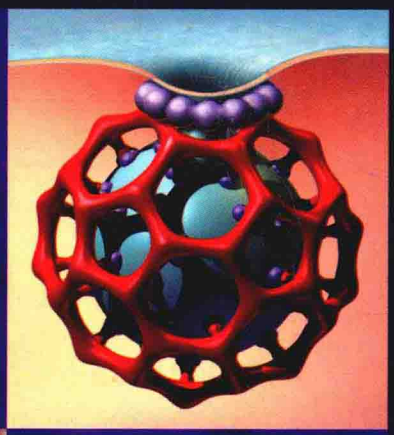
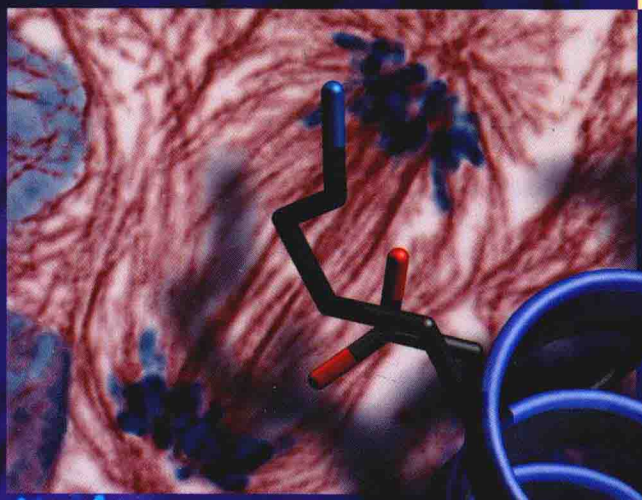
UPDATED EDITION

# CELL BIOLOGY

THOMAS D. POLLARD
WILLIAM C. EARNSHAW

Illustrated by Graham T. Johnson







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# CELL BIOLOGY

**Thomas D. Pollard, M.D.**
Higgins Professor of Molecular, Cellular and Developmental Biology
Yale University
New Haven, Connecticut

**William C. Earnshaw, Ph.D., FRSE**
Professor and Wellcome Trust Principal Research Fellow
University of Edinburgh
Scotland, United Kingdom

Illustrated by Graham T. Johnson

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chapter 1

# GENERAL PRINCIPLES OF CELLULAR ORGANIZATION

## Historical Prologue

Biology is based on the fundamental laws of nature embodied in chemistry and physics, but the origin and evolution of life on earth was an historical event. This makes biology more like astronomy than like chemistry and physics. Neither the organization of the universe nor life as we know it had to evolve as it did. Chance played a central role. Throughout history and continuing today, the genes of some organisms sustain chemical changes that are inherited by their progeny. Many of the changes reduce the fitness of the organism, but some improve fitness. Over the long term, competition between sister organisms with random differences in their genes determines which survive in various environments. Although these genetic differences assure survival, they do not necessarily optimize each chemical life process. The variants that survive merely have a selective advantage over the alternatives. Thus, the molecular strategy of life processes works well, but is often illogical. Readers would likely be able to suggest simpler or more elegant mechanisms for many cellular processes. This historical prologue sets the stage for all that follows. Recent research has redrawn the tree of life (Fig. 1–1), providing a sound basis for understanding how life evolved and how contemporary organisms are related to each other.

### The Unity of Biology at the Molecular Level

As the molecular mechanisms of life have become clearer, the underlying similarities are more impressive than the differences. Humans share with baker's yeast similar mechanisms to control our cell cycles, to guide protein secretion, and to segregate chromosomes at mitosis. Human versions of essential proteins can often substitute for their yeast counterparts. Biologists are confident that a limited number of general principles, summarizing common molecular mechanisms, will eventually explain even the most complex life processes in terms of straightforward chemistry and physics.

These general principles apply to all forms of life, because 3 or 4 billion years ago, all living things had a common ancestor (Box 1–1; see also Fig. 1–1). This organism no longer exists, but it must have utilized biochemical mechanisms similar to those that sustain contemporary cells. This retention of common molecular mechanisms in all parts of the **phylogenetic tree** is remarkable, given that the major phylogenetic groups have been separated for vast times and subjected to different selective pressures. The biochemical mechanisms in the branches of the phylogenetic tree could have diverged radically from each other, but they did not. To be sure, living things differ in size and complexity and are adapted to life in environments as extreme as deep sea hydrothermal vents at temperatures of 113°C or pockets of water at 0°C in frozen Antarctic lakes. They also differ in strategies to extract energy from their environments. Plants and some bacteria use sunlight for photosynthesis. Some bacteria and Archaea oxidize reduced inorganic compounds, such as hydrogen, hydrogen sulfide, or iron. Many organisms in all parts of the tree, including ourselves, extract energy from reduced organic compounds. Nevertheless, all organisms share a common genetic code, store genetic information in nucleic acids (usually **DNA**), transfer genetic information from DNA to **RNA** to protein, employ proteins (and occasionally, RNAs) to catalyze chemical reactions, synthesize proteins on **ribosomes,** derive energy by breaking down simple sugars, use adenosine triphosphate (**ATP**) as energy currency, and separate their cyto-

