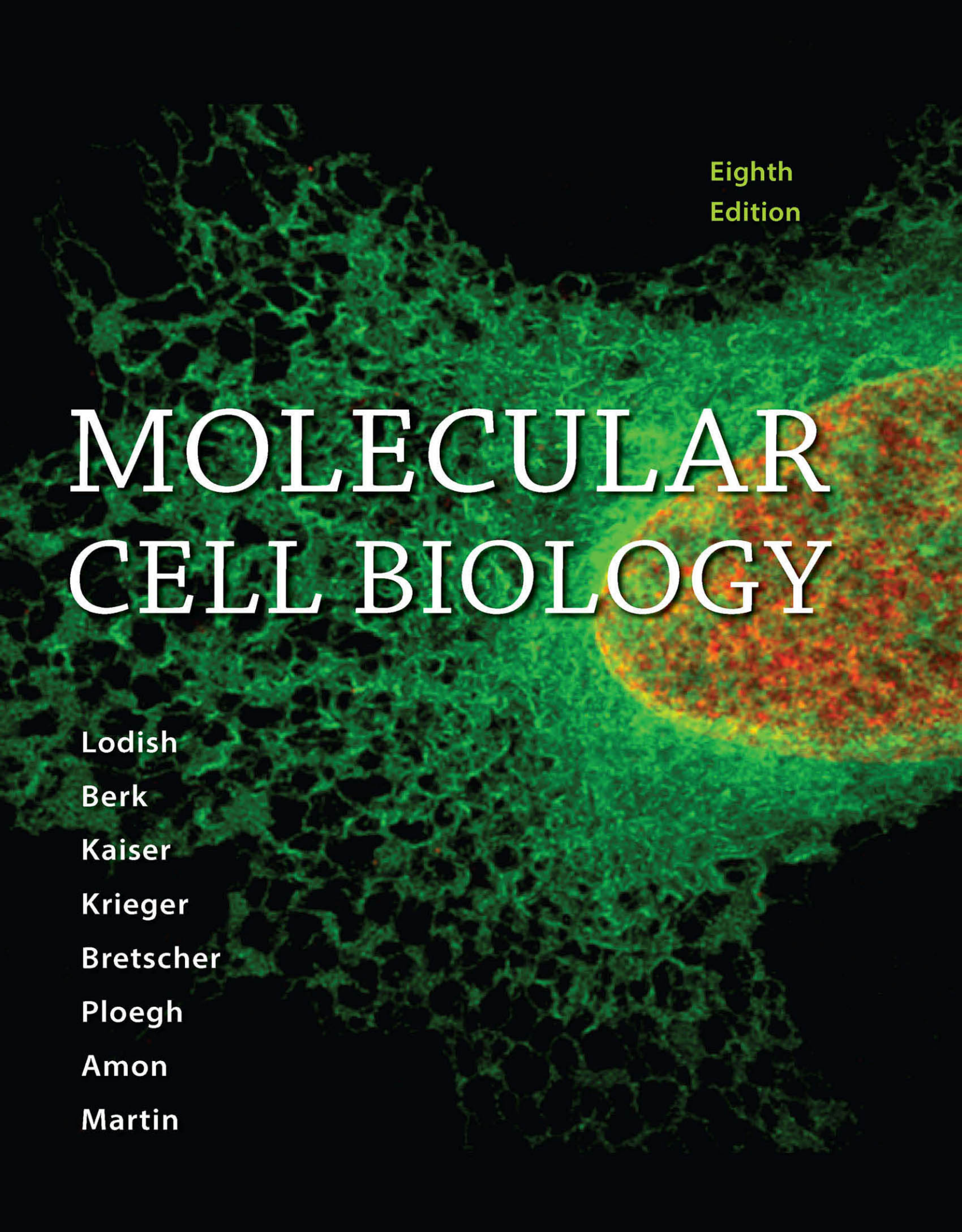
Eighth
Edition
MOLECULAR
CELL BIOLOGY
Lodish
Berk
Kaiser
Krieger
Bretscher
Ploegh
Amon
Martin

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Molecular Cell Biology

ABOUT THE AUTHORS

HARVEY LODISH is Professor of Biology and Professor of Biological Engineering at the Massachusetts Institute of Technology and a Founding Member of the Whitehead Institute for Biomedical Research. Dr. Lodish is also a member of the National Academy of Sciences and the American Academy of Arts and Sciences and was President (2004) of the American Society for Cell Biology. He is well known for his work on cell-membrane physiology, particularly the biosynthesis of many cell-surface proteins, and on the cloning and functional analysis of several cell-surface receptor proteins, such as the erythropoietin and TGF–β receptors. His laboratory also studies long noncoding RNAs and microRNAs that regulate the development and function of hematopoietic cells and adipocytes. Dr. Lodish teaches undergraduate and graduate courses in cell biology and biotechnology. *Photo credit: John Soares.*

ARNOLD BERK holds the UCLA Presidential Chair in Molecular Cell Biology in the Department of Microbiology, Immunology, and Molecular Genetics and is a member of the Molecular Biology Institute at the University of California, Los Angeles. Dr. Berk is also a fellow of the American Academy of Arts and Sciences. He is one of the discoverers of RNA splicing and of mechanisms for gene control in viruses. His laboratory studies the molecular interactions that regulate transcription initiation in mammalian cells, focusing in particular on adenovirus regulatory proteins. He teaches an advanced undergraduate course in cell biology of the nucleus and a graduate course in biochemistry. *Photo credit: Penny Jennings/UCLA Department of Chemistry & Biochemistry.*

CHRIS A. KAISER is the Amgen Inc. Professor in the Department of Biology at the Massachusetts Institute of Technology. He is also a former Department Head and former Provost. His laboratory uses genetic and cell biological methods to understand how newly synthesized membrane and secretory proteins are folded and stored in the compartments of the secretory pathway. Dr. Kaiser is recognized as a top undergraduate educator at MIT, where he has taught genetics to undergraduates for many years. *Photo credit: Chris Kaiser.*

MONTY KRIEGER is the Whitehead Professor in the Department of Biology at the Massachusetts Institute of Technology and a Senior Associate Member of the Broad Institute of MIT and Harvard. Dr. Krieger is also a member of the National Academy of Sciences. For his innovative teaching of undergraduate biology and human physiology as well as graduate cell biology courses, he has received numerous awards. His laboratory has made contributions to our understanding of membrane trafficking through the Golgi apparatus and has cloned and characterized receptor proteins important for pathogen recognition and the movement of cholesterol into and out of cells, including the HDL receptor. *Photo credit: Monty Krieger.*

ANTHONY BRETSCHER is Professor of Cell Biology at Cornell University and a member of the Weill Institute for Cell and Molecular Biology. His laboratory is well known for identifying and characterizing new components of the actin cytoskeleton and elucidating the biological functions of those components in relation to cell polarity and membrane traffic. For this work, his laboratory exploits biochemical, genetic, and cell biological approaches in two model systems, vertebrate epithelial cells and the budding yeast. Dr. Bretscher teaches cell biology to undergraduates at Cornell University. *Photo credit: Anthony Bretscher.*

HIDDE PLOEGH is Professor of Biology at the Massachusetts Institute of Technology and a member of the Whitehead Institute for Biomedical Research. One of the world's leading researchers in immune-system behavior, Dr. Ploegh studies the various tactics that viruses employ to evade our immune responses and the ways our immune system distinguishes friend from foe. Dr. Ploegh teaches immunology to undergraduate students at Harvard University and MIT. *Photo credit: Hidde Ploegh.*

ANGELIKA AMON is Professor of Biology at the Massachusetts Institute of Technology, a member of the Koch Institute for Integrative Cancer Research, and Investigator at the Howard Hughes Medical Institute. She is also a member of the National Academy of Sciences. Her laboratory studies the molecular mechanisms that govern chromosome segregation during mitosis and meiosis and the consequences—aneuploidy—when these mechanisms fail during normal cell proliferation and cancer development. Dr. Amon teaches undergraduate and graduate courses in cell biology and genetics. *Photo credit: Pamela DiFraia/ Koch Institute/MIT.*

KELSEY C. MARTIN is Professor of Biological Chemistry and Psychiatry and interim Dean of the David Geffen School of Medicine at the University of California, Los Angeles. She is the former Chair of the Biological Chemistry Department. Her laboratory studies the ways in which experience changes connections between neurons in the brain to store long-term memories—a process known as synaptic plasticity. She has made important contributions to elucidating the molecular and cell biological mechanisms that underlie this process. Dr. Martin teaches basic principles of neuroscience to undergraduates, graduate students, dental students, and medical students. *Photo credit: Phuong Pham.*

Molecular Cell Biology

EIGHTH EDITION

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Chris A. Kaiser
Monty Krieger
Anthony Bretscher
Hidde Ploegh
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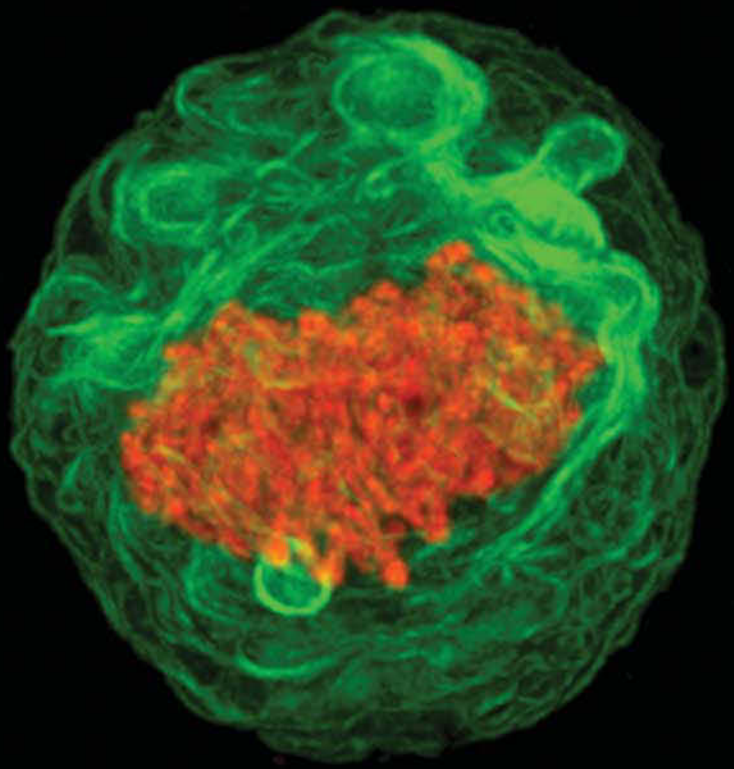

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ABOUT THE COVER: Imaging of the intracellular organelles of a live human HeLa cell shows the dramatic morphological changes that accompany the process of cell division. The membrane of the endoplasmic reticulum (ER) is labeled green by a fluorescently tagged component of the translocon (GFP-Sec61β) and chromatin is labeled red by a fluorescently tagged histone (H2B-mRFP). **Front:** An interphase cell showing uncondensed chromatin filling the nucleus, with the ER as a reticulum of cisternae surrounding the nucleus and interconnected with lace-like tubules at the cell periphery. **Back:** Prior to cell division the chromatin condenses to reveal the worm-like structure of individual chromosomes, the nuclear envelope breaks down, and the ER condenses into an array of cisternae surrounding the condensed chromosomes. As cell division proceeds the replicated chromosomes will segregate equally into two daughter cells, nuclear envelopes will form in the daughter cells, and the ER will return to its characteristic reticular organization. *Cover photo: Dr. Tomas Kirchhausen & Dr. Lei Lu.*

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TO OUR STUDENTS AND TO OUR TEACHERS,
from whom we continue to learn,

AND TO OUR FAMILIES,
for their support, encouragement, and love

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PREFACE

In writing the eighth edition of *Molecular Cell Biology*, we have incorporated many of the spectacular advances made over the past four years in biomedical science, driven in part by new experimental technologies that have revolutionized many fields. Fast techniques for sequencing DNA, allied with efficient methods to generate and study mutations in model organisms and to map disease-causing mutations in humans, have illuminated a basic understanding of the functions of many cellular components, including hundreds of human genes that affect diseases such as diabetes and cancer.

