncogene to be identified was the *src* gene of RSV. Subsequent studies have identified more than two dozen distinct oncogenes in different retroviruses. Retroviral oncogenes are abnormally expressed and mutated forms of normal cell genes, called proto-oncogenes. Cellular oncogenes are activated by point mutations, DNA rearrangements, and gene amplification in human cancers. Some of these human tumor oncogenes, such as the *ras* genes, are cellular homologs of oncogenes that were first described in retroviruses. Many oncogene proteins function as elements of signaling pathways that stimulate cell proliferation. The genes that encode cyclin D1, Cdk4, and Cdk6 can also act as oncogenes by stimulating cell cycle progression. Other oncogene proteins interfere with cell differentiation, and oncogenes encoding PI 3-kinase, Akt, and Bcl-2 inhibit apoptosis.

20.3 Tumor Suppressor Genes

In contrast with oncogenes, tumor suppressor genes inhibit tumor development. Loss or mutational inactivation of tumor suppressor genes, including *Rb* and *p53*, contributes to the development of a wide variety of human cancers. The proteins encoded by most tumor suppressor genes act as inhibitors of cell proliferation or survival. Mutations in both oncogenes and tumor suppressor genes contribute to the progressive development of human cancers. The many different genes that can contribute to tumor development affect the activities of a relatively small number of cell regulatory pathways.

20.4 Molecular Approaches to Cancer Treatment

Genetic testing to identify individuals with inherited mutations in oncogenes or tumor suppressor genes may allow early detection and more effective treatment of high-risk patients. The development of drugs targeted against specific oncogenes has led to the discovery of new therapeutic agents that act selectively against cancer cells. Advances in immunotherapy have led to effective cancer treatments by strengthening the immune response against cancer cells.

Key Terms

abl
adenoma
Akt
angiogenesis
apoptosis
autocrine growth stimulation
Bcl-2
benign tumor
cancer
carcinogen
carcinoma
CAR-T cell therapy
CCND1
cell transformation
clonal selection
c-myc
contact inhibition
density-dependent inhibition
ErbA
*erb*B-2
Fos
immunotherapy
Jun
leukemia
lymphoma
malignant tumor
metastasis
oncogene addiction
oncogene
p53
PI 3-kinase
PML/RARα
polyp
programmed cell death
proto-oncogene
PTEN
raf
ras
Rb
Rous sarcoma virus (RSV)
sarcoma
src
stability gene
tumor
tumor initiation
tumor progression
tumor promoter
tumor suppressor gene
tumor virus

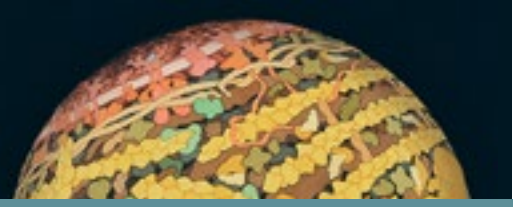
Additional Media and Supplements for Use in the Classroom

Additional instructor materials to help you and your students get the most out of this chapter can be found at oup.com/uk/cooper8e. These include:

All textbook figures and tables (PowerPoint slides and JPEGs)
Test Bank
*Videos**
*Animations**
*Micrographs**
*Flashcards**
*References**
*Web Links**
*Online Quiz**

*Also available to students on the Companion Website

The **Active Learning Guide** that follows will help you create a dynamic learning environment in your classroom. It provides in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the chapter's Learning Objectives.



CHAPTER 20 Cancer

Active Learning Activities for the Classroom

20.1 The Development and Causes of Cancer

Learning Objectives

You should be able to:

20.1.1 Explain the difference between benign and malignant tumors.
20.1.2 Describe tumor progression.
20.1.3 Summarize the properties of cancer cells.
20.1.4 Compare cancer induction by chemicals and viruses.

Media Available on Companion Website oup.com/uk/cooper8e

Animation 20.1 Metastasis of a Cancer
Animation 20.2 Density-Dependent Inhibition
Video 20.1 Normal vs. Cancer Cells
Video 20.2 Breast Cancer Cells Dividing

Active Learning Exercises

1. Have students prepare a **T table** with the terms *benign tumor*, *carcinoma*, *leukemia*, *lymphoma*, *malignant tumor*, *metastasis*, *sarcoma*, and *tumor* in the left column and a definition of each in the right column. Then instruct students, in pairs, to quiz each other on the definitions. (LO 20.1.1)

   Answer: *Definitions are in the textbook glossary.*

2. Have students write a **minute paper** that defines clonal selection in the process of tumor progression. (LO 20.1.2)

   Answer: *Clonal selection is the process by which random mutations in tumor cells confer a selective advantage to certain cell lines. Those cells (clones) eventually dominate the tumor population.*

3. Provide students with Column 1 in the **matrix** below, and instruct them to complete the other two columns comparing the properties of normal cells and cancer cells for each of the processes. (LO 20.1.3)

   Answer: *See matrix, below.*

Process	Normal cells	Cancer cells
Density-dependent inhibition	Cease growth and enter G_0 phase upon depletion of growth factors in medium	Continue growth in absence of growth factors
Contact inhibition	Cease growth and enter G_0 phase when contacting neighboring cell	Continue growth after cell–cell contact
Autostimulation of cell division	Do not produce their own growth factors	Produce their own growth factors (autocrine growth stimulation)
Cell–cell and cell–matrix interactions	Strong adhesion mediated by cell surface adhesion molecules	Weak adhesion due to reduced expression of cell surface adhesion molecules
Secretion of extracellular matrix proteases	Do not secrete extracellular matrix proteases	Secrete proteases to break down extracellular matrix
Secretion of angiogenic factors	Do not secrete angiogenic factors	Secrete angiogenic factors to stimulate the supply of capillaries to tumor
Differentiation	Normal differentiation into mature cell types	Defective differentiation, may remain in the stem cell stage
Programmed cell death	Present and under normal control	Lacking, giving long life to cancer cells
Telomerase	Low levels that limit the number of cell division	High levels that maintain telomer integrity over many cell divisions