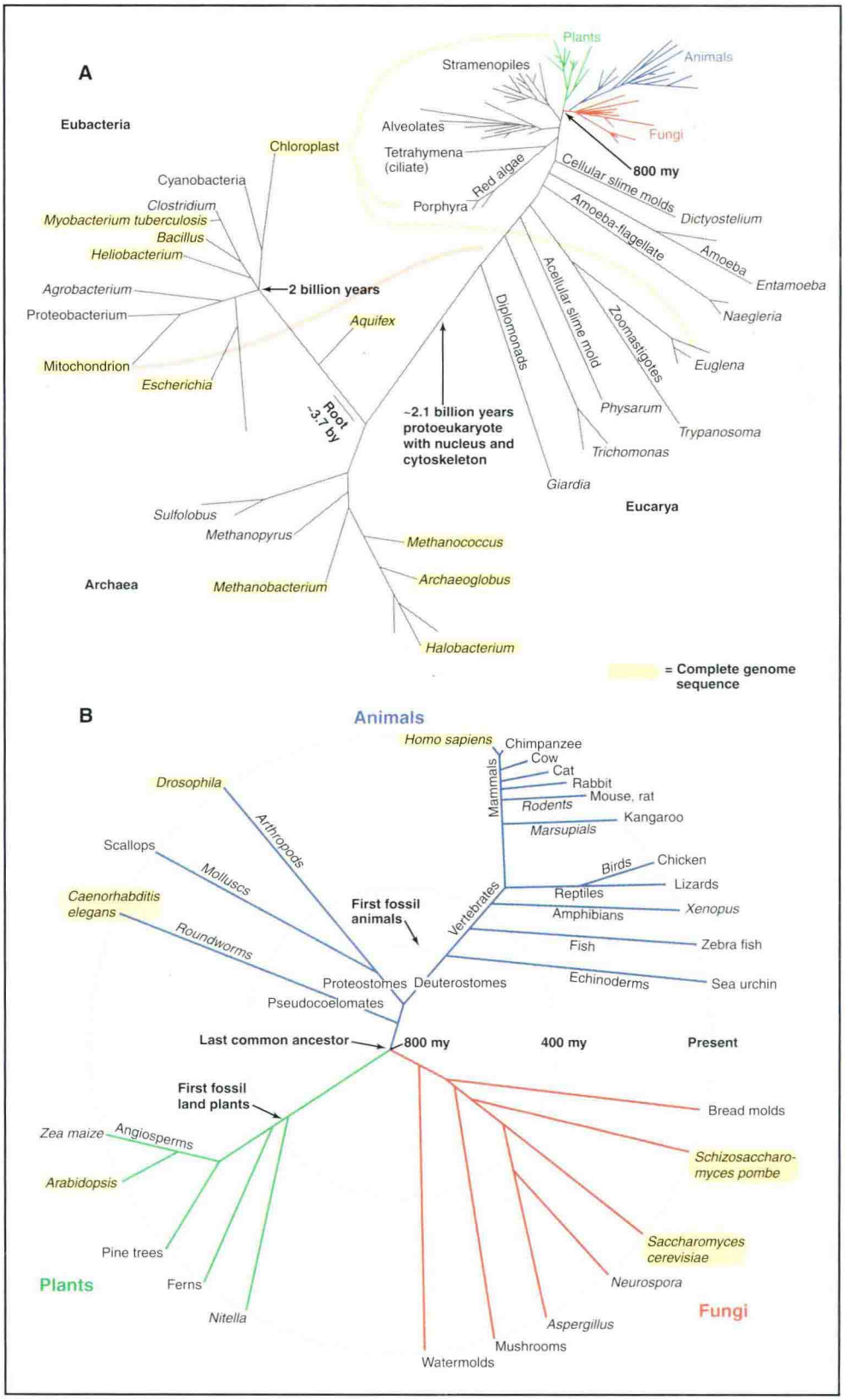


**Figure 1–1** *See legend on opposite page*

plasm from their environment by means of phospholipid **membranes** containing **pumps, carriers,** and **channels.** These ancient biochemical strategies are so well adapted for survival that they have been protected from change during natural selection of the surviving species.

The common evolutionary origin of contemporary forms of life explains the underlying similarity of biochemical mechanisms across the phylogenetic tree. A practical consequence of the common ground provided by evolution is that the general principles of cellular function can be learned by studying any cell that is favorable for experimentation. This text will cite many examples where research on bacteria, insects, protozoa, or fungi has revealed fundamental mechanisms shared by human cells.

Not all cells are the same (Fig. 1–2). In particular, all eukaryotes (protists, plants, fungi, and animals) differ in important ways from the two extensive groups of prokaryotes (Eubacteria and Archaea). All eukaryotic cells have a compartmentalized cytoplasm (consisting of organelles including a nucleus) and a cytoskeleton. The basic features of eukaryotic organelles and the cytoskeleton were refined more than 1.5 billion years ago, before the major groups of eukaryotes diverged. To put human life in perspective, note that multicellular eukaryotes (green, blue, red in Fig. 1–1) evolved relatively recently, hundreds of millions of years after earlier, single-celled eukaryotes. Also note that plants branched off before fungi, our nearest relatives on the tree of life.

Many interesting creatures have been lost to extinction during evolution. Extinction is irreversible because the cell is the only place where the entire range of life-sustaining biochemical reactions, including gene replication, molecular biosynthesis, targeting, and assembly, can go to completion. Thus, cells are such a special environment that the chain of life has required an unbroken lineage of cells stretching from each contemporary organism back to the earliest forms of life.

## Introduction to Cells

This text focuses on the underlying molecular mechanisms of biological function at the cellular level. This chapter starts with a brief description of the main features that set eukaryotes apart from prokaryotes and then covers the general principles that apply equally well to eukaryotes and prokaryotes. It closes with a preview of the major components of eukaryotic cells.

### Two Features That Distinguish Eukaryotic and Prokaryotic Cells

1. *Eukaryotic cells are compartmentalized.* A plasma membrane surrounds all cells, and additional in-

**Figure 1–1** The tree of life. *A,* Universal tree based on comparisons of ribosomal RNA sequences. The tree has its root deep in the Eubacterial lineage 3 to 4 billion years ago. All current organisms, arrayed at the ends of branches, fall into three domains: Bacteria, Archaea and Eucarya (eukaryotes). The lengths of the segments and branches are based solely on differences in RNA sequences. Because the rate of random changes in the genes for rRNA has not been constant, the lengths of the lines leading to all contemporary organisms are not equal. Fossil records provide the estimated times of a few key events. Complete sequences of a few genomes (*orange,* see ⟨*tigr.org/tdbv/mdb.html*⟩) verify this tree, but also show that genes moved laterally between Eubacteria and Archaea and within each of these domains. Genes also moved from Eubacteria to Eucarya when proteobacteria gave rise to mitochondria (transferring many of their genes to the eukaryotic nucleus) and when cyanobacteria gave rise to chloroplasts by a similar mechanism. Protozoa branched near the bottom of the eukaryotic lineage and relatively recently gave rise to other eukaryotic kingdoms: plants, fungi, and animals (*enlarged in Fig. 1–1*B). Analysis of rRNA sequences shows that organisms formerly classified as algae, as well as organisms formerly classified elsewhere, actually belong to four large branches near the top of the tree: alveolates (including dinoflagellates, ciliates, and sporozoans), stramenopiles (including diatoms and brown algae), rhodophytes (red algae), and plants (including the green alga *Chlamydomonas*). Molecular analysis also established that cellular slime molds (e.g., *Dictyostelium*) and acellular slime molds (e.g., *Physarum*) are not fungi and arose at different times. Unicellular amoeboid organisms arose multiple times during evolution and do not form a coherent group. *B,* Time line for the divergence of animals, plants, and fungi. In contrast to *A,* this tree has a radial time scale originating about 800 million years (my) ago with the last common ancestor. Contemporary organisms and time are at the circumference. Lengths of branches are arbitrary. With one exception, the order of branching is firmly established, based on comparisons of gene sequences. The exception is the branching of nematode round worms, shown here as an early event. New work suggests that nematodes are more closely related to arthropods. The times of branching of the oldest common ancestor of each pair of diverging lineages are only estimates, since the calibration of the molecular clocks is uncertain and the early fossil records are sparse. (*A,* Original drawing, adapted from the branching pattern from Sogin M, Marine Biological Laboratory, Pace N: A molecular view of microbial diversity and the biosphere. Science 276:734–740, 1997. *B,* Original drawing, based on timing for animals, adapted from Kuman S, Hedges SB: A molecular timescale for vertebrate evolution. Nature 392:917–920, 1998; based on timing for plants, adapted from ⟨ucjeps.herb.berkeley.edu/bryolab/greenplantpage.html⟩; based on timing for fungi, adapted from ⟨phylogeny.arizona.edu/tree/eukaryotes/fungi/ascomycota/axcomycota.html⟩.)

*box 1–1*

## ORIGIN AND EVOLUTION OF LIFE

All living things belong to one of three great divisions: Eubacteria, Archaea, or Eucarya (see Fig. 1–1). Archaea and Eubacteria were considered as one kingdom until the 1970s when ribosomal RNA sequences revealed that they were different divisions of the tree of life, having branched from each other almost as long ago as they branched from eukaryotes.

No one is certain how life began, but the ancestor of all living things populated the earth nearly 4 billion years ago, not long after the earth formed 4.6 billion years ago. Common biochemical features of all succeeding cells suggest that this primitive microscopic cell had about a thousand genes. These genes diversified in later cells by the process of duplication and random mutations in their sequences. Where these modified genes provided a selective advantage, they were retained in future generations. This mechanism accounts for the huge families of related but specialized proteins, such as pumps and carriers found in the cell membranes of all forms of life. Where conditions did not require a gene, it was lost. For example, the simple pathogenic bacteria, *Mycoplasma genitalium,* has but 470 genes, since it can rely on its animal host for most nutrients, rather than making them de novo. Similarly, the slimmed down genome of budding yeast, with only 6144 genes, lost nearly 400 genes common to lower organisms. Vertebrates also lost many genes that had been maintained for 3 billion years in earlier forms of life. For instance, humans lack the enzymes to synthesize certain essential amino acids, which must be supplied in our diets.

The Eubacteria and Archaea that branched nearest the base of the tree of life mainly live at high temperatures and use hydrogen as their energy source. The common ancestor may have shared these features. Archaea and Eucarya briefly shared a common lineage. This is reflected in similarities in their apparatus for copying DNA into messenger RNA, but Archaea are closer to bacteria than Eucarya in most other ways.