For example, advances in genomics and bioinformatics have uncovered thousands of novel long noncoding RNAs that regulate gene expression, and have generated insights into and potential therapies for many human diseases. Powerful genome editing technologies have led to an unprecedented understanding of gene regulation and function in many types of living organisms. Advances in mass spectrometry and cryoelectron microscopy have enabled dynamic cell processes to be visualized in spectacular detail, providing deep insight into both the structure and the function of biological molecules, post-translational modifications, multiprotein complexes, and organelles. Studies of specific nerve cells in live organisms have been advanced by optogenetic technologies. Advances in stem-cell technology have come from studies of the role of stem cells in plant development and of regeneration in planaria.

Exploring the most current developments in the field is always a priority in writing a new edition, but it is also important to us to communicate the basics of cell biology clearly by stripping away as much extraneous detail as possible to focus attention on the fundamental concepts of cell biology. To this end, in addition to introducing new discoveries and technologies, we have streamlined and reorganized several chapters to clarify processes and concepts for students.

New Co-Author, Kelsey C. Martin

The new edition of *MCB* introduces a new member to our author team, leading neuroscience researcher and educator Kelsey C. Martin of the University of California, Los Angeles. Dr. Martin is Professor of Biological Chemistry and Psychiatry and interim Dean of the David Geffen School of Medicine at UCLA. Her laboratory uses *Aplysia* and mouse models to understand the cell and molecular biology of long-term memory formation. Her group has made important contributions to elucidating the molecular and cell biological mechanisms by which experience changes connections between neurons in the brain to store long-term memories—a process known as synaptic plasticity. Dr. Martin received her undergraduate degree in English and American Language and Literature at Harvard University. After serving as a Peace Corps volunteer in the Democratic Republic of the Congo, she earned an MD and PhD at Yale University. She teaches basic neurobiology to undergraduate, graduate, dental, and medical students.

Revised, Cutting-Edge Content

The eighth edition of *Molecular Cell Biology* includes new and improved chapters:

- "Molecules, Cells, and Model Organisms" (Chapter 1) is an improved and expanded introduction to cell biology. It retains the overviews of evolution, molecules, different forms of life, and model organisms used to study cell biology found in previous editions. In this edition, it also includes a survey of eukaryotic organelles, which was previously found in Chapter 9.

- "Culturing and Visualizing Cells" (Chapter 4) has been moved forward (previously Chapter 9) as the techniques used to study cells become ever more important. Light-sheet microscopy, super-resolution microscopy, and two-photon excitation microscopy have been added to bring this chapter up to date.

- All aspects of mitochondrial and chloroplast structure and function have been collected in "Cellular Energetics" (Chapter 12). This chapter now begins with the structure of the mitochondrion, including its endosymbiotic origin and organelle genome (previously in Chapter 6). The chapter now discusses the role of mitochondria-associated membranes (MAMs) and communication between mitochondria and the rest of the cell.

- Cell signaling has been reframed to improve student accessibility. "Signal Transduction and G Protein–Coupled Receptors" (Chapter 15) begins with an overview of the concepts of cell signaling and methods for studying it, followed by examples of G protein–coupled receptors performing multiple roles in different cells. "Signaling Pathways That Control Gene Expression" (Chapter 16) now focuses on gene expression, beginning with a new discussion of Smads. Further examples cover the major signaling pathways that students will encounter in cellular metabolism, protein degradation, and cellular differentiation. Of particular interest is a new section on Wnt and Notch signaling pathways controlling stem-cell differentiation in planaria. The chapter ends by describing how signaling pathways are integrated

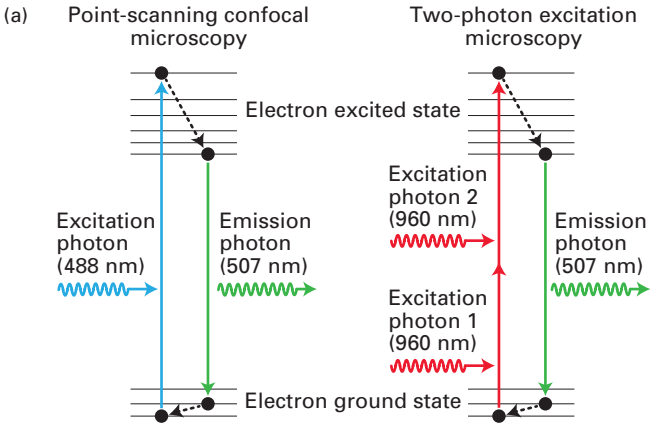


FIGURE 4-21 Two-photo excitation microscopy allows deep penetration for intravital imaging. (a) In conventional point-scanning confocal microscopy, absorption of a single photon results in an electron jumping to the excited state. In two-photon excitation, two lower-energy photons arrive almost instantaneously and induce the electron to jump to the excited state. (b) Two-photon microscopy can be used to observe cells up to 1 mm deep within a living animal immobilized on the microscope stage. (c) Neurons in a lobster were imaged using two-photon excitation microscopy.
[Part (c) unpublished data from Peter Kloppenburg and Warren R. Zipfel.]

to form a cellular response in insulin and glucagon control of glucose metabolism.

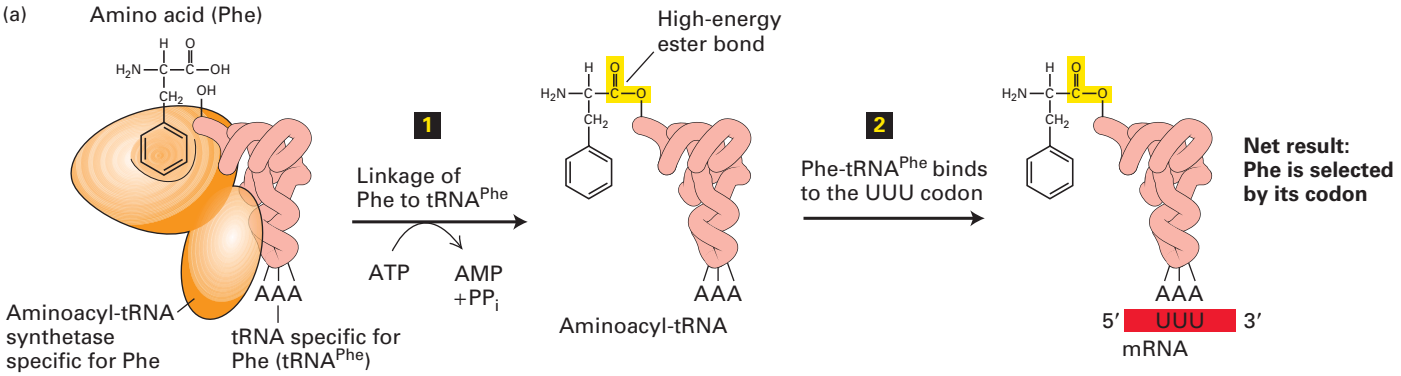
- Our new co-author, Kelsey C. Martin, has extensively revised and updated "Cells of the Nervous System" (Chapter 22) to include several new developments in the field. Optogenetics, a technique that uses channelrhodopsins and light to perturb the membrane potential of a cell, can be used in live animals to link neural pathways with behavior. The formation and pruning of neural pathways in the central nervous system is under active investigation, and a new discussion of signals that govern these processes focuses on the cell-cell contacts involved. This discussion leads to an entirely new section on learning and memory, which explores the signals and molecular mechanisms underlying synaptic plasticity.

Increased Clarity, Improved Pedagogy

As experienced teachers of both undergraduate and graduate students, we are always striving to improve student understanding. Being able to visualize a molecule in action can have a profound effect on a student's grasp of the molecular processes within a cell. With this in mind, we have updated many of the molecular models for increased clarity and added models where they can deepen student understanding. From the precise fit required for tRNA charging, to the conservation of ribosome structure, to the dynamic strength of tropomyosin and troponin in muscle contraction, these figures communicate the complex details of molecular structure that cannot be conveyed in schematic diagrams alone. In conjunction with these new models, their schematic icons have been revised to more accurately represent them, allowing students a smooth transition between the molecular details of a structure and its function in the cell.

New Discoveries, New Methodologies

- Model organisms *Chlamydomonas reinhardtii* (for study of flagella, chloroplast formation, photosynthesis, and phototaxis) and *Plasmodium falciparum* (novel organelles and a complex life cycle) (Ch. 1)
- Intrinsically disordered proteins (Ch. 3)
- Chaperone-guided folding and updated chaperone structures (Ch. 3)
- Unfolded proteins and the amyloid state and disease (Ch. 3)
- Hydrogen/deuterium exchange mass spectrometry (HXMS) (Ch. 3)
- Phosphoproteomics (Ch. 3)
- Two-photon excitation microscopy (Ch. 4)
- Light-sheet microscopy (Ch. 4)
- Super-resolution microscopy (Ch. 4)



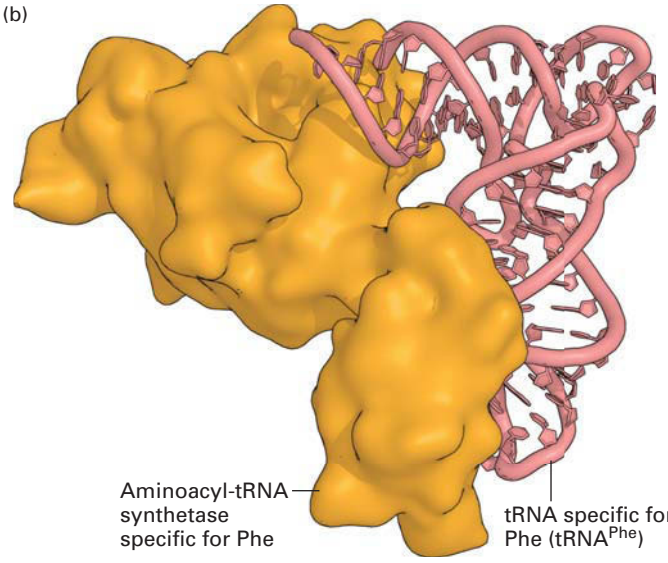


FIGURE 5-19 (a) Translating nucleic acid sequence into amino acid sequence requires two steps. Step 1: An aminoacyl-tRNA synthetase couples a specific amino acid to its corresponding tRNA. Step 2: The anticodon base-pairs with a codon in the mRNA specifying that amino acid. (b) Molecular model of the human mitochondrial aminoacyl-tRNA synthetase for Phe in complex with tRNA^{Phe}.

- Three-dimensional culture matrices and 3D printing (Ch. 4)
- Ribosome structural comparison across domains shows conserved core (Ch. 5)
- CRISPR–Cas9 system in bacteria and its application in genomic editing (Ch. 6)
- Chromosome conformation capture techniques reveal topological domains in chromosome territories within the nucleus (Ch. 8)
- Mapping of DNase I hypersensitive sites reveals cell developmental history (Ch. 9)
- Long noncoding RNAs involved in X inactivation in mammals (Ch. 9)
- ENCODE databases (Ch. 9)
- Improved discussion of mRNA degradation pathways and RNA surveillance in the cytoplasm (Ch. 10)
- Nuclear bodies: P bodies, Cajal bodies, histone locus bodies, speckles, paraspeckles, and PML nuclear bodies (Ch. 10)
- GLUT1 molecular model and transport cycle (Ch. 11)
- Expanded discussion of the pathway for import of PTS1-bearing proteins into the peroxisomal matrix (Ch. 13)
- Expanded discussion of Rab proteins and their role in vesicle fusion with target membranes (Ch. 14)
- Human G protein–coupled receptors of pharmaceutical importance (Ch. 15)
- The role of Smads in chromatin modification (Ch. 16)

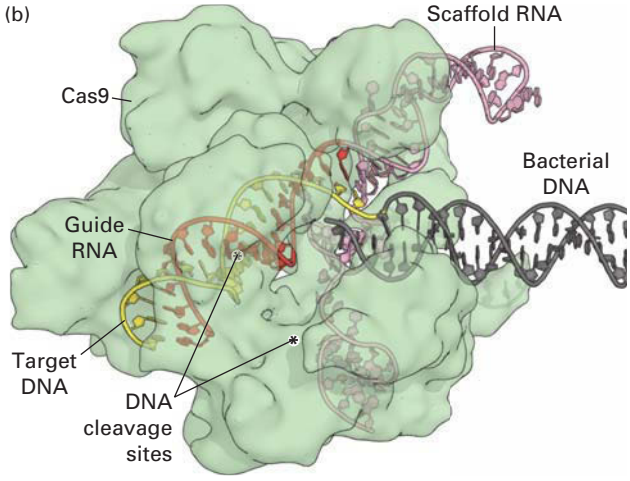


FIGURE 6-43b Cas9 uses a guide RNA to identify and cleave a specific DNA sequence.