4. Have students form **small discussion groups** to research and discuss epidemiology and the limitations of epidemiological studies. Choose one group to present findings to the class. (LO 20.1.4)

   Answer: *From the World Health Organization,* "Epidemiology is the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. Various methods can be used to carry out epidemiological investigations: surveillance and descriptive studies can be used to study distribution; analytical studies are used to study determinants." *An epidemiological study can find correlation between a risk factor and a disease but cannot show causation.*

Clicker Questions

1. Benign tumors are cancerous. (LO 20.1.1)
   a. True
   b. False

2. What would happen if the basal lamina of the colon epithelium were weakened? (LO 20.1.2)
   a. Adenomas (polyps) would spread to nearby internal organs.
   b. Rapidly growing clones would be selected against and die off.
   c. It would be easier for carcinoma cells to metastasize.
   d. The rate of clonal mutation would increase.

3. A fundamental characteristic of cancer cells it that they (LO 20.1.3)
   a. are capable of growth in the absence of a food source.
   b. have lost control over mitosis.
   c. are capable of growth in the absence of oxygen.
   d. have lost control over the cell cycle.

4. Angiogenesis is important to cancer cells because (LO 20.1.3)
   a. it increases oxygen supply to the tumor.
   b. it increases nutrient supply to the tumor.
   c. it increases cancer cell access to the vascular system.
   d. it increases the metastatic capabilities of the cancer cells.

Answers: *1: b; 2: c; 3: d; 4: a, b, c, d*

20.2 Oncogenes

Learning Objectives

You should be able to:

20.2.1 Explain how retroviral oncogenes were identified.
20.2.2 Contrast oncogenes and proto-oncogenes.
20.2.3 Describe the ways in which oncogenes are formed in human cancers.
20.2.4 Summarize the functions of oncogene proteins.

Media Available on Companion Website oup.com/uk/cooper8e

Data Analysis Problem 20.2 The Enzyme Activity Associated with an Oncogenic RNA Virus

Key Experiment The Discovery of Proto-Oncogenes

Active Learning Exercises

1. Have students write a **minute paper** that describes the source of retroviral oncogenes that cause cancer in humans. Students may wish to review Chapter 4 for information on retroviruses. (LO 20.2.1)

   Answer: *When retroviruses infect a human cell, they replicate by RNA-directed DNA synthesis. The viral "DNA" is intercalated into the host genome, where those genes are transcribed to make multiple copies of viral RNA. Occasionally, human proto-oncogenes are mistakenly transcribed and added to the viral genome. All progeny viruses will then carry the human proto-oncogene.*

2. Have students form **small discussion groups** to consider why a human cell would contain potentially dangerous proto-oncogenes. Choose a group to present conclusions to the class. (LO 20.2.2)

   Answer: *Proto-oncogenes are normal genes that are under strict control and code for cell regulatory proteins. They are essential for normal cell activity and division. Loss of control of these genes converts them to oncogenes.*

3. Have students prepare a **sequence map** showing the steps in the functioning of *ras* oncogenes. (LO 20.2.3)

   Answer: *The ras genes encode guanine nucleotide-binding proteins that play a role in control of the cell cycle and switch between active (GTP-bound) and inactive (GDP-bound) states. 1) A mutation in a ras gene converts it to the active (GTP-bound) state. 2) The mutated Ras protein can no longer be inactive by GAP (GTPase-activating protein). 3) The oncogenic Ras proteins remain in the active GTP-bound state and drive unregulated cell proliferation.*

4. Have students form **small discussion groups** to research and evaluate whether acute promyelocytic leukemia is an inherited disorder. Then, solicit an explanation from the class. (LO 20.2.4)

   Answer: *Acute promyelocytic leukemia is not an inherited disorder. The mutations that lead to acute promyelocytic leukemia occur in somatic cells and cannot be inherited.*

Clicker Questions

1. While there are similarities, the main difference between avian leukosis virus (ALV) and Rouse sarcoma virus (RSV) is that (LO 20.2.1)
   a. only RSV causes cancer.
   b. only RSV causes cell transformation.
   c. ALV induces cancer, whereas RSV is merely infectious.
   d. both viruses cause cancer, but ALV uses reverse transcriptase.

2. Many retroviral oncogenes are chimeras of viral and host DNA. (LO 20.2.2)
   a. True
   b. False

3. Proto-oncogenes may be converted to oncogenes by (LO 20.2.3)
   a. G_0 arrest.
   b. *ras* gene products.
   c. translocations.
   d. mutations.

4. Because signaling pathways can contain multiple components, they may be susceptible to activation via different oncogenes. (LO 20.2.4)
   a. True
   b. False

Answers: *1: a, b; 2: a; 3: c, d; 4: a*

20.3 Tumor Suppressor Genes

Learning Objectives

You should be able to:

20.3.1 Contrast tumor suppressor genes and oncogenes.

20.3.2 Give examples of the functions of tumor suppressor gene products in signal transduction, cell cycle progression, and cell survival.