Since the beginning, microorganisms dominated the earth in terms of numbers, variety of species, and range of habitats. Eubacteria and Archaea remain the most abundant organisms in the seas and in the earth. Less than 1% of Eubacteria and Archaea can be grown in the laboratory, so most varieties have escaped detection by traditional means. Now, new species can be identified by amplifying and sequencing characteristic genes from minute samples. Remarkably, only a very small proportion of Eubacterial species and no Archaea cause human disease. Chlorophyll-based photosynthesis originated in Eubacteria. More recently, the form of photosynthesis that produces reduced carbon compounds and oxygen from carbon dioxide and water was perfected in cyanobacteria. This raised the oxygen concentration in the earth's atmosphere to current levels and generated the organic compounds that many other forms of life depend upon for energy.

We know little about the earliest Eucarya other than the fact that their genomes may be nearly as old as those of Eubacteria and Archaea. The most primitive-appearing contemporary **eukaryote** is an amoeba lacking mitochondria called *Pelomyxa palustris.* Throughout evolution, the most numerous and heterogeneous eukaryotes have been microscopic single-celled protists. Symbiotic bacteria similar to proteobacteria (see Fig. 1–1*A*) brought respiration to early eukaryotes. Over time, most of the bacterial genes moved to the host **nucleus,** leaving behind a small number of genes in the organelle that we call a **mitochondrion.** Organisms that branched first from the eukaryotic lineage, such as *Giardia* (the cause of "hiker's diarrhea"), lack mitochondria, but the presence of a few bacterial genes in their nuclei may be evidence of transient associations with bacteria. Relatively late during evolution, cyanobacterial symbionts brought photosynthesis to red algae, brown algae, and green algae/plants. As the bacteria evolved into **chloroplasts,** most of the bacterial genes moved to the nucleus of the host.

The multicellular lifestyle emerged multiple times more than a billion years ago in colonial bacteria, cellular slime molds, and red, brown, and green algae. Some of these organisms, such as kelp, a tree-size brown alga found along many seashores, are huge. According to analysis of ribosomal RNA, animals, plants, and fungi arose from algae-like organisms some time between 670 and 1200 million years ago, well before the first fossils of these types. The existence of fossils about 570 million years old that are strikingly similar to contemporary animal embryos supports a hypothesis that early multicellular animals were small creatures similar to contemporary invertebrate larvae or embryos. Similar, tiny, early animals may have existed much earlier. If the major branches of the animal tree diverged before macroscopic animals developed, this might account for the disagreement between the molecular data and the fossil record, which suggests a much more recent divergence of animals.

tracellular membranes divide eukaryotes into compartments, each with a characteristic structure, biochemical composition, and function (see Fig. 1–2). The **nuclear envelope** separates the two major compartments: nucleoplasm and cytoplasm. The **chromosomes** carrying the cell's genes and the machinery to express these **genes** reside inside the nucleus; they are in the cytoplasm of prokaryotes. Most eukaryotic cells have **endoplasmic reticulum** (the site of protein and phospholipid synthesis), a **Golgi apparatus** (an organelle that adds sugars to membrane proteins,

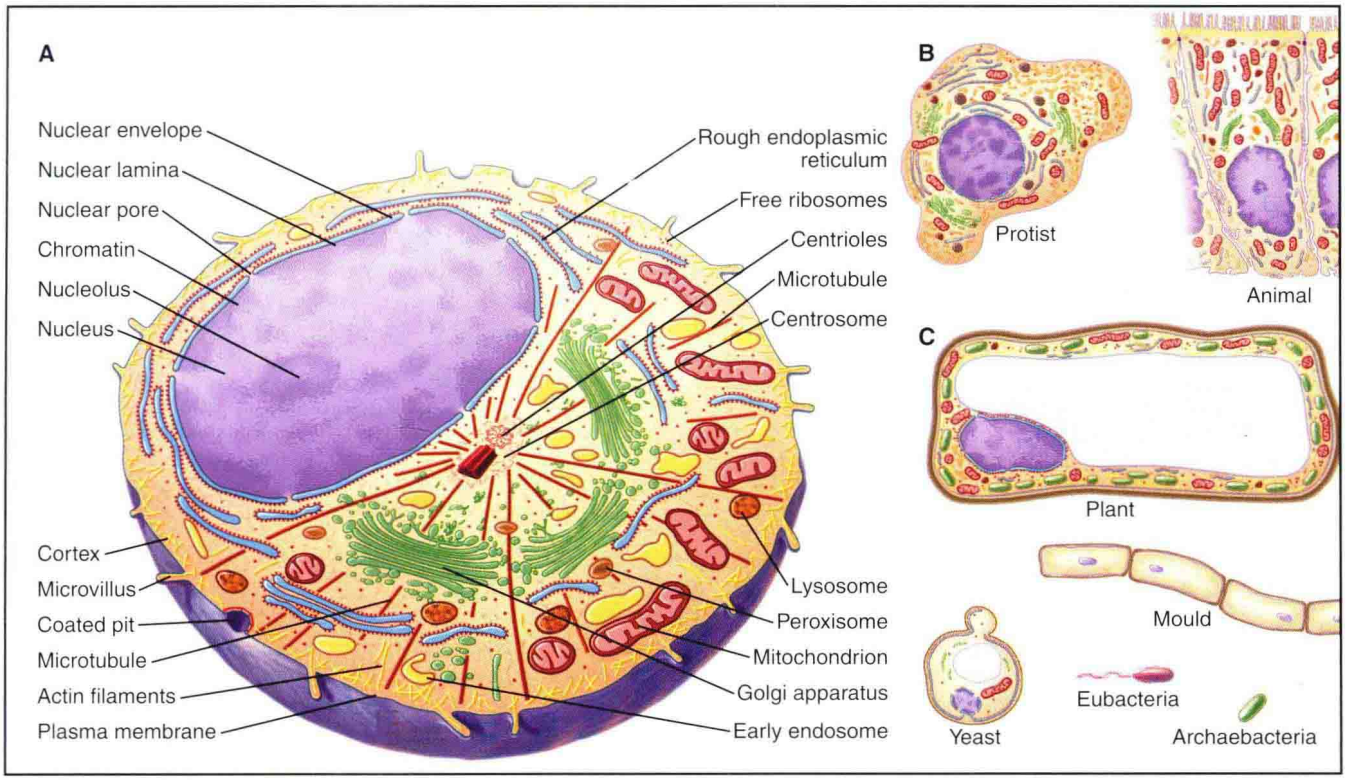


**Figure 1–2** Basic cellular architecture. *A,* Drawing of a section through a eukaryotic cell showing the internal components. *B and C,* Drawings comparing cells from the major branches of the phylogenetic tree with color-coded components.

lysosomal proteins, and secretory proteins), **lysosomes** (a compartment for digestive enzymes), **peroxisomes** (containers for enzymes involved in oxidative reactions), and **mitochondria** (structures that convert energy stored in the chemical bonds of nutrients into ATP). Table 1–1 lists the major cellular components and some of their functions.

Compartments give eukaryotic cells a number of advantages. The membranes provide a barrier that allows each type of organelle to maintain novel ionic and enzymatic interior environments. Each of these special environments favors a subset of the biochemical reactions required for life. The following three examples demonstrate this concept.

- Segregation of digestive enzymes in lysosomes prevents them from destroying other cellular components.
- ATP synthesis depends on the impermeable membrane around mitochondria; energy-releasing reactions produce a proton gradient across the membrane that enzymes in the membrane use to drive ATP synthesis.
- The nuclear envelope provides a compartment where the synthesis and editing of RNA copies of the genes can be completed before the mature messenger RNAs exit to the cytoplasm where they direct protein synthesis.