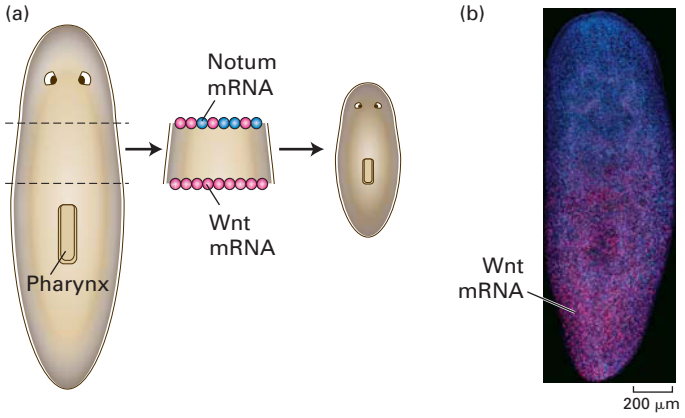


FIGURE 16-31 Gradients of Wnt and Notum guide regeneration of a head and tail by planaria. [Part (b) Jessica Witchley and Peter Reddien.]

- Wnt concentration gradients in planarian development and regeneration (Ch. 16)
- Inflammatory hormones in adipose cell function and obesity (Ch. 16)
- Regulation of insulin and glucagon function in control of blood glucose (Ch. 16)
- Use of troponins as an indicator of the severity of a heart attack (Ch. 17)
- Neurofilaments and keratins involved in skin integrity, epidermolysis bullosa simplex (Ch. 18)
- New structures and understanding of function of dynein and dynactin (Ch. 18)
- Expanded discussion of lamins and their role in nuclear membrane structure and dynamics during mitosis (Ch. 18)
- Diseases associated with cohesin defects (Ch. 19)
- The Hippo pathway (Ch. 19)
- Spindle checkpoint assembly and nondisjunction and aneuploidy in mice; nondisjunction increases with maternal age (Ch. 19)
- Expanded discussion of the functions of the extracellular matrix and the role of cells in assembling it (Ch. 20)
- Mechanotransduction (Ch. 20)
- Structure of cadherins and their cis and trans interactions (Ch. 20)
- Cadherins as receptors for class C rhinoviruses and asthma (Ch. 20)
- Improved discussion of microfibrils in elastic tissue and in LTBP-mediated TGF-β signaling (Ch. 20)
- Tunneling nanotubes (Ch. 20)
- Functions of WAKs in plants as pectin receptors (Ch. 20)
- Pluripotency of mouse ES cells and the potential of differentiated cells derived from iPS and ES cells in treating various diseases (Ch. 21)
- Pluripotent ES cells in planaria (Ch. 21)
- Cells in intestinal crypts that dedifferentiate to replenish intestinal stem cells (Ch. 21)
- Cdc42 and feedback loops that control cell polarity (Ch. 21)
- Prokaryotic voltage-gated Na^+ channel structure, allowing comparison with voltage-gated K^+ channels (Ch. 22)
- Optogenetics techniques for linking neural circuits with behavior (Ch. 22)
- Mechanisms of synaptic plasticity that govern learning and memory (Ch. 22)

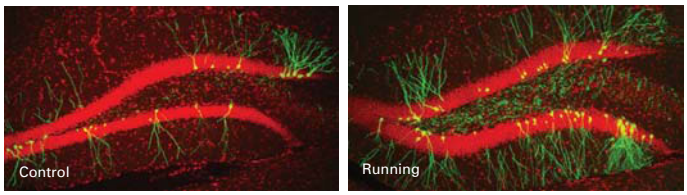


Figure 22-8 Neurogenesis in the adult brain. Newly born neurons were labeled with GFP in the dentate gyrus of control mice and mice that were allowed to exercise on a running wheel. [Chunmei Zhao and Fred H. Gage.]

- Inflammasomes and non-TLR nucleic acid sensors (Ch. 23)
- Expanded discussion of somatic hypermutation (Ch. 23)
- Improved discussion of the MHC molecule classes; MHC-peptide complexes and their interactions with T-cells (Ch. 23)
- Lineage commitment of T cells (Ch. 23)
- Tumor immunology (Ch. 23)
- The characteristics of cancer cells and how they differ from normal cells (Ch. 24)
- How carcinogens lead to mutations and how mutations accumulate to cancer (Ch. 24)

Medical Connections

Many advances in basic cellular and molecular biology have led to new treatments for cancer and other human diseases. Examples of such medical advances are woven throughout the chapters to give students an appreciation for the clinical applications of the basic science they are learning. Many of these applications hinge on a detailed understanding of multiprotein complexes in cells—complexes that catalyze cell movements; regulate DNA transcription,

replication, and repair; coordinate metabolism; and connect cells to other cells and to proteins and carbohydrates in their extracellular environment.

- Stereoisomers of small molecules as drugs—sterically pure molecules have different effects from mixtures (Ch. 2)
- Cholesterol is hydrophobic and must be transported by lipoprotein carriers LDL and HDL (Ch. 2)
- Essential amino acids must be provided in livestock feed (Ch. 2)
- Saturated, unsaturated, and trans fats: their molecular structures and nutritional consequences (Ch. 2)
- Protein misfolding and amyloids in neurodegenerative diseases such as Alzheimer's and Parkinson's (Ch. 3)
- Small molecules that inhibit enzyme activity can be used as drugs (aspirin) or in chemical warfare (sarin gas) (Ch. 3)
- Small-molecule inhibitors of the proteasome are used to treat certain cancers (Ch. 3)
- Disruptions of GTPases, GAPs, GEFs, and GDIs by mutations and pathogens cause a wide variety of diseases (Ch. 3)
- 3-D printing technology may be used to grow replacement organs (Ch. 4)
- The high-resolution structures of ribosomes can help identify small-molecule inhibitors of bacterial, but not eukaryotic, ribosomes (Ch. 5)
- Mutations in mismatch repair proteins lead to hereditary nonpolyposis colorectal cancer (Ch. 5)
- Nucleotide excision-repair proteins were identified in patients with xeroderma pigmentosum (Ch. 5)
- Human viruses HTLV, HIV-1, and HPV initiate infection by binding to specific cell-surface molecules, and some integrate their genomes into the host cell's DNA (Ch. 5)
- The sickle-cell allele is an example of one that exhibits both dominant and recessive properties depending on the phenotype being examined (Ch. 6)
- DNA microarrays can be useful as medical diagnostic tools (Ch. 6)
- Recombinant DNA techniques are used to mass-produce therapeutically useful proteins such as insulin and G-CSF (Ch. 6)
- Most cases of genetic diseases are caused by inherited rather than de novo mutations (Ch. 6)
- A *CFTR* knockout mouse line is useful in studying cystic fibrosis (Ch. 6)
- ABO blood types are determined by the carbohydrates attached to glycoproteins on the surfaces of erythrocytes (Ch. 7)
- Atherosclerosis, marked by accumulation of cholesterol, other lipids, and other biological substances in an artery, is responsible for the majority of deaths due to cardiovascular disease in the United States (Ch. 7)
- Microsatellite repeats have a tendency to expand and can cause neuromuscular diseases such as Huntington disease and myotonic dystrophy (Ch. 8)
- L1 transposable elements can cause genetic diseases by inserting into new sites in the genome (Ch. 8)
- Exon shuffling can result in bacterial resistance to antibiotics, a growing challenge in hospitals (Ch. 8)
- The *NF1* gene, which is mutated in patients with neurofibromatosis, is an example of how bioinformatics techniques can be used to identify the molecular basis of a genetic disease (Ch. 8)
- Telomerase is abnormally activated in most cancers (Ch. 8)
- TFIIH subunits were first identified based on mutations in those subunits that cause defects in DNA repair associated with a stalled RNA polymerase (Ch. 9)
- HIV encodes the Tat protein, which inhibits termination of transcription by RNA polymerase II (Ch. 9)
- Synthetic oligonucleotides are being used in treatment of Duchenne muscular dystrophy (DMD)(Ch. 10)
- Mutations in splicing enhancers can cause exon skipping, as in spinal muscular atrophy (Ch. 10)
- Expansion of microsatellite repeats in genes expressed in neurons can alter their relative abundance in different regions of the central nervous system, resulting in neurological disorders (Ch. 10)
- Thalassemia commonly results from mutations in globin-gene splice sites that decrease splicing efficiency but do not prevent association of the pre-mRNA with snRNPs (Ch. 10)
- Genes encoding components of the mTORC1 pathway are mutated in many cancers, and mTOR inhibitors combined with other therapies may suppress tumor growth (Ch. 10)
- Aquaporin 2 levels control the rate of water resorption from urine being formed by the kidney (Ch. 11)
- Certain cystic fibrosis patients are being treated with a small molecule that allows a mutant protein to traffic normally to the cell surface (Ch. 11)
- SGLT2 inhibitors are in development or have been approved for treatment of type II diabetes (Ch. 11)
- Antidepressants and other therapeutic drugs, as well as drugs of abuse, target Na^+-powered symporters because of their role in the reuptake and recycling of neurotransmitters (Ch. 11)

- Drugs that inhibit the Na^+/K^+ ATPase in cardiac muscle cells are used in treating congestive heart failure (Ch. 11)
- Oral rehydration therapy is a simple, effective means of treating cholera and other diseases caused by intestinal pathogens (Ch. 11)
- Mutations in CIC-7, a chloride ion channel, result in defective bone resorption characteristic of the hereditary bone disease osteopetrosis (Ch. 11)
- The sensitivity of mitochondrial ribosomes to the aminoglycoside class of antibiotics, including chloramphenicol, can cause toxicity in patients (Ch. 12)
- Mutations and large deletions in mtDNA cause certain diseases, such as Leber's hereditary optic neuropathy and Kearns-Sayre syndrome (Ch. 12)
- Cyanide is toxic because it blocks ATP production in mitochondria (Ch. 12)
- Reduction in amounts of cardiolipin, as well as an abnormal cardiolipin structure, results in the heart and skeletal muscle defects and other abnormalities that characterize Barth's syndrome (Ch. 12)
- Reactive oxygen species are by-products of electron transport that can damage cells (Ch. 12)
- ATP/ADP antiporter activity was first studied over 2000 years ago through the examination of the effects of poisonous herbs (Ch. 12)
- There are two related subtypes of thermogenic fat cells (Ch. 12)
- A hereditary form of emphysema results from misfolding of proteins in the endoplasmic reticulum (Ch. 13)
- Autosomal recessive mutations that cause defective peroxisome assembly can lead to several developmental defects often associated with craniofacial abnormalities, such as those associated with Zellweger syndrome (Ch. 13)
- Certain cases of cystic fibrosis are caused by mutations in the CFTR protein that prevent movement of this chloride channel from the ER to the cell surface (Ch. 14)
- Study of lysosomal storage diseases has revealed key elements of the lysosomal sorting pathway (Ch. 14)
- The hereditary disease familial hypercholesterolemia results from a variety of mutations in the *LDLR* gene (Ch. 14)
- Therapeutic drugs using the TNFα-binding domain of TNFα receptor are used to treat arthritis and other inflammatory conditions (Ch. 15)
- Monoclonal antibodies that bind HER2 and thereby block signaling by EGF are useful in treating breast tumors that overexpress HER2 (Ch. 15)
- The agonist isoproterenol binds more strongly to epinephrine-responsive receptors on bronchial smooth muscle cells than does epinephrine, and is used to treat bronchial asthma, chronic bronchitis, and emphysema (Ch. 15)
- Some bacterial toxins (e.g., *Bordetella pertussis*, *Vibrio cholerae*, certain strains of *E. coli*) catalyze a modification of a G protein in intestinal cells, increasing intracellular cAMP, which leads to loss of electrolytes and fluids (Ch. 15)
- Nitroglycerin decomposes to NO, a natural signaling molecule that, when used to treat angina, increases blood flow to the heart (Ch. 15)
- PDE inhibitors elevate cGMP in vascular smooth muscle cells and have been developed to treat erectile dysfunction (Ch. 15)
- Many tumors contain inactivating mutations in either TGF-β receptors or Smad proteins and are resistant to growth inhibition by TGF-β (Ch. 16)
- Epo and G-CSF are used to boost red blood cells and neutrophils, respectively, in patients with kidney disease and during certain cancer therapies that affect blood cell formation in the bone marrow (Ch. 16)
- Many cases of SCID result from a deficiency in the IL-2 receptor gamma chain and can be treated by gene therapy (Ch. 16)
- Mutant Ras proteins that bind but cannot hydrolyze GTP, and are therefore locked in an active GTP-bound state, contribute to oncogenic transformation (Ch. 16)
- Potent and selective inhibitors of Raf are being clinically tested in patients with melanomas caused by mutant Raf proteins (Ch. 16)
- The deletion of the *PTEN* gene in multiple types of advanced cancers results in the loss of the PTEN protein, contributing to the uncontrolled growth of cells (Ch. 16)
- High levels of free β-catenin, caused by aberrant hyperactive Wnt signaling, are associated with the activation of growth-promoting genes in many cancers (Ch. 16)
- Inappropriate activation of Hh signaling associated with primary cilia is the cause of several types of tumors (Ch. 16)
- Increased activity of ADAMs can promote cancer development and heart disease (Ch. 16)
- The brains of patients with Alzheimer's disease accumulate amyloid plaques containing aggregates of the $A\beta_{42}$ peptide (Ch. 16)
- Diabetes mellitus is characterized by impaired regulation of blood glucose, which can lead to major complications if left untreated (Ch. 16)
- Hereditary spherocytic anemias can be caused by mutations in spectrin, band 4.1, and ankyrin (Ch. 17)
- Duchenne muscular dystrophy affects the protein dystrophin, resulting in progressive weakening of skeletal muscle (Ch. 17)