20.3.3 Explain the major types of genetic alterations in human cancers.

Media Available on Companion Website oup.com/uk/cooper8e

Video 20.3 Tumor Suppressor Gene Regulation

Active Learning Exercises

1. Have students write a **minute paper** that contrasts tumor suppressor genes and proto-oncogenes. (LO 20.3.1)

   Answer: *Tumor suppressor genes must be inactivated for cancer to develop. Proto-oncogenes must be activated for cancer to develop.*

2. Provide students with the first column of the **T table** below and have them complete the second column. (LO 20.3.2)

   Answer: *See below.*

Gene(s)	Process affected
Rb tumor suppressor genes *INK4* tumor suppressor gene	Cell cycle progression
PTEN tumor suppressor gene	Cell survival
Smad tumor suppressor genes	Transcriptional regulation
p53 gene product	Cell cycle progression and apoptosis
BRCA1 and *BRCA2* genes	Cell cycle progression and DNA repair

3. Have students form **small discussion groups** to consider how the development of one type of cancer can be under the influence of several different oncogenes. (LO 20.3.3)

   Answer: *Many cell proliferation signaling pathways have multiple, sequential components. A mutation of any of the genes in that pathway will lead to the same cancer.*

Clicker Questions

1. About 50 percent of the genes that contribute to human cancers are tumor suppressor genes and half are oncogenes. (LO 20.3.1)
   a. True
   b. False

2. The development of retinoblastoma requires which two things? (LO 20.3.1)
   a. The conversion of a proto-oncogene to an oncogene
   b. The inheritance of a defective copy of the *Rb* gene
   c. A somatic mutation in the normal *Rb* gene
   d. The inheritance of two mutated alleles for the Rb protein

3. How are many tumor suppressor genes and oncogenes functionally related? (LO 20.3.2)
   a. They often act synergistically.
   b. They often act antagonistically.
   c. They often act in alliance.
   d. They often act in sequence.

4. Genome-scale sequencing of cancer patients can be used to reveal (LO 20.3.3)
   a. the genetic history of the patient and his/her parents/children.
   b. the anticipated life expectancy of the patient.
   c. the oncogenes involved in a particular type of cancer.
   d. the relationships between different oncogenes.

Answers: *1: a; 2: b, c; 3: b; 4: c, d*

20.4 Molecular Approaches to Cancer Treatment

Learning Objectives

You should be able to:

20.4.1 Explain the importance of early diagnosis.
20.4.2 Describe the basis for selectivity of oncogene-targeted drugs.
20.4.3 Summarize strategies of immunotherapy.

Media Available on Companion Website oup.com/uk/cooper8e

Data Analysis Problem 20.1 The Effect of the BCR-ABL in Hematopoietic Cells
Data Analysis Problem 20.3 Analysis of the Effect of Gleevec
Molecular Medicine Imatinib: Cancer Treatment Targeted against the *bcr/abl* Oncogene

Active Learning Exercises

1. Assign one-quarter of the class to consider each of the following approaches to reducing health care costs in the United States: 1) Expanding cancer prevention efforts; 2) Expanding early detection programs; 3) Expanding chemotherapy treatments; 4) Expanding genetic screening. Allow 10 minutes for students to discuss their assigned approach and **compose a brief argument** to support it, then choose one representative to present each group's case to the class. Finally, have students use clickers to "vote" on the best approach. (LO 20.4.1)

   Answer: *There is no right answer, though the first and last approaches are best supported by the textbook. The idea is to get students to reflect on their reading and to consider the larger implications of scientific data on health policy and the economy.*

2. Have students research and write a **minute paper** on colonoscopy: what it is, how it works, and the current alternatives. (LO 20.4.1)

   Answer: *A colonoscopy uses a long, flexible camera to look for polyps and cancerous growth on the inner wall of the colon. Prior to the procedure, a patient typically uses laxatives to clean out the colon and make viewing easier. The patient is anesthetized and asleep during the procedure. Alternatives include at-home test kits, in which a stool sample is collected and sent to a laboratory to test for blood and other indicators of pre-cancerous or cancerous growths.*

3. Have students write a **minute paper** to explain how a tumor cell can become addicted to an oncogene. (LO 20.4.2)

   Answer: *Once an oncogene takes control of a major signaling pathway in a cell, the other pathways are less important. Therefore, targeting a drug to the oncogene protein product can have important clinical implications.*

Clicker Questions

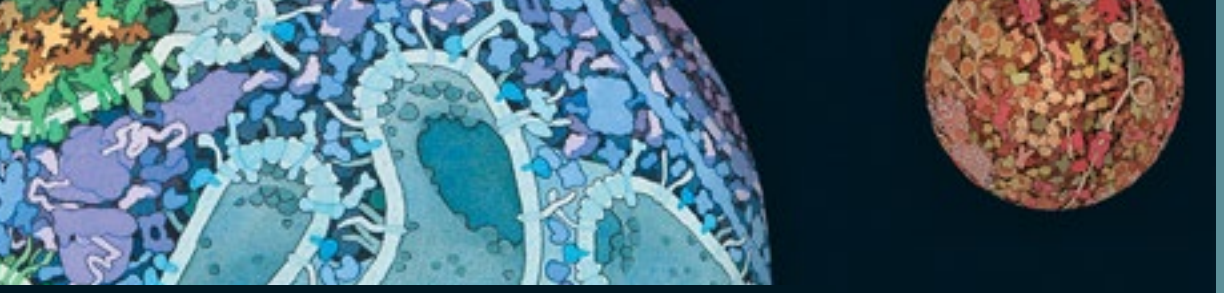
1. Adenomas in the colon are easy to detect early because (LO 20.4.1)
   a. blood in the stool is one of the first symptoms of colon cancer.
   b. they start in the colon epithelium, so the adenomas are on the surface.
   c. adenomas cause changes in one's appetite that are easy to recognize.
   d. lethargy and sleeplessness accompany adenoma development.