2. *Eukaryotic cells have a cytoskeleton.* Three protein polymers—**actin filaments, microtubules,** and **intermediate filaments**—form a viscous and elastic cytoplasmic matrix to provide mechanical support for the cell. In addition, actin filaments and microtubules are tracks for a variety of motor proteins that move the whole cell and the organelles within the cytoplasm. The actin filament and microtubule **cytoskeletons** are essential for life even in fungi and plants, which have rigid cell walls that provide mechanical support and prevent locomotion of the whole cell. Although encased in their cell walls, these cells depend on the cytoskeleton and its associated motors to transport organelles in the cytoplasm and to segregate the chromosomes.

## Some Universal Principles of Living Cells

1. *Genetic information stored in one-dimensional chemical sequences in DNA (occasionally RNA) is duplicated and passed on to daughter cells* (Fig. 1–3). The information required for cellular growth, multiplication, and function is stored in long polymers of DNA called chromosomes. Each

*table 1–1*

**INVENTORY OF CELLULAR COMPONENTS***

| Cellular Component | Description |
|---|---|
| Plasma membrane | A lipid bilayer, 7 nm thick, with integral and peripheral proteins; the membrane surrounds cells and contains channels and pumps for ions and nutrients, receptors for growth factors, hormones and (in nerves and muscles) neurotransmitters, plus the molecular machinery to transduce these stimuli into intracellular signals |
| Adherens junction | A punctate or belt-like link between cells with actin filaments attached on the cytoplasmic surface |
| Desmosome | A punctate link between cells associated with intermediate filaments on the cytoplasmic surface |
| Gap junction | A localized region where the plasma membranes of two adjacent cells join to form minute intercellular channels for small molecules to move from the cytoplasm of one cell to the other |
| Tight junction | An annular junction sealing the gap between epithelial cells |
| Actin filament | "Microfilaments," 8 nm wide; form a viscoelastic network in the cytoplasm and act as tracks for myosin-powered movements |
| Intermediate filament | Filaments, 10 nm wide, composed of keratin-like proteins that act as inextensible "tendons" in the cytoplasm |
| Microtubule | A tubular polymer of tubulin, 25 nm in diameter, that is the main structural component of cilia, flagella, and the mitotic spindle; microtubules provide tracks for organelle movements powered by dynein and kinesin |
| Centriole | A short cylinder of 9 microtubule triplets located in the cell center (centrosome) and at the base of cilia and flagella; pericentrosomal material nucleates and anchors microtubules |
| Microvillus (or filopodium) | A thin, cylindrical projection of the plasma membrane supported internally by a bundle of actin filaments |
| Cilia/flagella | Motile organelles projecting from the cell surface and surrounded by plasma membrane; their bending motions are powered by an axoneme consisting of 9 doublet and 2 singlet microtubules with the energy-transducing enzyme, dynein |
| Glycogen particle | Storage form of polysaccharide |
| Ribosome | RNA/protein particle that catalyzes protein synthesis |
| Rough endoplasmic reticulum | Flattened, intracellular bags of membrane with associated ribosomes that synthesize secreted and integral membrane proteins |
| Smooth endoplasmic reticulum | Flattened, intracellular bags of membrane without ribosomes involved in lipid synthesis, drug metabolism, and sequestration of $Ca^{2+}$ |
| Golgi apparatus | A stack of flattened membrane bags and vesicles that packages secretory proteins and participates in protein glycosylation |
| Nuclear envelope | A pair of membranes connected to the endoplasmic reticulum that limits the nucleus |
| Nuclear pore | Large, gated channels across the nuclear envelope that control all traffic of proteins and RNA in and out of the nucleus |
| Euchromatin | Dispersed, active form of interphase chromosomes |
| Heterochromatin | Condensed, inactive chromatin |
| Nucleolus | Intranuclear site of ribosomal RNA synthesis and processing; ribosome assembly |
| Lysosome | Impermeable, membrane-bound bags of hydrolytic enzymes |
| Peroxisome | Membrane-bound bags containing catalase and various oxidases |
| Mitochondria | Organelles surrounded by a smooth outer membrane and a convoluted inner membrane folded into cristae; they contain enzymes for fatty acid oxidation and oxidative phosphorylation of ADP |

*See Figure 1–2.

DNA molecule is composed of a covalently linked linear sequence of four different nucleotides (adenine [A], cytosine [C], guanine [G], and thymine [T]). In the double-helix DNA molecule, each nucleotide base preferentially forms a specific complex with a complementary base on the other strand. Specific noncovalent interactions stabilize the pairing between complementary nucleotide bases, A with T and C with G. During DNA replication, the two DNA strands are separated, each serving as a template for the synthesis of a new complementary strand. The enzymes that carry

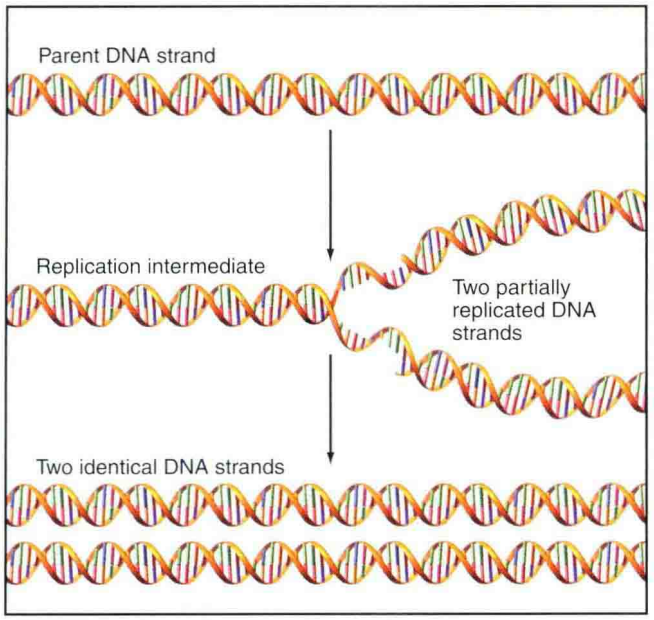


**Figure 1–3** DNA structure and replication. The genes stored as the sequence of bases in DNA are replicated enzymatically, forming two identical copies from one double-stranded original.

out DNA synthesis recognize the structure of complementary base pairs and insert only the correct complementary nucleotide at each position, thereby producing two identical copies of the DNA. Precise segregation of one, newly duplicated, double helix to each daughter cell then guarantees the transmission of intact genetic information to the next generation.

2. *One-dimensional chemical sequences are stored in DNA code for both the linear sequences and three-dimensional structures of RNAs and proteins* (Fig. 1–4). Enzymes called polymerases copy the information stored in genes into linear sequences of nucleotides of RNA molecules. Some genes specify RNAs with structural roles or enzymatic activity, but most genes produce **messenger RNA** (mRNA) molecules that act as templates for protein synthesis specifying the sequence of amino acids during the synthesis of **polypeptides** by ribosomes. The amino acid sequence of most polypeptides contains sufficient information to determine how to fold into a unique three-dimensional structure with biological activity. Genetically encoded control circuits, which are modified by environmental stimuli, control the production and processing of RNA and protein from tens of thousands of genes. The basic plan for the cell contained in the genome, together with ongoing regulatory mechanisms (see points 7 and 8 below), work so well that each human develops with few defects from a single fertilized egg into a complicated ensemble of trillions of specialized cells that function harmoniously for decades in an ever-changing environment.
3. *Macromolecular structures assemble from subunits* (Fig. 1–5). Many cellular components form by **self-assembly** of their constituent molecules without the aid of templates or enzymes. The protein, nucleic acid, and lipid molecules themselves contain the information required to assemble complex structures. Diffusion usually brings the molecules together during these assembly processes. Exclusion of water from their complementary surfaces ("lock and key" packing), as well as electrostatic and hydrogen bonds, provide the energy to hold the subunits together. In some cases, protein chaperones assist with assembly by preventing the precipitation of partially or incorrectly folded intermediates. Examples of important macromolecular assemblies include the packaging of DNA by proteins to form **chromatin,** the co-