- Hypertrophic cardiomyopathies result from various mutations in proteins of the heart contractile machinery (Ch. 17)
- Blood tests that measure the level of cardiac-specific troponins are used to determine the severity of a heart attack (Ch. 17)
- Some drugs (e.g., colchicine) bind tubulin dimers and restrain them from polymerizing into microtubules, whereas others (e.g., taxol) bind microtubules and prevent depolymerization (Ch. 18)
- Defects in LIS1 cause Miller-Dieker lissencephaly in early brain development, leading to abnormalities (Ch. 18)
- Some diseases, such as ADPKD and Bardet-Biedl syndrome, have been traced to defects in primary cilia and intraflagellar transport (Ch. 18)
- Keratin filaments are important to maintaining the structural integrity of epithelial tissues by mechanically reinforcing the connections between cells (Ch. 18)
- Mutations in the human gene for lamin A cause a wide variety of diseases termed laminopathies (Ch. 18)
- In cohesinopathies, mutations in cohesion subunits or cohesion loading factors disrupt expression of genes critical for development, resulting in limb and craniofacial abnormalities and intellectual disabilities (Ch. 19)
- Aneuploidy leads to misregulation of genes and can contribute to cancer development (Ch. 19)
- Aneuploid eggs are largely caused by chromosome missegregation in meiosis I or nondisjunction, leading to miscarriage or Down syndrome (Ch. 19)
- The protein CDHR3 enables class C rhinoviruses (RV-C) to bind to airway epithelial cells, enter them, and replicate, causing respiratory diseases and exacerbating asthma (Ch. 20)
- The cadherin desmoglein is the predominant target of autoantibodies in the skin disease pemiphigus vulgaris (Ch. 20)
- Some pathogens, such as hepatitis C virus and the enteric bacterium *Vibrio cholerae*, have evolved to exploit the molecules in tight junctions (Ch. 20)
- Mutations in connexin genes cause a variety of diseases (Ch. 20)
- Defects in the glomerular basement membrane can lead to renal failure (Ch. 20)
- In cells deprived of ascorbate, the pro-α collagen chains are not hydroxylated sufficiently to form the structural support of collagen necessary for healthy blood vessels, tendons, and skin, resulting in scurvy (Ch. 20)
- Mutations affecting type I collagen and its associated proteins cause a variety of diseases, including osteogenesis imperfecta (Ch. 20)
- A variety of diseases, often involving skeletal and cardiovascular abnormalities (e.g., Marfan syndrome), result from mutations in the genes encoding the structural proteins of elastic fibers or the proteins that contribute to their proper assembly (Ch. 20)
- Connections between the extracellular matrix and cytoskeleton are defective in muscular dystrophy (Ch. 20)
- Leukocyte-adhesion deficiency is caused by a genetic defect that results in the leukocytes' inability to fight infection, thereby increasing susceptibility to repeated bacterial infections (Ch. 20)
- The stem cells in transplanted bone marrow can generate all types of functional blood cells, which makes such transplants useful for patients with certain hereditary blood diseases as well as cancer patients who have received irradiation or chemotherapy (Ch. 21)
- Channelopathies, including some forms of epilepsy, are caused by mutations in genes that encode ion channels (Ch. 22)
- The topical anesthetic lidocaine works by binding to amino acid residues along the voltage-gated Na^+ channel, locking it in the open but occluded state (Ch. 22)
- The cause of multiple sclerosis is not known, but seems to involve either the body's production of auto-antibodies that react with myelin basic protein or the secretion of proteases that destroy myelin proteins (Ch. 22)
- Peripheral myelin is a target of autoimmune disease, mainly involving the formation of antibodies against P_o (Ch. 22)
- The key role of VAMP in neurotransmitter exocytosis can be seen in the mechanism of action of botulinum toxin (Ch. 22)
- Neurotransmitter transporters are targets of a variety of drugs of abuse (e.g., cocaine) as well as therapeutic drugs commonly used in psychiatry (e.g., Prozac, Zoloft, Paxil) (Ch. 22)
- Nicotinic acetylcholine receptors produced in brain neurons are important in learning and memory; loss of these receptors is observed in schizophrenia, epilepsy, drug addiction, and Alzheimer's disease (Ch. 22)
- Studies suggest that the voltage-gated Na^+ channel Nav1.7 is a key component in the perception of pain (Ch. 22)
- People vary significantly in sense of smell (Ch. 22)
- Synaptic translation of localized mRNAs is critical to the formation and the experience-dependent plasticity of neural circuits, and alterations in this process result in neurodevelopmental and cognitive disorders (Ch. 22)
- The immunosuppressant drug cyclosporine inhibits its calcineurin activity through the formation of a

cyclosporine-cyclophilin complex, thus enabling successful allogenic tissue transplantation (Ch. 23)

- Vaccines elicit protective immunity against a variety of pathogens (Ch. 23)
- Increased understanding of the molecular cell biology of tumors is revolutionizing the way cancers are diagnosed and treated (Ch. 24)

Plant Biology Connections

Developments in agriculture, environmental science, and alternative energy production have demonstrated that the molecular cell biology of plants is increasingly relevant to our lives. Understanding photosynthesis and chloroplasts is just the beginning of plant biology. Throughout the text, we have highlighted plant-specific topics, including aspects of cell structure and function that are unique to plants, plant development, and plant biotechnology applications directed toward solving problems in agriculture and medicine. ■

- Vascular plants have rigid cell walls and use turgor pressure to stand upright and grow (Ch. 11)
- Transgenic plants have been produced that overexpress the vacuolar Na^+/H^+ antiporter, and can therefore grow successfully in soils containing high salt concentrations (Ch. 11)
- Editing of plant mitochondrial RNA transcripts can convert cytosine residues to uracil residues (Ch. 12)
- Photosynthesis is an important process for synthesizing ATP (Ch. 12)
- Chloroplast DNAs are evolutionarily younger and show less structural diversity than mitochondrial DNAs (Ch. 12)
- Chloroplast transformation has led to engineered plants that are resistant to infections as well as plants that can be used to make protein drugs (Ch. 12)
- In giant green algae such as *Nitella*, the cytosol flows rapidly due to use of myosin V (Ch. 17)
- Formation of the spindle and cytokinesis have unique features in plants (Ch. 18)
- Meristems are niches for stem cells in plants (Ch. 21)
- A negative feedback loop maintains the size of the shoot apical stem-cell population (Ch. 21)
- The root meristem resembles the shoot meristem in structure and function (Ch. 21)

MEDIA AND SUPPLEMENTS

LaunchPad
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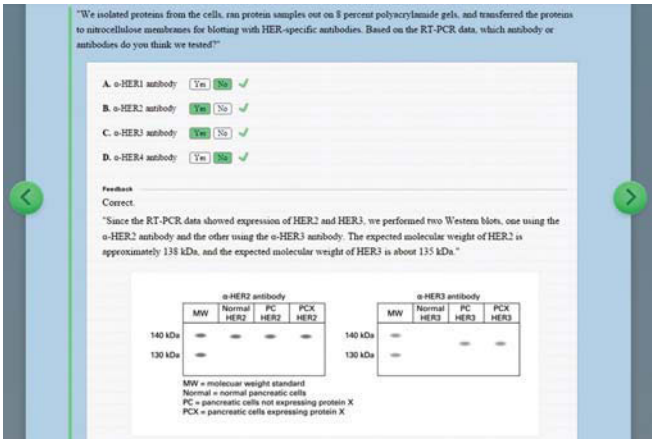
LaunchPad for *Molecular Cell Biology* is a robust teaching and learning tool with all instructor and student resources as well as a fully interactive e-Book.

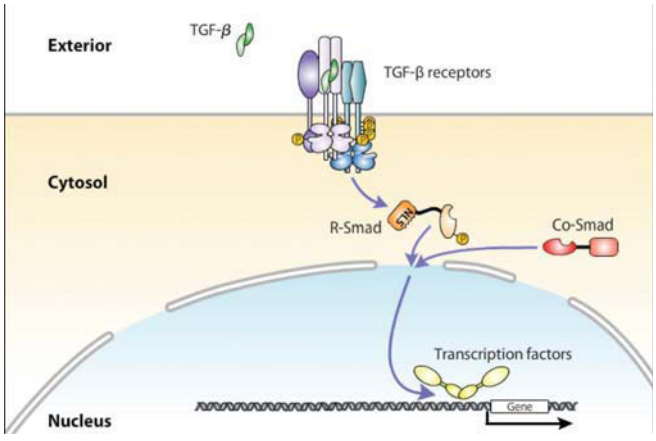
Student Resources

Interactive **Case Studies** guide students through applied problems related to important concepts; topics include cancer, diabetes, and cystic fibrosis.



Case Study "To Kill a Cancer Cell" leads students through the experiments needed to identify a perturbed signaling pathway.

Over 60 **Animations** based on key figures from the text illustrate difficult or important structures and processes.



Animation of Figure 16-3b depicts signal transduction in the TGF-β/Smad pathway.

Concept Check quizzes test student understanding of the most important concepts of each section.

LearningCurve
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LearningCurve, a self-paced adaptive quizzing tool for students, tailors questions to their target difficulty level and encourages them to incorporate content from the text into their study routine.

A collection of **Videos** shows students real cell processes as they appear in the lab.

Analyze the Data questions ask students to apply critical thinking and data analysis skills to solving complex problems.

Classic Experiments introduce students to the details of a historical experiment important to the cell and molecular biology fields.

Instructor Resources

All **Figures and Photos** from the text are optimized for classroom presentation and provided in several formats and with and without labels.

A comprehensive **Test Bank** provides a variety of questions for creating quizzes and exams.

Lecture Slides built around high-quality versions of text figures provide a starting point for in-class presentations.

Clicker Questions in slide format help instructors promote active learning in the classroom.

A PDF **Solutions Manual** provides answers to the Review the Concepts questions at the end of each chapter. An answer key for Analyze the Data questions is also included.