2. Most oncogene-targeted drugs inhibit protein kinases because (LO 20.4.2)
   a. protein kinases are key elements in the pathways that oncogenes disrupt.
   b. oncogenes use protein kinases to regulate their expression.
   c. protein kinases are the main extracellular proteins that recognize oncogene binding.
   d. oncogenes target protein kinases with an immuno-like cross reaction.

3. Viruses used to transform a patient's T cells with the CAR gene because (LO 20.4.3)
   a. viruses are too large to circulate in the patient's bloodstream.
   b. viruses are better at introducing foreign DNA into a cell than doctors are.
   c. T cells are easy to isolate from a patient's blood and grow in culture.
   d. T cells are immune to all other forms of transformation.

4. Immunotherapy differs from chemotherapy in that immunotherapy (LO 20.4.3)
   a. uses chemical treatments to boost the patient's immune system.
   b. uses antibodies to cross-react with oncogene receptor proteins on the cell surface.
   c. disables the patient's immune system to increase the efficacy of the chemotherapy treatment.
   d. seeks to use the patient's own defenses against the tumor cell.

Answers: *1: b; 2: a; 3: b; 4: d*



Appendix A: The Science of Active Learning

Major Reports and Initiatives That Recommend Active Learning

Active learning is recommended by most leading science organizations, and several reports provide guidelines for increasing active learning in science education. A 1991 report by the Association for the Study of Higher Education (ASHE) asserted that students must be engaged in problem solving, discussions, and writing in order to be active in the learning process, and that these types of activities better engage students in the kinds of higher-order thinking that instructors aim for (Bonwell and Eison, 1991).

Now, nearly all of the major stakeholder organizations in the sciences and science education have conducted their own evaluations about how best to educate future scientists and create scientifically literate citizens. The often-cited Vision and Change report by the American Association for the Advancement of Science (AAAS, 2011) listed four major directives for change: (1) integrate core concepts and competencies throughout the curriculum, (2) focus on student-centered learning, (3) promote a campus-wide commitment to change, and (4) engage the biology community in the implementation of change. In each of these directives, active learning is either specifically recommended or the practice is supported. The second directive explicitly encourages instructors to create "active, outcome oriented, inquiry driven" courses that include cooperative elements and many different types of instruction. The first directive supports active learning by addressing a common complaint among instructors—that the additional time used in active learning activities prevents instructors from teaching other content areas in their courses. This report argues that indeed there should be a reduction in the number of concepts taught in a course but that the concepts retained should be covered in greater depth, a philosophy well suited for an active learning classroom. Directives three and four address how the entire college community must be behind this effort, by rewarding effective and innovative teaching, encouraging faculty to design authentic learning experiences that include undergraduates in research, and providing training on teaching and learning to all science faculty, postdocs, and graduate students (AAAS, 2011).

On the heels of the Vision and Change report, the President's Council of Advisors on Science and Technology published Engage to Excel (PCAST, 2012). Echoing many of the ideas about the types of changes that should be made, the PCAST report framed its argument as a means to address a problem of future employment: How can educational changes help prevent the predicted shortage of 1 million STEM majors over the next decade (Lacey and Wright, 2009)? Its first recommendation was to improve STEM education by increasing active learning and student engagement, focusing specifically on foundational courses taken in the first year of college. Consequently, such efforts would address the loss in STEM majors by reducing the high attrition rate of STEM majors

early in their college careers, which has been linked to poor performance and negative experiences in introductory courses (Seymour and Hewitt, 1997). The PCAST report suggests that reaching this goal will require "widespread adoption of empirically validated teaching practices" and cites active learning as an essential evidence-based practice (PCAST, 2012).

Likewise, *A Framework for K–12 Science Education* (NRC, 2012) also considers active learning paramount for achieving its goals. Published by the National Academy of Sciences (NAS) and the National Research Council (NRC), the Framework concludes that active learning enhances student learning and thus should be a key focus within all science classrooms. The Framework also includes a comprehensive description of all of the science concepts that students should learn, and these ideas serve as the foundation for the Next Generation Science Standards.

The College Board, though it does not directly address teaching practices, clearly supports active learning methods in the teaching of Advanced Placement (AP) Biology and seems to assume that AP Biology teachers will teach interactively. The AP Biology course description urges movement away from memorization and toward deep conceptual learning, and it notes that this requires that the course will cover less material. This philosophy is directly in line with the goals and outcomes of active learning. The AP Biology Science Practice goals also engage students as active participants in class. For example, Science Practice 1 states that "the student can use representations and models to communicate scientific phenomena and solve scientific problems." The College Board is even more explicit in that it notes that students should build 3-D models and diagram biological processes, skills that would be difficult to master by simply listening to a lecture and would be best achieved through active practice and hands-on demonstrations (College Board, 2015). In this way, though the AP standards do not directly discuss the types of teaching strategies to be employed, it is clear that they are best suited for an active learning class.

Studies Demonstrating the Effectiveness of Active Learning

In the past several years, numerous studies have examined the efficacy of active learning practices for science teaching. With rare exceptions, these studies have found clear benefits for students in active learning classrooms as compared with lecture-based courses, and the types of benefits are varied.

STUDENT LEARNING GAINS Most studies of active learning look at differences in student performance. The best-designed of these types of studies include two or more course sections taught by the same instructor during either the same or successive semesters and compare the performance of an experimental group taught using active learning with that of a control group taught in traditional lecture format. Normalized learning gains in content knowledge are measured by differences in the scores of pre- and post-activity or pre- and post-semester assessments. Knight and Wood (2005) found that students in a developmental biology course taught via active learning techniques showed significantly higher learning gains than students in the lecture-based course, with 33% improvement from pre- to post-test.