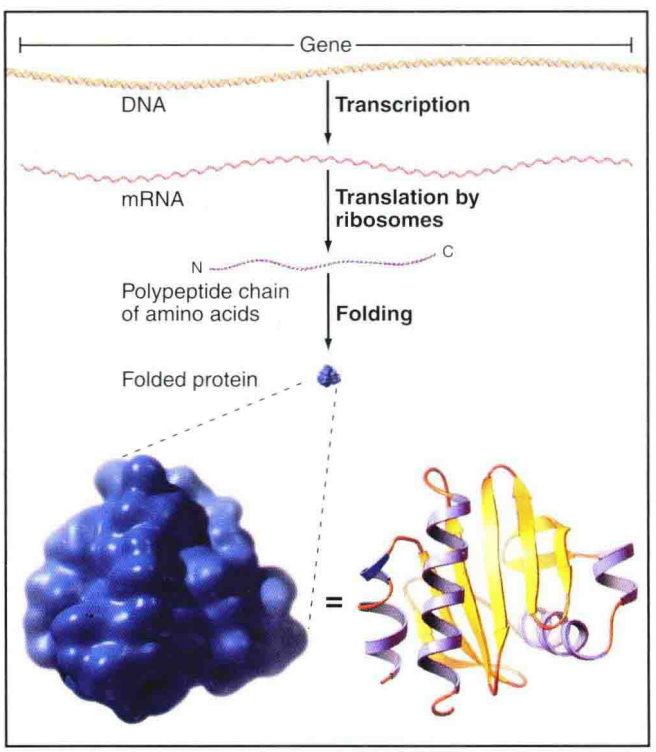


**Figure 1–4** Scale drawings showing how genetic information contained in the base sequence of DNA determines the amino acid sequence of a protein and its three-dimensional structure. Enzymes copy (transcribe) the sequence of bases in a gene to make a messenger RNA (mRNA). Ribosomes use the sequence of bases in the mRNA as a template to synthesize (translate) a corresponding linear polymer of amino acids. This polypeptide folds spontaneously to form a three-dimensional protein molecule, in this example, the actin-binding protein profilin. (Protein data base [PDB] file: 1ACF.)

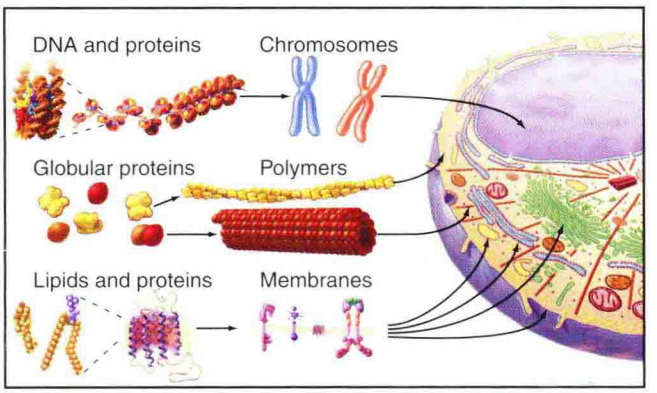


**Figure 1–5** Macromolecular assembly. Many macromolecular components of cells assemble spontaneously from the constituent molecules without the guidance of templates. Proteins and DNA assemble chromatin. Globular proteins assemble cytoskeletal filaments. Proteins and lipids assemble membranes that grow by lateral expansion of preexisting membranes. The endoplasmic reticulum is the site of most lipid biosynthesis and also the site where new proteins are inserted into the growing membrane.

assembly of RNA and proteins to form ribosomes, the polymerization of proteins to form cytoskeletal polymers, and the assembly of lipids and proteins to form membranes.

4. *Membranes grow by expansion of preexisting membranes* (see Figs. 1–5 and 1–6). Biological membranes composed of phospholipids and proteins do not form de novo in cells; instead, they grow only by expansion of preexisting lipid bilayers. As a consequence, organelles, such as mitochondria and endoplasmic reticulum, form only by growth and division of preexisting organelles and are inherited maternally starting from the egg. The endoplasmic reticulum (ER) plays a central role in membrane biogenesis as the site of phospholipid synthesis. Through a series of budding and fusion events, membrane made in the ER provides material for the Golgi apparatus, which, in turn, provides lipids and proteins for lysosomes and the plasma membrane.
5. *Signal-receptor interactions target cellular constituents to their correct locations* (see Fig. 1–6). Specific recognition signals incorporated into the structures of proteins and nucleic acids route these molecules to their proper cellular compartments. Receptors recognize these signals and guide each molecule to its correct compartment. For example, most proteins destined for the nucleus contain short sequences of amino acids that bind receptors that facilitate their passage through nuclear pores into the nucleus. Similarly, a peptide signal sequence first targets lysosomal proteins into the lumen of the ER. Subsequently, the Golgi apparatus adds a sugar-phosphate group recognized by receptors that target these proteins to lysosomes.
6. *Cellular constituents move by diffusion, pumps, and motors* (Fig. 1–7). Most small molecules move through the cell or across membrane channels by diffusion. Movements of small molecules across membranes against concentration gradients and movements of larger objects, like organelles, through cytoplasm, require the expenditure of energy. Electrochemical gradients or ATP hydrolysis provide energy for molecular pumps to drive molecules across membranes against concentration gradients. ATP-burning **motor proteins** move organelles and other cargo along microtubules or

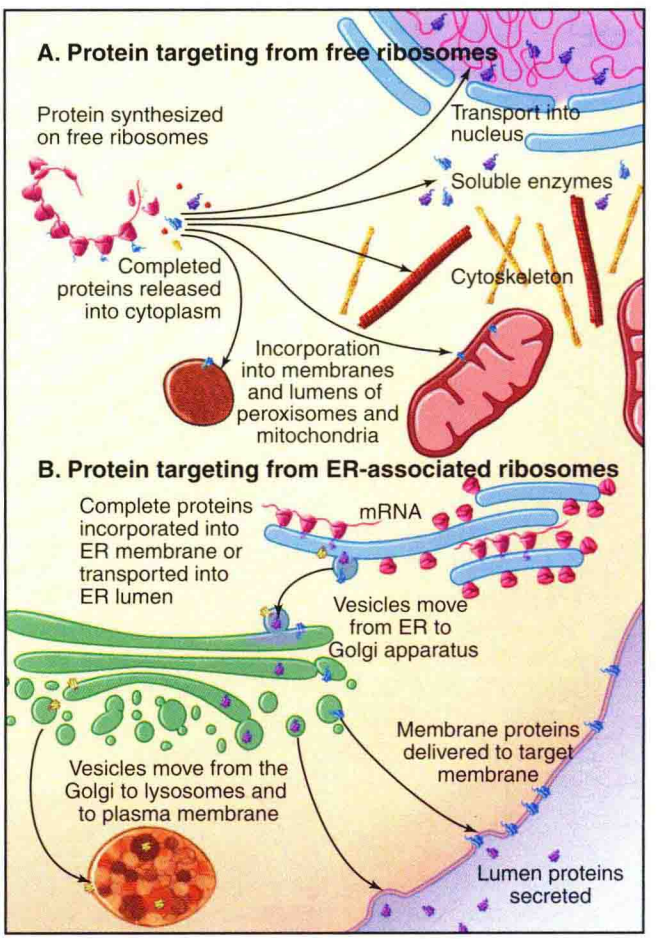


**Figure 1–6** Protein targeting. Signals built into the amino acid sequence of proteins target them to all compartments of the eukaryotic cell. *A,* Proteins synthesized on free ribosomes can be used locally in the cytoplasm or guided by different signals to the nucleus, mitochondria, or peroxisomes. *B,* Other signals target proteins for insertion into the membrane or lumen of the endoplasmic reticulum (ER). From there, a series of vesicular budding and fusion reactions carry the membrane proteins and lumen proteins to the Golgi apparatus, lysosomes, or plasma membrane.