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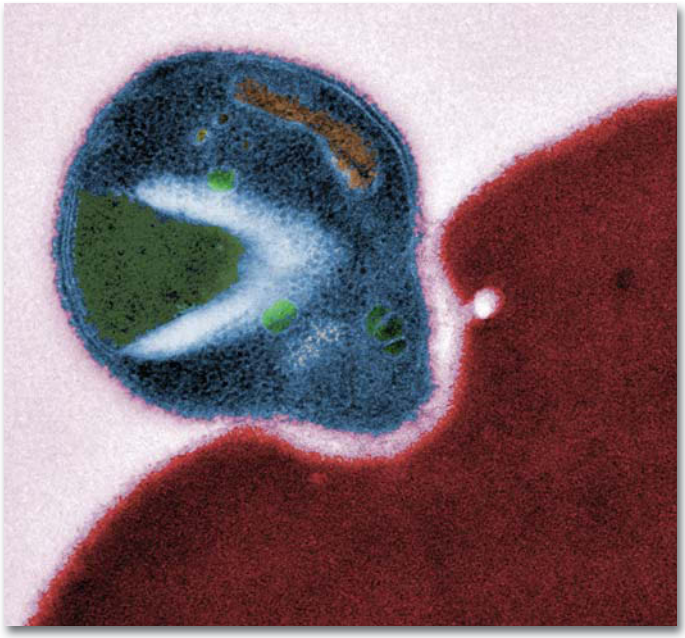
CONTENTS IN BRIEF

CONTENTS

Part III Cellular Organization and Function

CHAPTER

1



Two cells in mortal combat: a malaria parasite invading a human red blood cell. [Courtesy Dr. Stuart Ralph, University of Melbourne.]

Molecules, Cells, and Model Organisms

Nothing in biology makes sense except in the light of evolution.

—Theodosius Dobzhansky, 1973, essay in *American Biology Teacher* **35**:125–129

Biology is a science fundamentally different from physics or chemistry, which deal with unchanging properties of matter that can be described by mathematical equations. Biological systems, of course, follow the rules of chemistry and physics, but biology is a historical science, as the forms and structures of the living world today are the results of billions of years of evolution. Through evolution, all organisms are related in a family tree extending from primitive single-celled organisms that lived in the distant past to the diverse plants, animals, and microorganisms of the present era (Figure 1-1, Table 1-1). The great insight of Charles Darwin (Figure 1-2) was the principle of natural selection: organisms vary randomly and compete within their environment for resources. Only those that survive and reproduce are able to pass down their genetic traits.

At first glance, the biological universe does appear amazingly diverse—from tiny ferns to tall fir trees, from single-celled bacteria and protozoans visible only under a microscope to multicellular animals of all kinds. Indeed, cells come in an astonishing variety of sizes and shapes (Figure 1-3). Some move rapidly and have fast-changing structures, as we can see in movies of amoebae and rotifers. Others are largely stationary and structurally stable. Oxygen kills some cells but is an absolute requirement for others. Most cells in multicellular organisms are intimately involved with other cells. Although some unicellular organisms live in isolation (Figure 1-3a), others form colonies or live in close association with other types of organisms (Figure 1-3b, d), such as the bacteria that help plants to extract nitrogen from the air or the bacteria that live in our intestines and help us digest food.

Yet the bewildering array of outward biological forms overlies a powerful uniformity: thanks to our common ancestry, all biological systems are composed of cells containing the same types of chemical molecules and employing similar principles of organization at the cellular level. Although the

OUTLINE

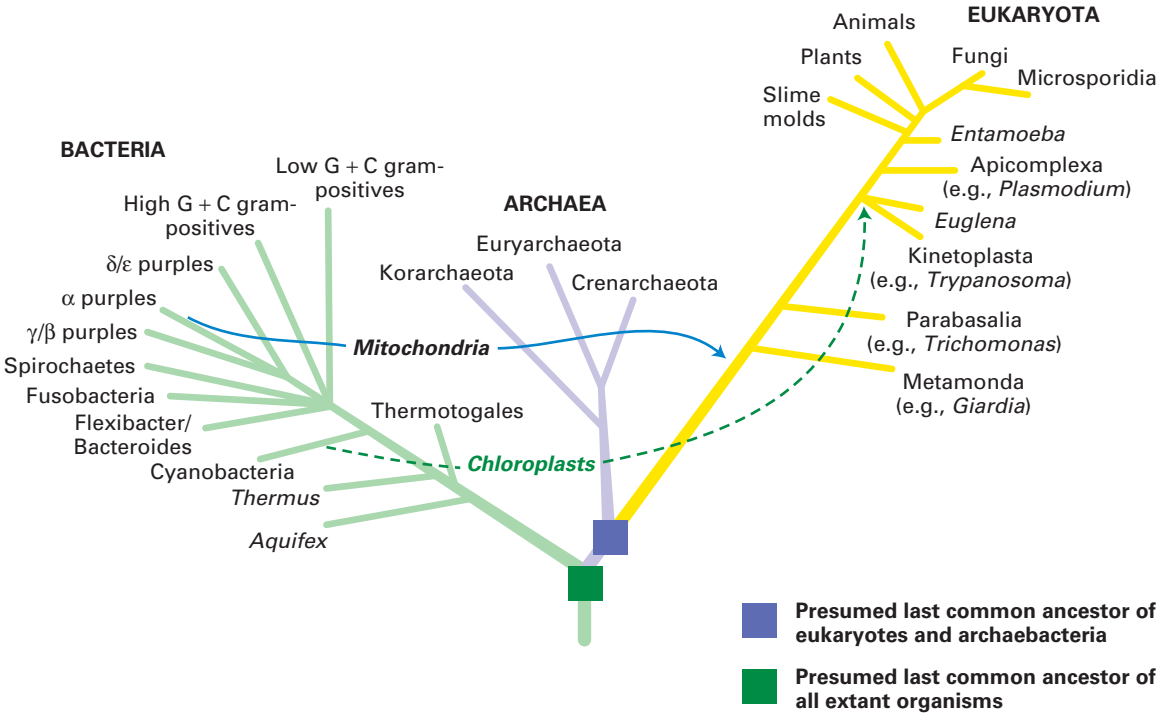


FIGURE 1-1 All living organisms descended from a common ancestral cell. All organisms, from simple bacteria to complex mammals, probably evolved from a common single-celled ancestor. This family tree depicts the evolutionary relationships among the three major lineages of organisms. The structure of the tree was initially ascertained from morphological criteria: creatures that look alike were put close together. More recently, the sequences of DNA and proteins found in organisms have provided more information-rich criteria for assigning relationships. The greater the similarities in these macromolecular sequences, the more closely related organisms are thought to be. The trees based on morphological comparisons and the fossil record generally agree well with those based on molecular data. [Data from J. R. Brown, 2005, "Universal tree of life," in *Encyclopedia of Life Sciences*, Wiley InterScience (online).]

basic kinds of biological molecules have been conserved during the billions of years of evolution, the patterns in which they are assembled to form functioning cells and organisms have undergone considerable change.

We now know that **genes**, which chemically are composed of **deoxyribonucleic acid** (**DNA**), ultimately define biological structure and maintain the integration of cellular function. Many genes encode **proteins**, the primary molecules that make up cell structures and carry out cellular activities. Alterations in the structure and organization of genes, or **mutations**, provide the random variation that can alter biological structure and function. While the vast majority of random mutations have no observable effect on a gene's or protein's function, many are deleterious, and only a few confer an evolutionary advantage on the organism. In all organisms, mutations in DNA are constantly occurring, allowing over time the small alterations in cellular structures and functions that may prove to be advantageous. Entirely new cellular structures are rarely created; more often, existing cellular structures undergo changes that better adapt the organism to new circumstances. Slight changes in a protein can cause important changes in its function or abolish its function entirely.

For instance, in a particular organism, one gene may randomly become duplicated, after which one copy of the gene and its encoded protein retain their original function while, over time, the second copy of the gene mutates such that its protein takes on a slightly different or even a totally new function. During the evolution of some organisms, the entire genome became duplicated, allowing the second copies of many genes to undergo mutations and acquire new functions. The cellular organization of organisms plays a fundamental role in this process because it allows these changes to come about by small alterations in previously evolved cells, giving them new abilities. The result is that closely related organisms have very similar genes and proteins as well as similar cellular and tissue organizations.

Multicellular organisms, including the human body, consist of such closely interrelated elements that no single element can be fully appreciated in isolation from the others. Organisms contain organs, organs are composed of tissues, tissues consist of cells, and cells are formed from molecules (Figure 1-4). The unity of living systems is coordinated by many levels of interrelationship: molecules carry messages from organ to organ and cell to cell, and tissues are delineated and integrated with other tissues by molecules secreted by cells. Generally all the levels into which we fragment biological systems interconnect.

TABLE 1-1 Timeline for Evolution of Life on Earth, as Determined from the Fossil Record

4600 million years ago	The planet Earth forms from material revolving around the young Sun.
~3900–2500 million years ago	Cells resembling prokaryotes appear. These first organisms are chemoautotrophs: they use carbon dioxide as a carbon source and oxidize inorganic materials to extract energy.
3500 million years ago	Lifetime of the last universal ancestor; the split between Eubacteria and Archaea occurs.
3000 million years ago	Photosynthesizing cyanobacteria evolve; they use water as a reducing agent, thereby producing oxygen as a waste product.
1850 million years ago	Unicellular eukaryotes appear.
1200 million years ago	Simple multicellular organisms evolve, mostly consisting of cell colonies of limited complexity.
580–500 million years ago	Most modern phyla of animals begin to appear in the fossil record during the Cambrian explosion.
535 million years ago	Major diversification of living things in the oceans: chordates, arthropods (e.g., trilobites, crustaceans), echinoderms, mollusks, brachiopods, foraminifers, radiolarians, etc.
485 million years ago	First vertebrates with true bones (jawless fishes) evolve.
434 million years ago	First primitive plants arise on land.
225 million years ago	Earliest dinosaurs (prosauropods) and teleost fishes appear.
220 million years ago	Gymnosperm forests dominate the land; herbivores grow to huge sizes.
215 million years ago	First mammals evolve.
65.5 million years ago	The Cretaceous-Tertiary extinction event eradicates about half of all animal species, including all of the dinosaurs.
6.5 million years ago	First hominids evolve.
2 million years ago	First members of the genus *Homo* appear in the fossil record.
350 thousand years ago	Neanderthals appear.
200 thousand years ago	Anatomically modern humans appear in Africa.
30 thousand years ago	Extinction of Neanderthals.

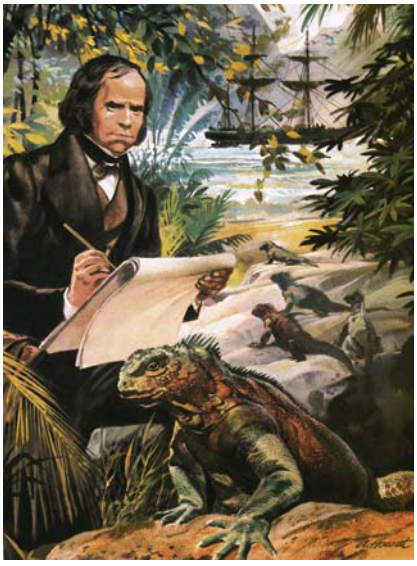


FIGURE 1-2 Charles Darwin (1809–1882). Four years after his epic voyage on HMS *Beagle*, Darwin had already begun formulating in private notebooks his concept of natural selection, which would be published in his *Origin of Species* (1859). [*Charles Darwin on the Galapagos Islands* by Howat, Andrew (20th century)/Private Collection/© Look and Learn/Bridgeman Images.]