Active learning has also been examined extensively in college physics courses, and studies with similar structure (and enormous data sets) have demonstrated increased

learning gains of up to two times greater in courses using peer instruction (see Vickrey et al., 2014) and other active learning methods than in traditional lecture courses (Hake, 1998; Crouch and Mazur, 2001). A recent meta-analysis of 255 studies across STEM disciplines found the impact of active learning on student performance to be dramatic: students participating in active learning classes scored half a letter grade (~6%) higher on exams, while students in traditional lecture classes were 1.5 times more likely to fail the course (Freeman et al., 2014).

REDUCING THE ACHIEVEMENT GAP Another compelling benefit of active learning is that underrepresented groups receive an additional advantage. Women, first-generation college students, and people of color not only are less likely to major in STEM and more likely to leave STEM fields, but also earn lower grades in STEM courses (Chen, 2013; PCAST, 2012; Sharkness et al., 2010). Active learning helps narrow the gap in academic achievement for these students, leveling the playing field and helping to retain diversity in STEM graduates. Several studies have shown that students from disadvantaged educational, social, or economic backgrounds receive the greatest benefit from active learning. Haak et al. (2011) examined the final course grades in introductory biology and found that the mean achievement gap between disadvantaged and non-disadvantaged students dropped from 0.80 grade points in the lecture course to 0.44 grade points in the active learning course (on the standard 4.0 grade point scale), representing a 45% reduction. In this study, students in the experimental group were members of a specific program targeting students who were either educationally or economically disadvantaged—most were first-generation college students, and more than three-fourths were underrepresented ethnic minorities. Similarly, Eddy and Hogan (2014) found that increasing active learning and course structure cut the achievement gap in half between black and white students and eliminated it entirely between first-generation and continuing-generation students.

Active learning also reduces the achievement gap between genders. In a study of high school physics courses in classrooms across the United States, Lawrenz et al. (2009) found that active learning reduced the gap between the final grades of boys and girls. Another study tested the effects of a flipped classroom structure (where lecture viewing is moved to pre-class assignments and replaced with active learning during class) in a college chemistry course. Gross et al. (2015) found that female students scored 4–5 percentage points lower than male students on all exams in a traditional, lecture-based classroom; however, in a class that utilized the flipped-classroom method, there was no significant difference between exam scores by gender.

In a recent study that examined academic achievement across a wide range of STEM courses at a single institution, Reimer et al. (2016) found that first-generation college students' performance improved in subsequent STEM courses after they took just one active learning course. This highlights another obvious benefit to active learning—when students become active participants in their own learning, they develop transferable skills (metacognition, critical thinking, problem solving) that help them to succeed in the future (Quitadamo et al., 2008). In addition, students in active learning classes express greater self-efficacy, which may help build motivation to persevere through more challenging courses (Wilke, 2003).

STUDENT ENGAGEMENT AND INTERACTION Many studies have found that active learning enhances student attitudes and that most students have a positive opinion of the method and believe it helps them learn. Active learning methods improve students' feelings of engagement and enjoyment in science courses (Armbruster et al., 2009). A few studies have reported that students particularly enjoy the use of personal response devices in the classroom and believe that they facilitate learning (Knight and Wood, 2005; Preszler et al., 2006). Furthermore, when their use is gamified and includes peer competition, students overwhelmingly (85%) report increased engagement in class (Pettit et al., 2015). These feelings of engagement and enjoyment may be a contributing factor to the reduction in student attrition observed in courses that use technology for collecting student responses in the classroom (reviewed in Caldwell, 2006).

Since active learning methods often involve group work and peer interaction, their implementation helps to form stronger social connections among students in a class. Frequent group work also builds accountability in many students and encourages them to come to class prepared. Smith et al. (2011) found that students in active learning classes were more likely to complete assigned pre-class reading. For students who are better prepared, there is an opportunity to take on mentoring roles within the classroom. This is possible in any course where teams of students collaborate, and some instructors also assign peer-learning assistants to facilitate group work in large-enrollment courses (Otero, 2006).

With all of the demonstrated benefits of active learning, it is no wonder that so many major organizations are pushing for the transformation of STEM courses to include these methods. Fortunately for instructors, there are countless resources available, from workshops and training institutes to websites and books, to help them adjust their courses for better student engagement and success. Instructors interested in developing skills in active learning techniques should consider attending the Summer Institutes on Scientific Teaching, held annually at sites across the United States. At these intensive five-day workshops, participants work together to create tangible products for implementation in active learning courses.

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Appendix B: Options for Active Learning Course Design

If you're curious about active learning but not prepared to engage fully from the start, you'll find tips here about easing into the active learning model.

Backward Course Design

Think of the way students experience a typical course: They receive an email or see a link on a registration page about required texts. By the first day of class, they receive a course syllabus. They spend a few weeks reading, doing homework, participating in activities, listening to lectures, etc. They take an exam.

These steps mirror the way many instructors prepare their courses. They choose a text (or one is chosen for them), flip through the book, and build a schedule of which chapters will be covered on which days. They make some PowerPoint slides, design homework and activities, and go into the classroom. Then, a few days before the first exam, they think to themselves, "Now what did I focus on, and what should I ask the students on the exam?" Using this standard course design, the learning objectives are established last, after most of the teaching is done, formed by the questions chosen for the exam. This method can be done well, but it can also cause a lot of stress for the instructor and, more importantly, it may not facilitate the desired learning by the students.

Backward course design reverses the sequence of tasks to focus the course, and all of its elements, on a set of well-considered learning objectives. It serves to align the daily elements of a course (readings, homework, activities, lectures) with the specific learning objectives that were established at the *start* of the semester. Connecting each activity to an assessment of a learning objective makes crafting effective and informative exams much easier. This student-centered method communicates to students what the learning goals are and how they can show that they have met them.