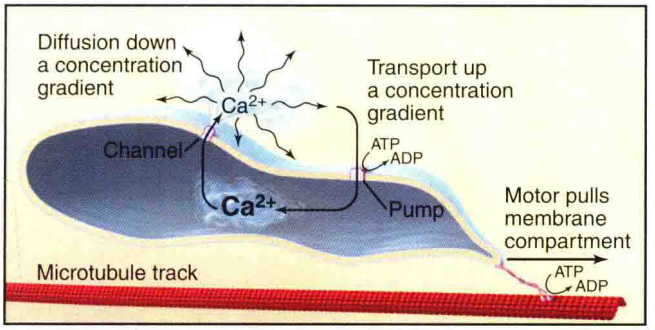


**Figure 1–7** Molecular movements by diffusion, pumps, and motors. *Diffusion*: Molecules up to the size of globular proteins diffuse in the cytoplasm. Concentration gradients can provide a direction to diffusion, such as the diffusion of $Ca^{++}$ from a region of high concentration inside the endoplasmic reticulum through a membrane channel to a region of low concentration in the cytoplasm. *Pumps*: ATP-driven protein pumps can transport ions up concentration gradients. *Motors*: ATP-driven motors move organelles and other large cargo along microtubules and actin filaments.

actin filaments. In a more complicated example, protein molecules destined for mitochondria diffuse from their site of synthesis in the cytoplasm to a mitochondrion (see Fig. 1–6) where they bind to a receptor. An energy-requiring reaction then transports the protein into the mitochondria.

7. *Receptors and signaling mechanisms allow cells to adapt to environmental conditions* (Fig. 1–8). Environmental stimuli modify cellular behavior and biochemistry. Faced with an unpredictable environment, cells must decide which genes to express, which way to move, and whether to proliferate, differentiate into a specialized cell, or die. Some of these choices are programmed genetically, but minute-to-minute decisions generally involve the reception of chemical or physical stimuli from outside the cell and the processing of these stimuli to change the behavior of the cell. Cells have an elaborate repertoire of **receptors** for a multitude of stimuli, including nutrients, growth factors, hormones, neurotransmitters, and toxins. Stimulation of these receptors activates signal-transducing mechanisms that produce chemical signals to generate a wide range of cellular responses. These responses regulate the electrical potential of the plasma membrane, gene expression, enzyme activity, cytoskeletal motors, and many other systems. Basic **signal transduction** mechanisms are very ancient, but many specific receptors and output systems have arisen during evolution. Thus, humans typically have a greater number of variations on the general themes than simpler organisms.
8. *Molecular feedback mechanisms control molecular composition, growth, and differentiation* (Fig. 1–9). Living cells are dynamic, constantly undergoing changes in composition or activity in response to external stimuli, nutrient availability, and internal signals. Change is constant, but through well-orchestrated recycling and renewal, the cell and its constituents remain relatively stable. Each cell regulates the balanced production and degradation of its constituent molecules to function optimally. Some "housekeeping" molecules are used by most cells for basic functions, such as intermediary metabolism. Other molecules are unique and are required for specialized functions of differentiated cells. The supply of each of thousands of proteins is controlled by a hierarchy of mechanisms: by regulatory proteins that turn specific genes on and off; by the rate of transla-

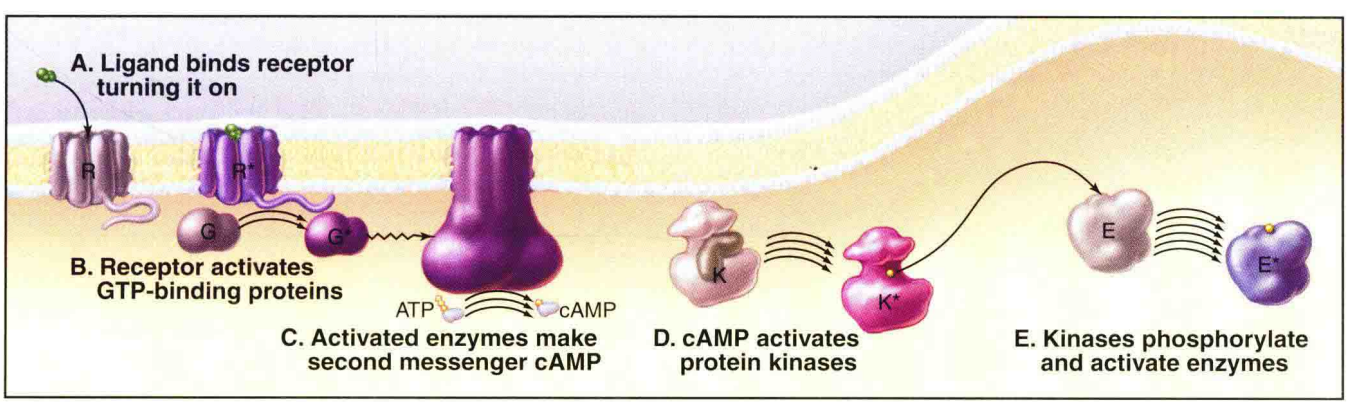


**Figure 1–8** Receptors and signals. Activation of cellular metabolism by an extracellular ligand, such as a hormone. In this example, binding of the hormone (*A*) triggers a series of linked biochemical reactions (*B* to *E*), leading through a second messenger molecule (cyclic adenosine monophosphate, or cAMP) and a cascade of three activated proteins to a metabolic enzyme. The response to a single ligand is multiplied at steps *B*, *C*, and *E*, leading to thousands of activated enzymes. GTP, guanosine triphosphate.