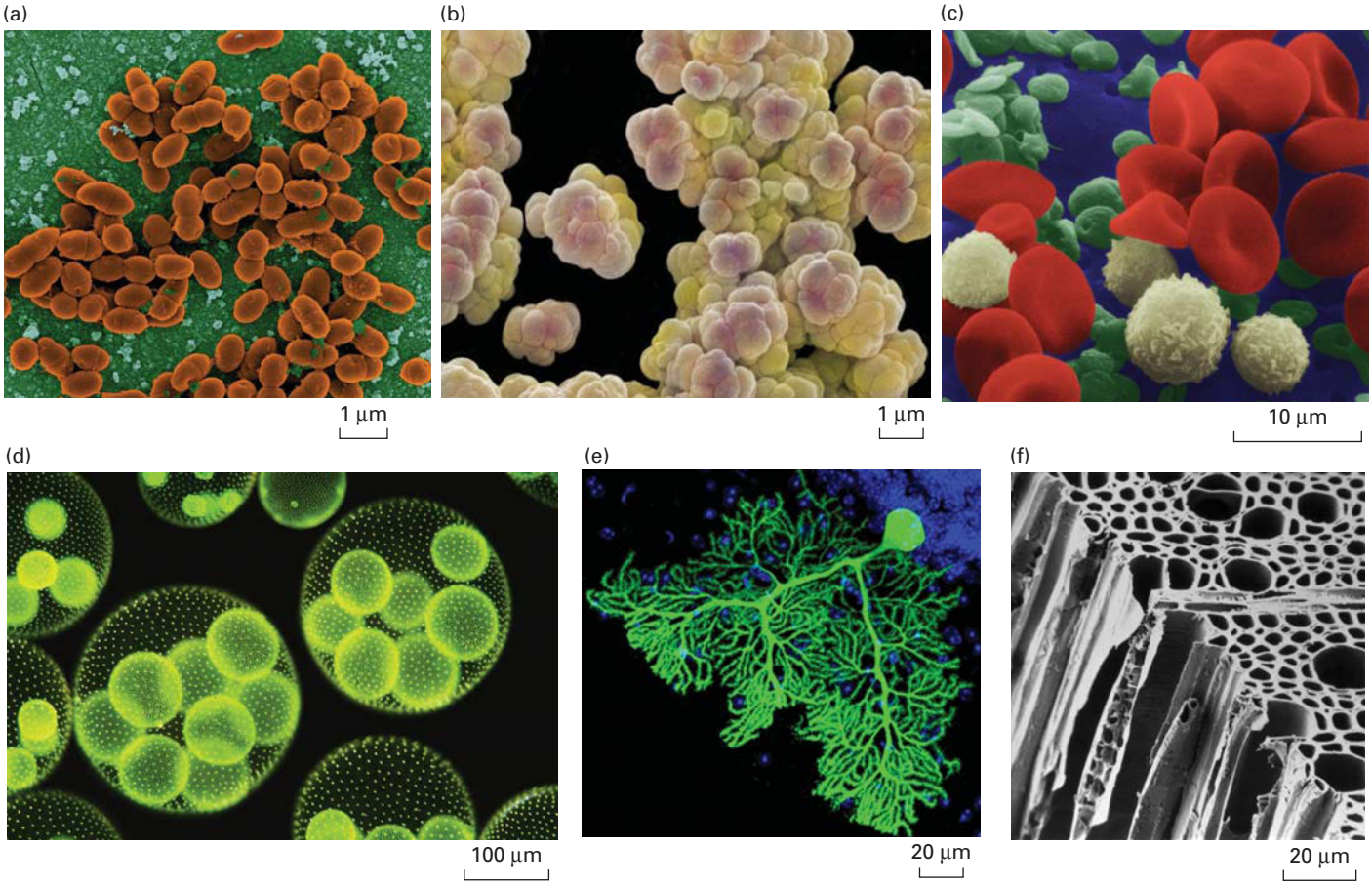


FIGURE 1-3 Cells come in an astounding assortment of shapes and sizes. Some of the morphological variety of cells is illustrated in these photographs. In addition to morphology, cells differ in their ability to move, internal organization (prokaryotic versus eukaryotic cells), and metabolic activities. (a) Eubacteria: *Lactococcus lactis*, which are used to produce cheese such as Roquefort, Brie, and Camembert. Note the dividing cells. (b) A mass of archaeans (*Methanosarcina*) that produce their energy by converting carbon dioxide and hydrogen gas to methane. Some species that live in the rumens of cattle give rise to >150 liters of methane gas each day. (c) Human blood cells, shown in false color. The red cells are oxygen-bearing erythrocytes, the white cells (leukocytes) are part of the immune system and fight infection, and the green cells are platelets that plug wounds and contain substances to initiate blood clotting. (d) A colonial single-celled green alga, *Volvox aureus*. The large spheres are made up of many individual cells, visible as blue or green dots. The yellow masses inside are daughter colonies, each made up of many cells. (e) A single Purkinje neuron of the cerebellum, which can form more than a hundred thousand connections with other cells through its branched network of dendrites. The cell was made visible by introduction of a green fluorescent protein; the cell body is the bulb at the upper right. (f) Plant cells are fixed firmly in place in vascular plants, supported by a rigid cellulose skeleton. Spaces between the cells are joined into tubes for transport of water and food. [Part (a) Gary Gaugler/Science Source. Part (b) Power and Syred/Science Source. Part (c) Science Source. Part (d) micro_photo/iStockphoto/Getty Images. Part (e) Courtesy of Dr. Helen M. Blau (Stanford University School of Medicine) and Dr. Clas B. Johansson (Karolinska Institutet). Part (f) Biophoto Associates/Science Source.]

To learn about biological systems, however, we must examine one small portion of a living system at a time. The biology of cells is a logical starting point because an organism can be viewed as consisting of interacting cells, which are the closest thing to autonomous biological units that exist. The last common ancestor of all life on Earth was a single cell (see Figure 1-1), and at the cellular level all life is remarkably similar. All cells use the same molecular building blocks, similar methods for the storage, maintenance, and expression of genetic information, and similar processes of energy metabolism, molecular transport, signaling, development, and structure.

In this chapter, we introduce the common features of cells. We begin with a brief discussion of the principal small molecules and macromolecules found in biological systems. Next we discuss the fundamental aspects of cell structure and function that are conserved in present-day organisms, focusing first on prokaryotic organisms—single-celled organisms without a nucleus—and their uses in studying the basic molecules of life. Then we discuss the structure and function of eukaryotic cells—cells with a defined nucleus—focusing on their many organelles. This discussion is followed by a section describing the use of unicellular eukaryotic organisms in investigations of molecular cell biology, focusing on yeasts and the parasite that causes malaria.

We now have the complete sequences of the genomes of several thousand **metazoans** (multicellular animals), and these sequences have provided considerable insight into the

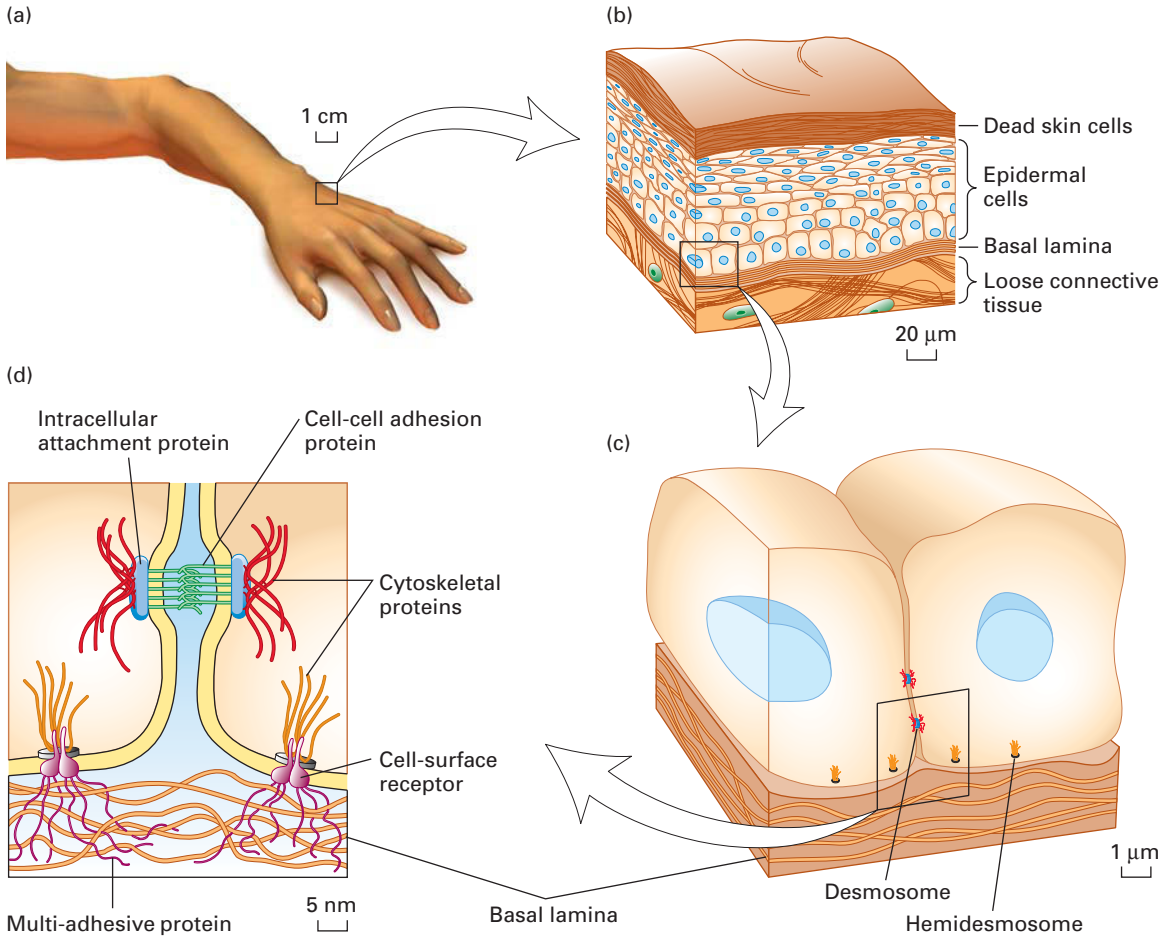


FIGURE 1-4 Living systems such as the human body consist of closely interrelated elements. (a) The surface of the hand is covered by a living organ, skin, that is composed of several layers of tissue. (b) An outer covering of hard, dead skin cells protects the body from injury, infection, and dehydration. This layer is constantly renewed by living epidermal cells, which also give rise to hair and fur in animals. Deeper layers of muscle and connective tissue give skin its tone and firmness. (c) Tissues are formed through subcellular adhesion structures (desmosomes and hemidesmosomes) that join cells to one another and to an underlying layer of supporting fibers. (d) At the heart of cell-cell adhesion are its structural components: phospholipid molecules that make up the cell-surface membrane, and large protein molecules. Protein molecules that traverse the cell membrane often form strong bonds with internal and external fibers made of multiple proteins.

evolution of genes and organisms. The final section in this chapter shows us how this information can be used to refine the evolutionary relationships among organisms as well as our understanding of human development. Indeed, biologists use evolution as a research tool: if a gene and its protein have been conserved in all metazoans but are not found in unicellular organisms, the protein probably has an important function in all metazoans and thus can be studied in whatever metazoan organism is most suitable for the investigation. Because the structure and function of many types of metazoan cells is also conserved, we now understand the structure and function of many cell types in considerable detail, including muscle and liver cells and the sheets of epithelial cells that line the intestine and form our skin. But other cells—especially the multiple types that form our nervous and immune systems—still remain mysterious; much important cell biological experimentation is needed on these and other cell systems and organs that form our bodies.

1.1 The Molecules of Life

While large polymers are the focus of molecular cell biology, small molecules are the stage on which all cellular processes are set. Water, inorganic ions, and a wide array of relatively small organic molecules (Figure 1-5) account for 75 to 80 percent of living matter by weight, and water accounts for about 75 percent of a cell's volume. These small molecules, including water, serve as substrates for many of the reactions that take place inside the cell, including energy metabolism and cell signaling. Cells acquire these small molecules in different ways. Ions, water, and many small organic molecules are imported into the cell (see Chapter 11); other small molecules are synthesized within the cell, often by a series of chemical reactions (see Chapter 12).