The concept of backward course design was first put forth by Wiggins and McTighe (1998) in their book *Understanding by Design*. They describe the process in three steps: (1) identify the desired results (learning objectives); (2) determine what evidence will demonstrate mastery of those objectives (assessments); and (3) plan learning experiences to provide students with the instruction and practice needed to achieve mastery (readings, homework, activities, lectures).

Backward course design is widely recommended as a method of instructional design, and several studies have documented its positive effects. Its use has been shown to facilitate the planning of brand-new lessons (Stiler, 2009), to improve teachers' feelings of preparedness, particularly for new teachers (Graff, 2011), and to encourage instructors to focus on outcomes rather than daily activities (Shumway and Berrett, 2004). Instructors trained in using backward course design also demonstrate improved content knowledge, set more appropriate goals for student learning, and better connect ideas across the curriculum (Kelting-Gibson, 2005).

Backward course design should be applied using a whole-course view, and it can also be used to ensure that individual units are well aligned. Let's consider how to apply backward course design to one unit in a hypothetical course.

ESTABLISH LEARNING OBJECTIVES The framework for measuring learning begins with a set of specific learning objectives (e.g., Summarize the action of telomerase.). You

may choose to use *The Cell*, Eighth Edition learning objectives, identify objectives based on recommendations from outside sources, or create your own.

DETERMINE EVIDENCE OF LEARNING Next, decide what evidence a student must provide to demonstrate that he or she has mastered the learning objectives. This often takes the form of summative assessments, such as exams or graded projects. Media resources that accompany *The Cell*, Eighth Edition, include a variety of measurement tools, such as textbook questions, Data Analysis Problems, active learning exercises, online quizzes, and test banks. Consider the level of mastery you would like students to reach for a particular concept. Bloom's Taxonomy (see Appendix C) describes six levels of learning that lead to complete mastery of a concept, starting with lower-order skills like basic retention of facts (remembering) and ending with higher-order skills, such as the ability to synthesize information (evaluating/creating). You may want to write multiple learning objectives at different levels or choose one level as the goal for a specific unit. However they are formed, good learning objectives should incorporate clear action verbs to describe what students should be able to *do*, not just what they know or understand. Knowing and understanding are not clearly measurable.

Small Steps

For instructors who may already have a complete lecture-based curriculum established, the prospect of overhauling a course can seem daunting. Rest assured, many seasoned educators have taken on the challenge with great success and, ultimately, joy. Taking small steps to incorporate active learning can help make the transition easier. For those already doing active learning, you may take small steps when trying new techniques or refreshing tired activities.

It is not always practical to commit to designing/redesigning your entire course using the backward course design method. Including even small pieces of active learning into your course will yield benefits. Each chapter in this Active Learning Guide contains numerous suggestions for short in-class activities, discussion questions, and supplementary media. These are easy to introduce into existing course lectures without doing a complete overhaul of your slides. Each chapter has its own unique collection of suggestions, and you can start small by incorporating one or two into your existing lectures each day.

Sacrificing class time is a frequent concern for those starting out in active learning. Assigning pre-class videos and media resources is a good way to make time for activities in the classroom. When students come to class better prepared, the need for information delivery is reduced, so lecture time can focus on only the most essential or most challenging material.

Fully Flipped Classroom

At the other end of the spectrum from the traditional lecture-based course, a flipped class is one in which virtually no lecture takes place during class meetings. Instead, students watch videos before class to replace lectures, and they work on activities in class. Some instructors make their own videos of lectures, while others curate

collections of videos available online. Most flipped classrooms make use of group work and incorporate any and all varieties of active learning strategies in class, many of which are described in this manual.

One of the key advantages of the flipped model is that the main content of the course (the lectures, now in video form) is always available to students. They can watch an entire lecture again or skip to a part that provides the reinforcement they need. Another major benefit is that the assignments used in class can be more challenging, because the activity is taking place in class where the instructor is available for guidance. Instructors can task students with mastering simple concepts on their own, learned outside of class through videos and readings, and save the tough material for group activities in class.

If you want to learn more about how a flipped class operates, there are myriad opportunities for professional development on the subject. Most university teaching and learning centers have online resources and/or host seminars on the topic, and in recent years, it seems that every major teaching conference includes sessions from instructors who have flipped their courses.

If you are teaching a flipped class, assign students pre-class readings, media, and videos; assess student understanding with pre-quizzes; use activities and wrap-up questions in class; and assign post-quizzes after class. Disseminate information via your school's webpage or learning management system (LMS).

Hybrid Classroom

The model of the hybrid classroom moves much of the coursework online, reducing the face-to-face time requirement for the course. It is different from the flipped model, where the types of activities done at home and in class are reversed but the amount of in-person class time does not change. If, for example, a course typically met two hours per week in person, the hybrid version of that course might meet on campus for one hour and students would complete additional work online for the second hour.

The kinds of activities that are done in person versus online can vary widely in hybrid courses. The in-person sessions may be used for lecture and class discussions, saving activities and quizzes to be done independently online. Or the lectures may be viewed online, with face-to-face meetings reserved for group activities and assessments. For courses that combine lecture and laboratory sections, hands-on lab activities are often conducted in person, and lecture and other independent work is moved online. This model can also be an effective way to overcome space and scheduling challenges, as lecture sections for lab courses at universities often have large enrollments and require large spaces, while lab sections are typically smaller and have their own dedicated facilities.