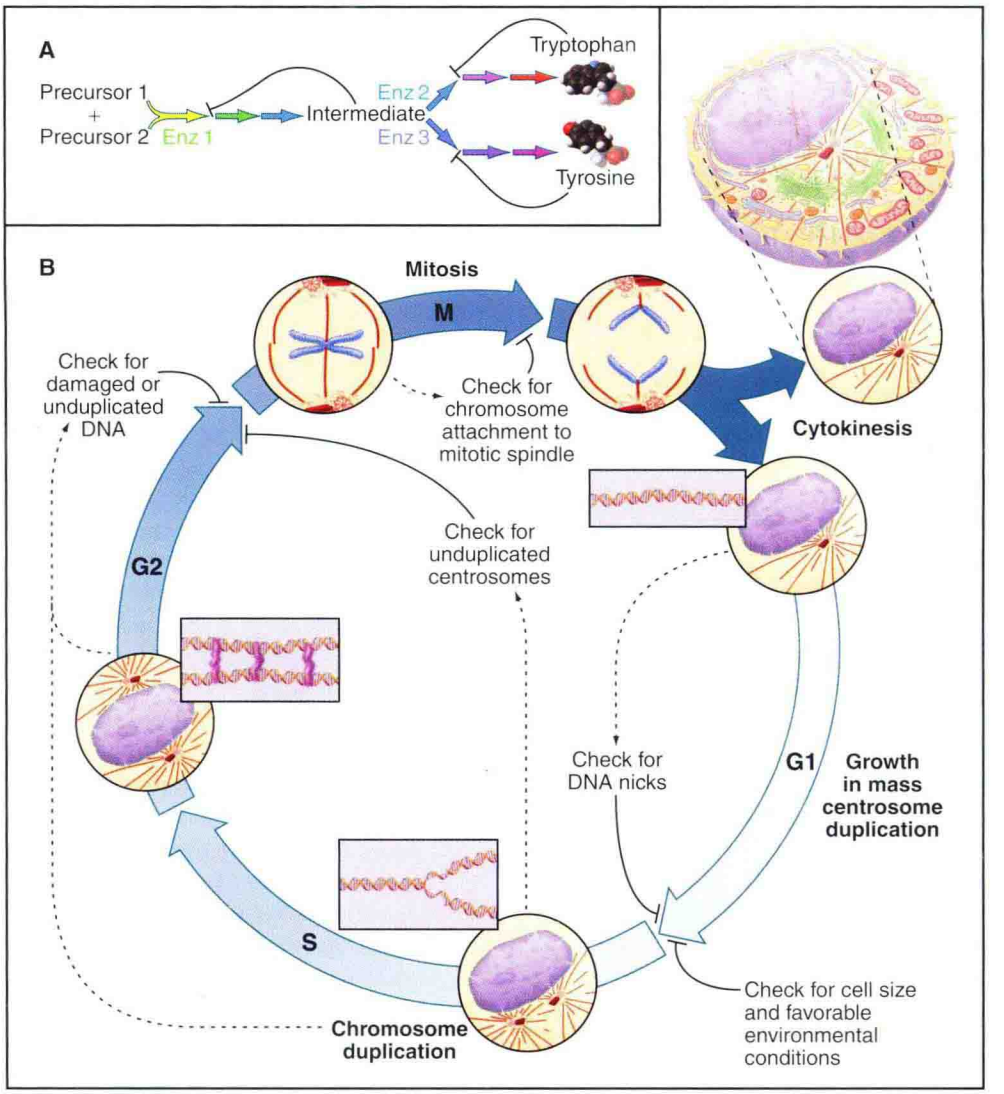


**Figure 1–9** Molecular feedback loops. *A,* Control of the synthesis of aromatic amino acids. An intermediate and the final products of this biochemical pathway inhibit three of nine enzymes (enz) in a concentration-dependent fashion, automatically turning down the reactions that produced them. This maintains constant levels of the final products, two amino acids that are essential for protein synthesis. *B,* Control of the cell cycle. The cycle consists of four stages. During the G1 phase, the cell grows in size. During the S phase, the cell duplicates the DNA of its chromosomes. During the G2 phase, the cell checks for completion of DNA replication. In M phase, chromosomes condense and attach to the mitotic spindle, which separates the duplicated pairs in preparation for the division of the cell at cytokinesis. Biochemical feedback loops called checkpoints halt the cycle (*blunt bars*) at several points until the successful completion of key preceding events.

tion of messenger RNAs into protein; by the rate of degradation of specific RNAs and proteins; and by regulation of the distribution of each molecule within the cell. Some proteins are enzymes that determine the rate of synthesis or degradation of other proteins, nucleic acids, sugars, and lipids. Molecular feedback loops regulate all of these processes to ensure the proper levels of each cellular constituent.

## Overview of Eukaryotic Cellular Organization and Functions

This section provides a brief preview of the major constituents and processes of eukaryotic cells. It is hoped that this will alleviate a practical problem with texts such as this, namely that all cellular components are interdependent. Thus, each chapter on a particular topic cross-references material covered in detail in

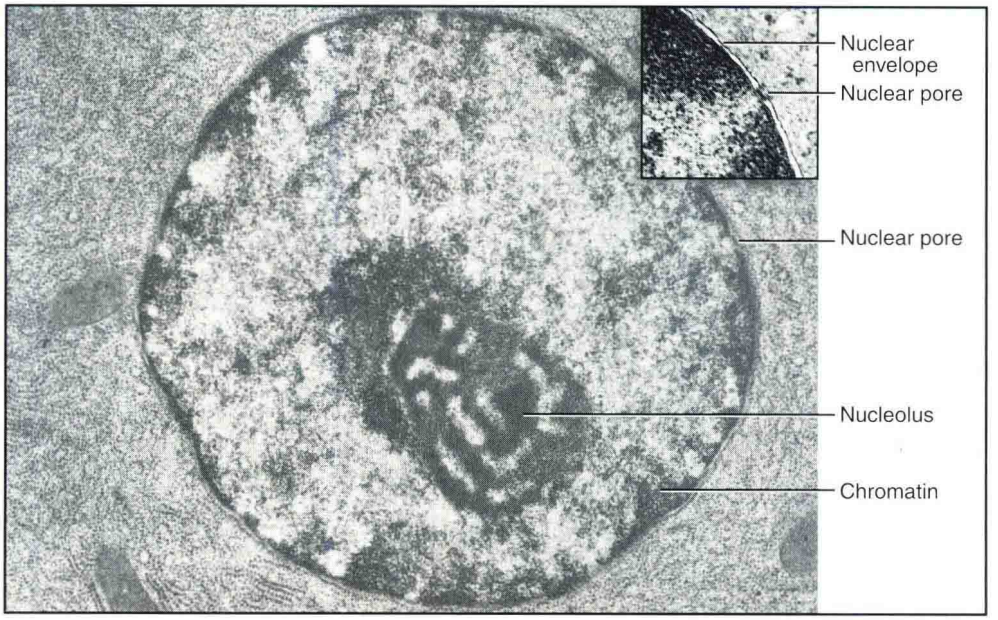


**Figure 1–10** Electron micrograph of a thin section of a nucleus. (Courtesy of Don Fawcett, Harvard Medical School.)

other chapters. This overview provides enough of a refresher on concepts first encountered in basic biology courses to appreciate references to material in later chapters.

### Nucleus

The nucleus (Fig. 1–10) stores genetic information in extraordinarily long DNA molecules called chromosomes. Surprisingly, genes make up only a small fraction (5%) of the 3 billion nucleotide pairs in human DNA, but more than 50% of the 97 million nucleotide pairs in a nematode worm. Most of the remaining DNA has no known function, although regions called telomeres stabilize the ends of chromosomes and centromeres ensure the distribution of chromosomes to daughter cells when cells divide. The DNA and its associated proteins are called chromatin. Interactions with histones and other proteins fold each chromosome compactly enough to fit inside the nucleus. During **mitosis,** chromosomes condense further into separate structural units that one can observe by light microscopy. Between cell divisions, chromatin becomes increasingly dispersed within the nucleus.

Proteins of the transcriptional machinery turn specific genes on and off in response to genetic, developmental, and environmental signals. Enzymes called polymerases make RNA copies of active genes. Messenger RNAs specify the amino acid sequences of proteins. Other RNAs have structural or catalytic functions. Most newly synthesized RNAs must be processed extensively before they are ready for use. Processing involves removal of intervening sequences or addition of specific structures at either end. For cytoplasmic RNAs, this processing occurs before RNA molecules are exported from the nucleus through **nuclear pores.** The **nucleolus** assembles ribosomes from more than 40 different proteins and 3 RNA molecules. Genetic errors resulting in altered RNA and protein products cause or predispose individuals to many inherited human diseases.

The nuclear envelope is a double membrane that separates the nucleus from the cytoplasm. All traffic into and out of the nucleus passes through nuclear pores that bridge the double membranes. Inbound traffic includes all nuclear proteins, such as transcription factors and ribosomal proteins. Outbound traffic includes messenger RNAs and ribosomal subunits. Some macromolecules shuttle back and forth between the nucleus and cytoplasm.