Even in the structures of many small molecules, such as sugars, vitamins, and amino acids, we see the footprint of evolution. For example, all amino acids save glycine have an

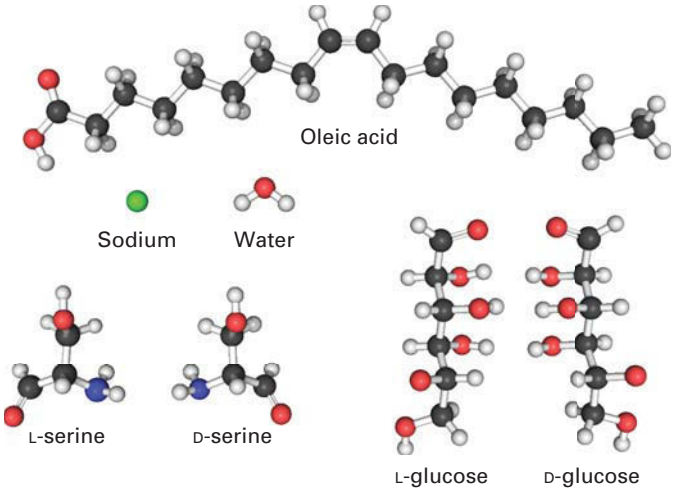


FIGURE 1-5 Some of the many small molecules found in cells. Only the L-forms of amino acids such as serine are incorporated into proteins, not their D-mirror images; only the D-form of glucose, not its L-mirror image, can be metabolized to carbon dioxide and water.

asymmetric carbon atom, yet only the L-stereoisomer, never the D-stereoisomer, is incorporated into proteins. Similarly, only the D-stereoisomer of glucose is invariably found in cells, never the mirror-image L-stereoisomer (see Figure 1-5). At an early stage of biological evolution, our common cellular ancestor evolved the ability to catalyze reactions with one stereoisomer instead of the other. How these selections happened is unknown, but now these choices are locked in place.

An important and universally conserved small molecule is **adenosine triphosphate** (**ATP**), which stores readily available chemical energy in two of its chemical bonds (Figure 1-6). When one of these energy-rich bonds in ATP is broken, forming **ADP** (**adenosine diphosphate**), the released energy can be harnessed to power energy-requiring processes such as muscle contraction or protein biosynthesis. To obtain energy for making ATP, all cells break down food molecules. For instance, when sugar is degraded to carbon dioxide and water, the energy stored in the sugar molecule's chemical bonds is released, and much of it can be "captured" in the energy-rich bonds in ATP. Bacterial, plant, and animal cells can all make ATP by this process. In addition, plants and a few other organisms can harvest energy from sunlight to form ATP in **photosynthesis**.

Other small molecules (e.g., certain hormones and growth factors) act as signals that direct the activities of cells (see Chapters 15 and 16), and neurons (nerve cells) communicate with one another by releasing and sensing certain small signaling molecules (see Chapter 22). The powerful physiological effects of a frightening event, for example, come from the instantaneous flooding of the body with the small-molecule hormone adrenaline, which mobilizes the "fight or flight" response.

Certain small molecules (**monomers**) can be joined to form **polymers** (also called **macromolecules**) through

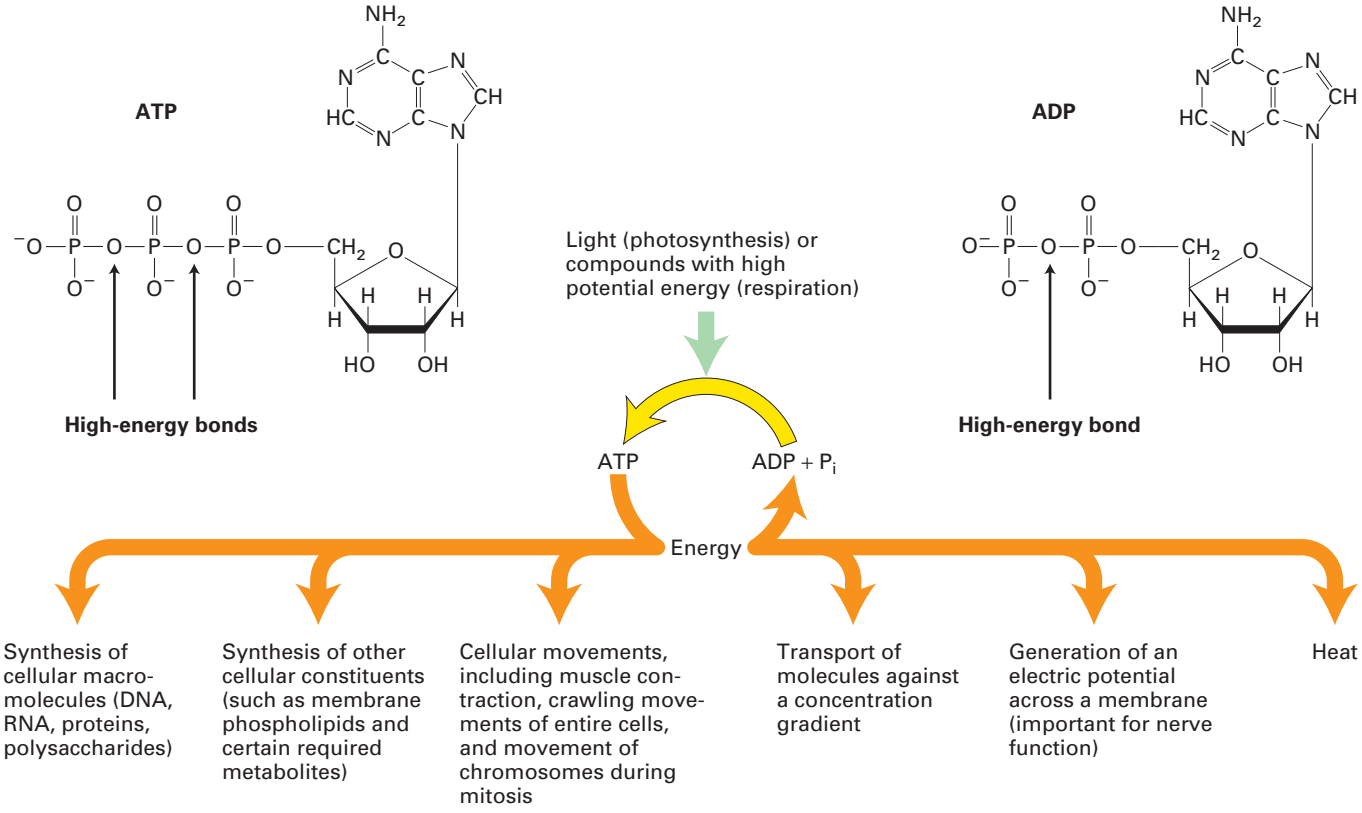


FIGURE 1-6 Adenosine triphosphate (ATP) is the most common molecule used by cells to capture, store, and transfer energy. ATP is formed from adenosine diphosphate (ADP) and inorganic phosphate (P_i) by photosynthesis in plants and by the breakdown of sugars and fats in most cells. The energy released by the splitting (hydrolysis) of P_i from ATP drives many cellular processes.

repetition of a single type of covalent chemical-linkage reaction. Cells produce three types of large macromolecules: polysaccharides, proteins, and nucleic acids. Sugars, for example, are the monomers used to form polysaccharides. Different polymers of D-glucose form cellulose, an important component of plant cell walls, and glycogen, a storage form of glucose found in liver and muscle. The cell is careful to provide the appropriate mix of small molecules needed as precursors for synthesis of macromolecules.

Proteins Give Cells Structure and Perform Most Cellular Tasks

Proteins, the workhorses of the cell, are the most abundant and functionally versatile of the cellular macromolecules. Cells string together 20 different **amino acids** in linear chains, each with a defined sequence, to form proteins (see Figure 2-14), which commonly range in length from 100 to 1000 amino acids. During or just after its polymerization, a linear chain of amino acids folds into a complex shape, conferring a distinctive three-dimensional structure and function on the protein (Figure 1-7). Humans obtain amino acids either by synthesizing them from other molecules or by breaking down proteins that we eat.

Proteins have a variety of functions in the cell. Many proteins are **enzymes**, which accelerate (catalyze) chemical reactions involving small molecules or macromolecules (see Chapter 3). Certain proteins catalyze steps in the synthesis of all proteins; others catalyze synthesis of macromolecules such as DNA and RNA. **Cytoskeletal proteins** serve as structural components of a cell; for example, by forming an internal skeleton. Other proteins associated with the cytoskeleton power the movement of subcellular structures such as chromosomes, and even of whole cells, by using energy stored in the chemical bonds of ATP (see Chapters 17 and 18). Still other proteins bind adjacent cells together or form parts of the extracellular matrix (see Figure 1-4). Proteins can be sensors that change shape as temperature, ion concentrations, or other properties of the cell change. Many proteins that are embedded in the cell-surface (plasma) membrane import and export a variety of small molecules and ions (see Chapter 11). Some proteins, such as insulin, are hormones; others are hormone receptors that bind their target protein or small molecule and then generate a signal that regulates a specific aspect of cell function. Other important classes of proteins bind to specific segments of DNA, turning genes on or off (see Chapter 9). In fact, much of molecular cell biology consists of studying the function of specific proteins in specific cell types.

Nucleic Acids Carry Coded Information for Making Proteins at the Right Time and Place

The macromolecule that garners the most public attention is deoxyribonucleic acid (DNA), whose functional properties make it the cell's "master molecule." The three-dimensional structure of DNA, first proposed by James D. Watson and Francis H. C. Crick in 1953, consists of two long helical strands that are coiled around a common axis to form a

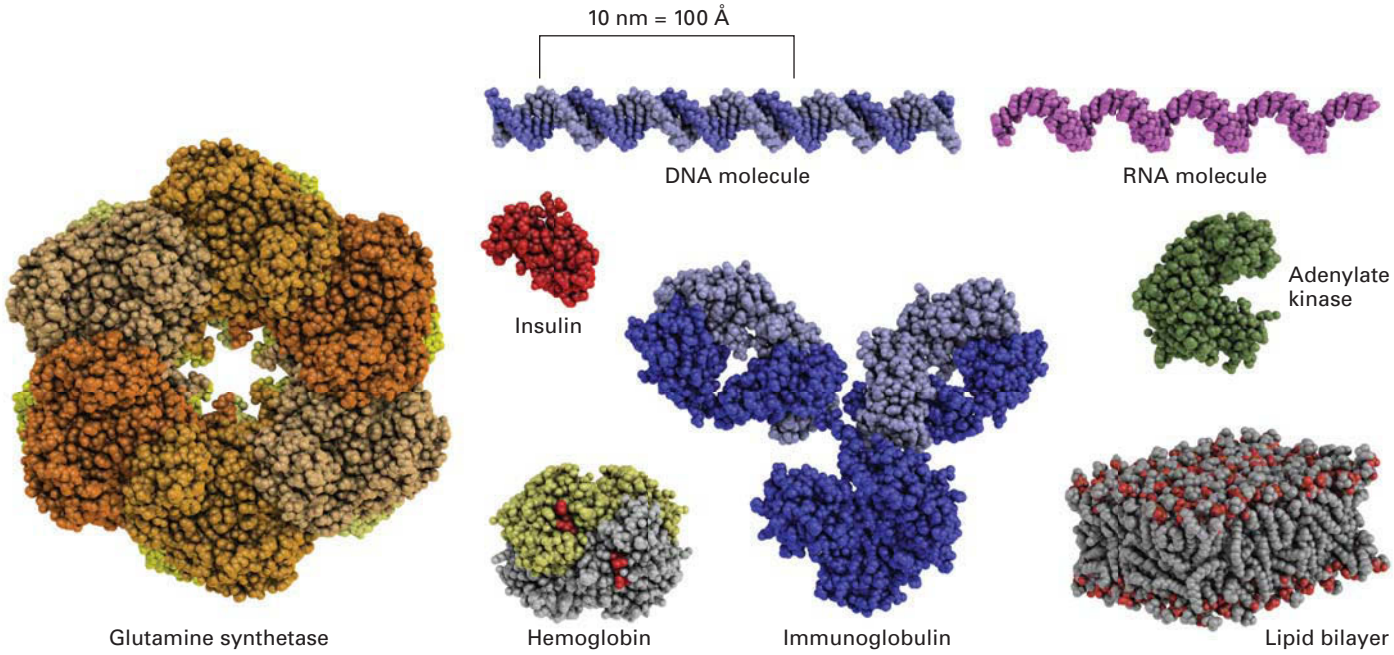


FIGURE 1-7 Models of some representative proteins drawn to a common scale and compared with a small portion of a lipid bilayer, a DNA molecule, and an RNA molecule. Each protein has a defined three-dimensional shape held together by numerous chemical bonds. The illustrated proteins include enzymes (glutamine synthetase and adenylate kinase), an antibody (immunoglobulin), a hormone (insulin), and the blood's oxygen carrier (hemoglobin). [Glutamine synthetase data from H. S. Gill and D. Eisenberg, 2001, *Biochemistry* **40**:1903–1912, PDB ID 1fpy. Insulin data from E. N. Baker et al., 1988, *Phil. Trans. R. Soc. Lond. B Biol. Sci.* **319**:369–456, PDB ID 4ins. Hemoglobin data from G. Fermi et al., 1984, *J. Mol. Biol.* **175**:159–174, PDB ID 2hhb. Immunoglobulin data from L. J. Harris et al., 1998, *J. Mol. Biol.* 275:861–872, PDB ID 1igy. Adenylate kinase data from G. Bunkoczi et al., PDB ID 2c9y.]