The online portion can include videos, multimedia resources, activities, and quizzes. In person, instructors can implement this manual's Active Learning Exercises and Clicker Questions, as well as lectures and discussions of their own design. Any inclusion of active learning in a course is a good thing, and the materials in this guide and in the ARC are ready-to-use options for getting your students engaged and thinking critically about course concepts. Whichever structure your class takes, from lecture-based to flipped to hybrid, and whatever your goals are for implementing active learning, the instructor materials provided here are intentionally varied and adaptable, so you have many options to fill content needs, both in and out of the classroom.

Recommended Resources

Handelsman, J., S. Miller, and C. Pfund. 2007. *Scientific teaching*. New York: W.H. Freeman and Company.

This text offers step-by-step guidance for science educators to create "teachable units" using backward course design.

Crowe, A., et al. 2008. Biology in bloom: Implementing Bloom's taxonomy to enhance student learning in biology. *CBE—Life Sciences Education* 7: 368–381.

This paper describes how to apply Bloom's taxonomy to biology courses and suggests dozens of activities aimed at each level, for individual or group assignments.

University of Washington http://www.washington.edu/teaching/teaching-resources/engaging-students-in-learning/

This resource from the University of Washington Center for Teaching and Learning covers many aspects of active learning, including flipping the classroom, teaching with technology, and large lecture instruction. It also provides many links to other excellent materials.

Videos

Bozeman Science www.bozemanscience.com/

Paul Anderson, a 20-year science educator, has created hundreds of videos on all kinds of science topics, including more than 100 in biology. These videos are more like traditional lectures and go into great depth on even small topics.

Crash Course Biology www.youtube.com/playlist?list=PL3EED4C1D684D3ADF

This YouTube channel, hosted by Hank Green, includes 40 videos that cover nearly every topic covered during a yearlong biology course, injected with humor and sarcasm.

PenguinProf www.youtube.com/user/ThePenguinProf

Valerie Pennington, Professor of Biology at Southwestern College, has created a rich collection of videos on biology content, history of biological discoveries, and skill tutorials.

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Appendix C: An Overview of Bloom's Taxonomy

> *"The major purpose in constructing a taxonomy of educational objectives is to facilitate communication."*
>
> —Benjamin S. Bloom, *Taxonomy of Educational Objectives*, 1956

In the 1950s, Dr. Benjamin Bloom and a team of educators created Bloom's Taxonomy of Educational Objectives as a pedagogical tool to standardize educational measurement and to stimulate higher levels of thinking and learning (e.g., analyzing and evaluating concepts rather than simply recalling stated facts). The resulting Bloom's hierarchy and its 2002 revision have been used widely across the field of education as a means of supporting meaningful curriculum planning, instruction, and assessment. *The Cell*, Eighth Edition uses Bloom's taxonomy throughout the Test Bank to ensure that questions address various cognitive levels of knowledge—from simple to complex and from concrete to abstract.

Bloom's taxonomy employs six levels. Mastery at each level requires general mastery at the level before it. Levels 1 through 3 are considered lower-order skills, requiring simple recall and application of instructional material. Levels 4 through 6 are considered higher-order skills that involve critical thinking and creative problem solving.

Understanding and employing the principles of Bloom's Taxonomy will help you generate meaningful and engaging materials for your active-learning classroom. As you prepare to teach each concept, consider the depth of knowledge you'd like students to take from the lesson, then direct your planning accordingly. For example, you may want students to memorize terms and diagrams for a unit on cell structure. Memorization, a valid "building-block" goal, is a lower-level cognitive skill (Bloom's Category 1). A more conceptual topic, such as stem-cell research, would lend itself well to the higher-level skills of analysis and evaluation (Bloom's 4 and 5). By identifying appropriate learning goals, you'll find it easier to prepare and choose pre-class materials, in-class activities, and assessments to achieve your objectives.

The six Bloom's levels are described below. Examples of keywords indicate the depth of understanding required to answer questions at each level.

Level 1: Remembering Students retrieve and repeat information from long-term memory. (Information is explicitly stated in the text or other course content.)

> ***Keywords:*** define, describe, enumerate, find, identify, label, list, match, name, recall, recognize, record, reproduce, retrieve, select

Level 2: Understanding Students demonstrate an ability to construct meaning from acquired knowledge. (Questions are based on information covered in the text, but they require mental processing beyond simple recall.)

> ***Keywords:*** cite, classify, compare, contrast, convert, demonstrate, describe, discuss, estimate, explain, extend, generalize, give examples, illustrate, infer, interpret, make sense of, outline, paraphrase, predict, relate, restate (in own words), show, summarize, translate

Level 3: Applying Students solve problems and carry out procedures by utilizing knowledge, facts, techniques, and rules in a new way. (Learned information is applied to a novel situation.)

> ***Keywords:*** act, administer, apply, articulate, assess, build, calculate, chart, choose, classify, collect, compute, construct, contribute, control, demonstrate, determine, develop, discover, draw, establish, execute, experiment with, extend, illustrate, imple-ment, include, inform, instruct, interview, make use of, model, operationalize, organize, participate, plan, predict, prepare, preserve, produce, project, provide, relate, report, select, show, solve, teach, transfer, use, utilize

Level 4: Analyzing Students examine data or other material to determine how parts are related and what they indicate in a larger context. (Questions may require use of data from graphs and tables, working through a given problem, or extrapolating from the information given.)

> ***Keywords:*** analyze, assume, break down, categorize, classify, compare, conclude, contrast, correlate, deconstruct, diagram, differentiate, discover, discriminate, distin-guish, divide, examine, explain, find relationships, group, illustrate, infer, inspect, inte-grate, make distinctions, order, organize, outline, prioritize, recognize, select, separate, sequence, simplify, subdivide

Level 5: Evaluating Students make independent judgments and justify positions based on established criteria and reasoned thought. (Results might include a subjective but well-informed conclusion.)

> ***Keywords:*** agree, appraise, assess, award, check, choose, compare, conclude, contrast, convince, criticize, critique, decide, defend, determine, disprove, evaluate, influence, interpret, judge, justify, measure, prioritize, prove, rank, rate, recommend, reframe, select, support, value

Level 6: Creating Students work toward solutions by designing, describing, or creating practical experiments, diagrams, models, and other original materials. (Possible responses include a sketch, a new hypothesis, an experimental design, a plan, or a model.)

> ***Keywords:*** adapt, anticipate, categorize, change, collaborate, combine, commu-nicate, compile, compose, construct, create, design, develop, devise, elaborate, express, facilitate, formulate, generate, hypothesize, imagine, improve, incorporate, individualize, initiate, integrate, intervene, invent, model, modify, negotiate, plan, pro-duce, progress, propose, rearrange, reconstruct, reinforce, reorganize, revise, solve, structure, substitute, validate

Sample questions at each Bloom's level

1. Histone genes have
   a. a single long intron.
   b. no introns.
   c. larger introns than exons.
   d. larger exons than introns.

   Bloom's Category: *1. Remembering*

2. The MDR ABC transporter functions in a number of animal cells to transport
   a. glucose into cells.
   b. ions into cells.
   c. poisons and drugs out of cells.
   d. amino acids across epithelia.

   Bloom's Category: *1. Remembering*

3. During the processing of miRNAs, which of the following cleaves the 5′ and 3′ tails away from the hairpin structure in the primary miRNA transcript?
   a. Drosha
   b. Dicer
   c. RNAse
   d. Integrase

   Bloom's Category: *1. Remembering*

4. Nuclease digestion of chromatin occurs at sites separated by approximately 200 base pairs because
   a. an AT-rich region occurs every 200 base pairs.
   b. nucleosomes are spaced 200 base pairs apart.
   c. a restriction nuclease site occurs every 200 base pairs.
   d. two turns of the DNA around the nucleosome consist of 200 base pairs.

   Bloom's Category: *2. Understanding*

5. Compared to their normal counterparts, leukemic cells
   a. continue to differentiate.
   b. fail to proliferate.
   c. fail to undergo apoptosis.
   d. induce widespread apoptosis.

   Bloom's Category: *2. Understanding*

6. Explain why a deleterious genetic mutation in a gene on the X chromosome would be more likely to affect a male than a female.

   Bloom's Category: *2. Understanding*

7. A researcher is trying to determine the contents of a viral genome. Upon chemical analysis, the nucleic acid is found to contain 27% cytosine, 27% adenine, 23% uracil, and 23% guanine. Based on these data, the viral genome most likely consists of
   a. single-stranded DNA.
   b. double-stranded DNA.
   c. single-stranded RNA.
   d. double-stranded RNA.

   Bloom's Category: *3. Applying*

8. What would be the resting potential across an artificial membrane if all charged molecules on both sides were equally permeable?
   a. –60 mV
   b. –1 mV
   c. 0 mV
   d. +60 mV

   Bloom's Category: *3. Applying*

9. Briefly describe two molecular mechanisms that give rise to gene duplication.

   Bloom's Category: *3. Applying*

10. What type of DNA damage would you expect to occur more frequently in populations as they near the equator?

    Bloom's Category: *4. Analyzing*

11. A common method of DNA sequencing is based on the premature termination of DNA synthesis that accompanies the use of dideoxynucleotides in the PCR reactions. Why does elongation of a growing strand cease when a dideoxynucleotide is incorporated?

    Bloom's Category: *4. Analyzing*

12. Suppose you are studying the transport of glucose into red blood cells and find that as you increase the concentration of glucose outside of the cells, you discover a concentration at which there is no further increase in the rate of accumulation of glucose in the cells. How would you explain this?

    Bloom's Category: *4. Analyzing*

13. The drug 2,4-dinitrophenol (DNP) destroys the proton gradient across the inner mitochondrial membrane. What would be the effect of incubating isolated mitochondria in a solution of DNP?
    a. Glycolysis would stop.
    b. No ATP would be made.
    c. Oxygen would no longer be reduced to water.
    d. Mitochondria would switch from glycolysis to fermentation.
    e. Mitochondria would show a burst of increased ATP synthesis.

    Bloom's Category: *5. Evaluating*

14. The statements below describe prokaryotes and eukaryotes. Which provides evidence that prokaryotes and eukaryotes have a common ancestry?
    a. Eukaryotes contain mitochondria, whereas prokaryotes do not.
    b. Eukaryotes are generally larger and more complex than prokaryotes.
    c. Eukaryotes and prokaryotes have similar cellular structures for harvesting energy from fuel molecules.
    d. Both eukaryotes and prokaryotes obtain the energy they need to sustain life from their surroundings.
    e. Both eukaryotes and prokaryotes are capable of living under anaerobic conditions.

    Bloom's Category: *5. Evaluating*

15. In visualizing protein localization within a cell, what are the relative advantages and disadvantages of tagging proteins with green fluorescent protein (GFP) versus using a fluorescent antibody specific to the protein of interest (immunofluorescence)?

    Bloom's Category: *5. Evaluating*

16. Suppose you have a cell line that expresses a protein whose structure you know but whose function you do *not* know. Outline an experiment that would help you determine the protein's function.

    Bloom's Category: *6: Creating*

17. Complete the table below with examples of how each reaction relates to various types of cell functions.

Hydrolysis of ATP → ADP + Pi	**Synthesis of ADP + Pi → ATP**

    Bloom's Category: *6: Creating*