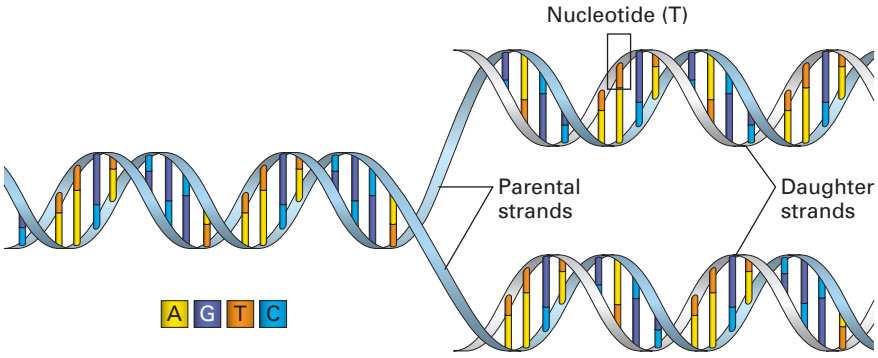


FIGURE 1-8 DNA consists of two complementary strands wound around each other to form a double helix. The double helix is stabilized by weak hydrogen bonds between the A and T bases and between the C and G bases. During replication, the two strands are unwound and used as templates to produce complementary strands. The outcome is two identical copies of the original double helix, each containing one of the original strands and one new daughter (complementary) strand.

double helix (Figure 1-8). The double-helical structure of DNA, one of nature's most magnificent constructions, is critical to the phenomenon of **heredity**, the transfer of genetically determined characteristics from one generation to the next.

DNA strands are composed of monomers called **nucleotides**; these monomers are often referred to as *bases* because they contain cyclic organic bases (see Chapter 5). Four different nucleotides, abbreviated A, T, C, and G, are joined to form a DNA strand, with the base parts projecting inward from the backbone of the strand. Two strands bind together via the bases and twist to form a double helix. Each DNA double helix has a simple construction: wherever one strand has an A, the other strand has a T, and each C is matched with a G (see Figure 1-8). This **complementary** matching of the two strands is so strong that if complementary strands are separated under the right salt concentration and temperature conditions, they will spontaneously zip back together. This property is critical for DNA replication and inheritance, as we will learn in Chapter 5, and also underlies many of the techniques for studying DNA molecules that are detailed in Chapter 6.

The genetic information carried by DNA resides in its *sequence*, the linear order of nucleotides along a strand. Specific segments of DNA, termed genes, carry instructions for making specific proteins. Commonly, genes contain two parts: the coding region specifies the amino acid sequence of a protein; the regulatory region binds specific proteins and controls when and in which cells the gene's protein is made.

Most bacteria have a few thousand protein-coding genes; yeasts and other unicellular eukaryotes have about 5000. Humans and other metazoans have between 13,000 and 23,000, while many plants have more. As we discuss later in this chapter, many of the genes in bacteria specify the sequences of proteins that catalyze reactions that occur universally, such as the metabolism of glucose and the synthesis of nucleic acids and proteins. These genes, and the proteins encoded by them, are conserved throughout all living organisms, and thus studies on the functions of these genes and proteins in bacterial cells have yielded profound insights into these basic life processes. Similarly, many genes in unicellular eukaryotes such as yeasts encode proteins that are conserved throughout all eukaryotes; we will see how yeasts have been used in studies of processes such as cell division that have yielded profound insights into human diseases such as cancer.

How is information stored in the sequence of DNA used? Cells use two processes in series to convert the coded information in DNA into proteins (Figure 1-9). In the first process, called **transcription**, the protein-coding region of a gene is copied into a single-stranded **ribonucleic acid** (**RNA**) whose sequence is the same as one of the two in the double-stranded DNA. A large enzyme, **RNA polymerase**, catalyzes the linkage of nucleotides into an RNA chain using DNA as a template. In eukaryotic cells, the initial RNA product is processed into a smaller **messenger RNA** (**mRNA**) molecule, which moves out of the nucleus to the **cytoplasm**, the region of the cell outside of the nucleus. Here the **ribosome**, an enormously complex molecular machine composed of both RNA and proteins, carries out the second process, called **translation**. During translation, the ribosome assembles and links together amino acids in the precise order dictated by the mRNA sequence according to the nearly universal **genetic code**. We examine the cell components that carry out transcription and translation in detail in Chapter 5.

In addition to its role in transferring information from nucleus to cytoplasm, RNA can serve as a framework for building a molecular machine. The ribosome, for example, is built of four RNA chains that bind to more than 50 proteins to make a remarkably precise and efficient mRNA reader and protein synthesizer. While most chemical reactions in cells are catalyzed by proteins, a few, such as the formation by ribosomes of the peptide bonds that connect amino acids in proteins, are catalyzed by RNA molecules.

Well before the entire human genome was sequenced, it was apparent that only about 10 percent of human DNA consists of protein-coding genes, and for many years the remaining 90 percent was considered "junk DNA"! In recent years, we've learned that much of the so-called junk DNA is actually copied into thousands of RNA molecules that, though they do not encode proteins, serve equally important purposes in the cell (see Chapter 10). At present, however, we know the function of only a very few of these abundant noncoding RNAs.

Like enzymes, certain RNA molecules, termed **ribozymes**, catalyze chemical reactions, as exemplified by the RNA inside a ribosome. Many scientists support the *RNA world* hypothesis, which proposes that RNA molecules that could replicate themselves were the precursors of current life forms;

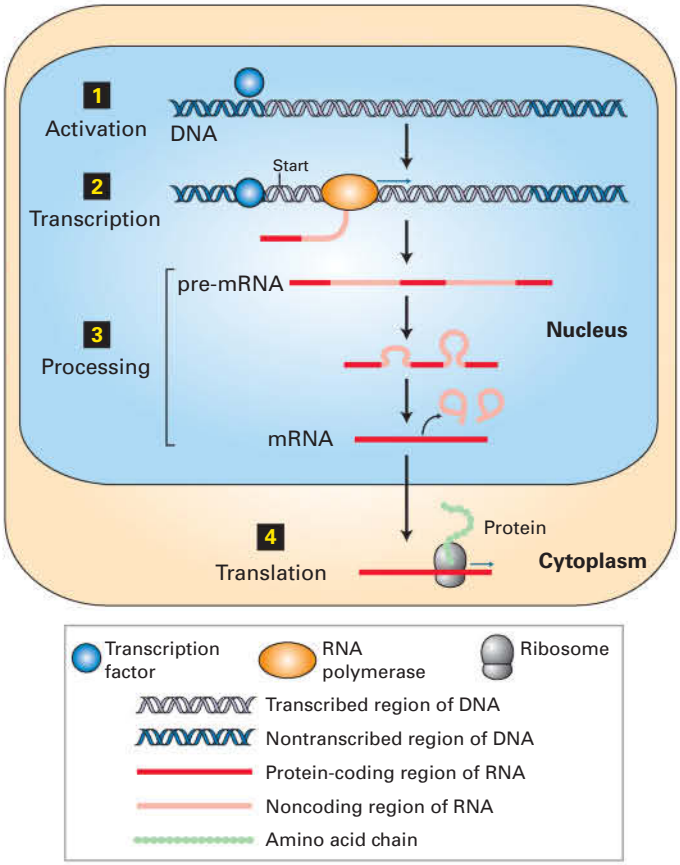


FIGURE 1-9 The information encoded in DNA is converted into the amino acid sequences of proteins by a multistep process. Step 1: Transcription factors and other proteins bind to the regulatory regions of the specific genes they control to activate those genes. Step 2: RNA polymerase begins transcription of an activated gene at a specific location, the start site. The polymerase moves along the DNA, linking nucleotides into a single-stranded pre-mRNA transcript using one of the DNA strands as a template. Step 3: The transcript is processed to remove noncoding sequences. Step 4: In a eukaryotic cell, the mature mRNA moves to the cytoplasm, where it is bound by ribosomes that read its sequence and assemble a protein by chemically linking amino acids into a linear chain.

billions of years ago, the RNA world gradually evolved into the DNA, RNA, and protein world of today's organisms.

All organisms must control when and where their genes are transcribed. Nearly all the cells in our bodies contain the full set of human genes, but in each cell type only some of these genes are active, or turned on, and used to make proteins. For instance, liver cells produce some proteins that are not produced by kidney cells, and vice versa. Moreover, many cells respond to external signals or changes in external conditions by turning specific genes on or off, thereby adapting their repertoire of proteins to meet current needs. Such control of gene activity depends on DNA-binding proteins called **transcription factors**, which bind to specific sequences of DNA and act as switches, either activating or repressing transcription of particular genes, as discussed in Chapter 9.

Phospholipids Are the Conserved Building Blocks of All Cellular Membranes

In all organisms, cellular membranes are composed primarily of a bilayer (two layers) of phospholipid molecules. Each of these bipartite molecules has a "water-loving" (hydrophilic) "head" and a "water-hating" (hydrophobic) "tail." The two phospholipid layers of a membrane are oriented with all the hydrophilic heads directed toward the inner or outer surfaces of the membrane and the hydrophobic tails buried within its interior (Figure 1-10). Smaller amounts of other lipids, such as cholesterol, are inserted into this phospholipid framework. Cellular membranes are extremely thin relative to the size of a cell. If you magnify a bacterium or yeast cell about 10,000 times to the size of a soccer ball, the plasma membrane is about as thick as a sheet of paper!

Phospholipid membranes are impermeable to water, all ions, and virtually all hydrophilic small molecules. Thus each membrane in each cell also contains groups of proteins that allow specific ions and small molecules to cross. Other membrane proteins serve to attach the cell to other cells or to polymers that surround it; still others give the cell its shape or allow its shape to change. We will learn more about membranes and how molecules cross them in Chapters 7 and 11.

New cells are always derived from parental cells by cell division. We've seen that the synthesis of new DNA molecules is templated by the two strands of the parental DNA such that each daughter DNA molecule has the same sequence as the parental one. In parallel, new membranes are made by incorporation of lipids and proteins into existing membranes in the parental cell and divided between daughter cells by fission. Thus membrane synthesis, like DNA synthesis, is templated by a parental structure.

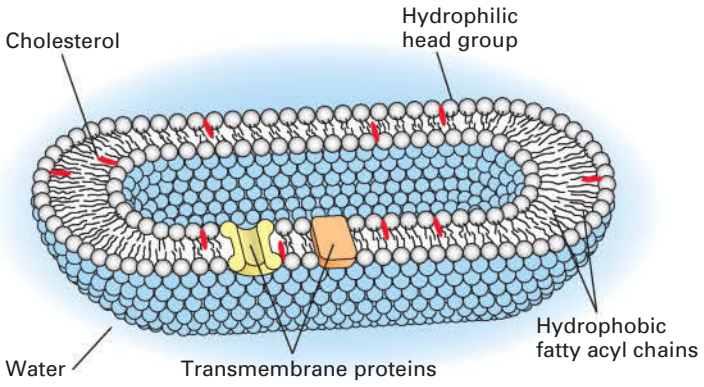


FIGURE 1-10 The watery interior of cells is surrounded by the plasma membrane, a two-layered shell of phospholipids. The phospholipid molecules are oriented with their hydrophobic fatty acyl chains (black squiggly lines) facing inward and their hydrophilic head groups (white spheres) facing outward. Thus both sides of the membrane are lined by head groups, mainly charged phosphates, adjacent to the watery spaces inside and outside the cell. All biological membranes have the same basic phospholipid bilayer structure. Cholesterol (red) and various proteins are embedded in the bilayer. The interior space is actually much larger relative to the volume of the plasma membrane than is depicted here.