### Cell Cycle

Cellular growth and division are regulated by an integrated molecular network consisting of protein kinases (enzymes that add phosphate to the side chains of proteins), specific kinase inhibitors, transcription factors, and highly specific proteases. When conditions inside and outside a cell are appropriate for cell division (see Fig. 1–9*B*), changes in the stability of key proteins allow specific protein kinases to escape from negative regulators and to trigger a chain of events leading to DNA replication and cell division. Once DNA replication is initiated, the specific destruction of components of these kinases allows cells to complete the process. Once DNA replication is complete, activation of the cell cycle kinase Cdk1 pushes the cell into mitosis, the process that separates chromosomes into two daughter cells. Three controls sequentially activate Cdk1: (1) synthesis of a regulatory subunit; (2) trans-

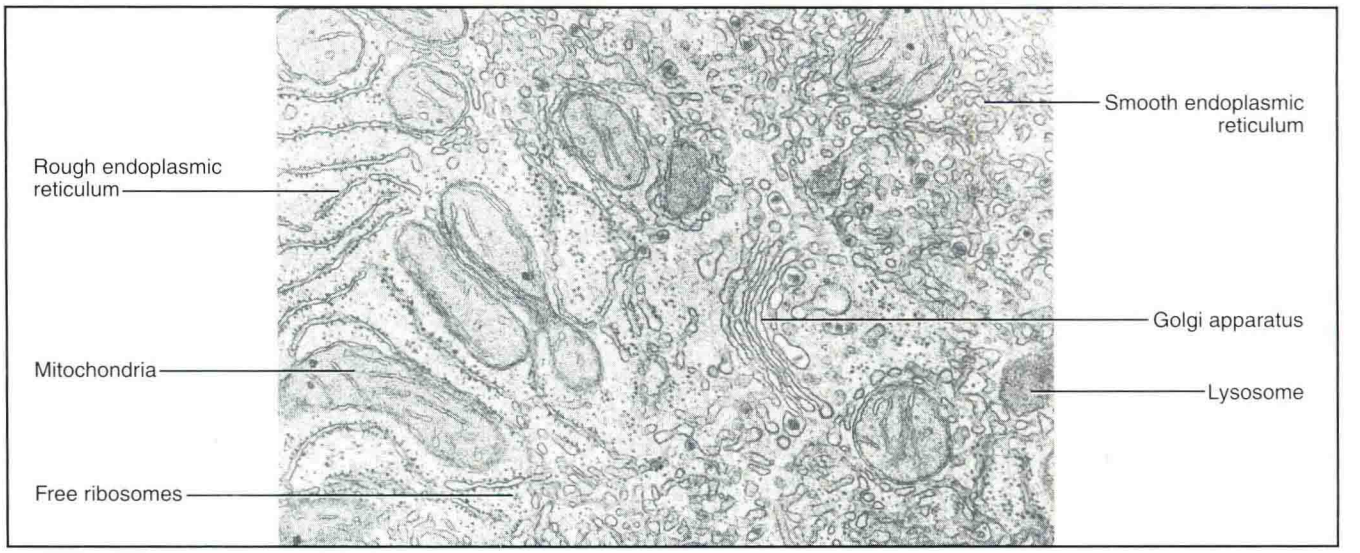


**Figure 1–11** Electron micrograph of a thin section of a liver cell showing organelles. (Courtesy of Don Fawcett, Harvard Medical School.)

port into the nucleus; and (3) removal of inhibitory phosphate groups.

Phosphorylation of proteins by Cdk1 leads directly or indirectly to disassembly of the nuclear envelope (in most but not all cells), condensation of mitotic chromosomes, and assembly of the **mitotic spindle.** Selective proteolysis of Cdk1 regulatory subunits and key chromosomal proteins then leads to segregation of identical copies of each chromosome to each daughter cell and division of the two cells. At the end of mitosis, the nuclear envelope reassembles on the surface of the clustered chromosomes.

A key feature of the cell cycle is built-in quality controls, called **checkpoints** (see Fig. 1–9), that ensure that each stage of the cycle is completed successfully before allowing the process to continue. These checkpoints also detect damage to cellular constituents and block cell cycle progression until the damage is repaired. Misregulation of checkpoints and other cell cycle controls is a common cause of cancer. Remarkably, the entire cycle of DNA replication, chromosomal condensation, nuclear envelope breakdown, and reformation, including the modulation of these events by checkpoints, can be carried out in cell-free extracts in a test tube.

### Ribosomes and Protein Synthesis

Ribosomes catalyze the synthesis of proteins using the nucleotide sequences of messenger RNA molecules to specify the sequence of amino acids (see Figs. 1–4, 1–6, and 1–11). If the protein being synthesized has a signal sequence for ER receptors, the ribosome is bound to the ER, so that the protein can be inserted into the ER membrane bilayer or into the lumen of the ER. Otherwise, ribosomes are free in cytoplasm and the newly synthesized protein enters the cytoplasm.

### Endoplasmic Reticulum

The endoplasmic reticulum is a continuous system of flattened membrane sacks and tubules (see Fig. 1–11) that is specialized for protein processing and lipid biosynthesis. Motor proteins move along microtubules to pull the ER membranes into a branching network spread throughout the cytoplasm. ER also forms the outer half of the nuclear envelope. ER pumps and channels regulate the cytoplasmic $Ca^{++}$ concentration, and ER enzymes metabolize drugs.

Ribosomes synthesizing proteins for insertion into cellular membranes or for export from the cell associate with specialized regions of the ER, called rough ER owing to the attached ribosomes (see Fig. 1–6). These proteins carry **signal sequences** of amino acids that guide their ribosomes to ER receptors. As a polypeptide chain grows, its sequence determines whether the protein folds up in the lipid bilayer or translocates into the lumen of the ER. Some of these proteins are retained in the ER, but most move on to other parts of the cell.

Endoplasmic reticulum is very dynamic. Continuous bidirectional traffic moves small vesicles between the ER and the Golgi apparatus. These vesicles carry soluble proteins in their lumens, in addition to membrane lipids and proteins. Proteins on the cytoplasmic surface of the membranes catalyze each membrane budding and fusion event. The use of specialized proteins for budding and fusion of membranes at different sites in the cell prevents the membrane components from getting mixed up.

### Golgi Apparatus

The Golgi apparatus processes the sugar side chains of secreted and membrane glycoproteins and sorts the proteins for transport to other parts of the cell (see Figs. 1–6 and 1–11). The Golgi apparatus is a stack of flattened, membrane-bound sacks with many associated vesicles. Membrane vesicles come from the ER and fuse with the Golgi apparatus. As a result of a series of vesicle budding and fusion events, the membrane molecules and soluble proteins in the lumen pass through the stacks of Golgi apparatus from one side to the other. During this passage, Golgi enzymes, retained in specific layers of the Golgi apparatus by transmembrane anchors, modify the sugar side chains of secretory and membrane proteins. On the downstream side of the Golgi apparatus, the processed proteins segregate into different vesicles destined for lysosomes or the plasma membrane. The Golgi apparatus is characteristically located in the middle of the cell near the nucleus and the centrosome.

### Lysosomes

An impermeable membrane separates degradative enzymes inside lysosomes from other cellular components. Lysosomal proteins are synthesized by rough ER and transported to the Golgi apparatus where enzymes recognize a three-dimensional site on the proteins' surface that targets them for addition of a modified sugar, phosphorylated mannose (see Fig. 1–6). Vesicular transport, guided by phosphomannose receptors, delivers the lysosomal proteins to the lumen of the lysosome.

Membrane vesicles, called **endosomes** and **phagosomes,** deliver ingested microorganisms and other materials destined for destruction to lysosomes. Fusion of these vesicles with lysosomes exposes these substrates to lysosomal enzymes in the lumen. Deficiencies of lysosomal enzymes cause many congenital diseases. In each of these diseases, a deficiency in the ability to degrade a particular biomolecule leads to its accumulation in quantities that can impair the function of the brain, liver, or other organs.

### Plasma Membrane

The plasma membrane is the interface of the cell with its environment (Fig. 1–12). Owing to the hydrophobic interior of its lipid bilayer, the plasma membrane is impermeable to ions and most water-soluble

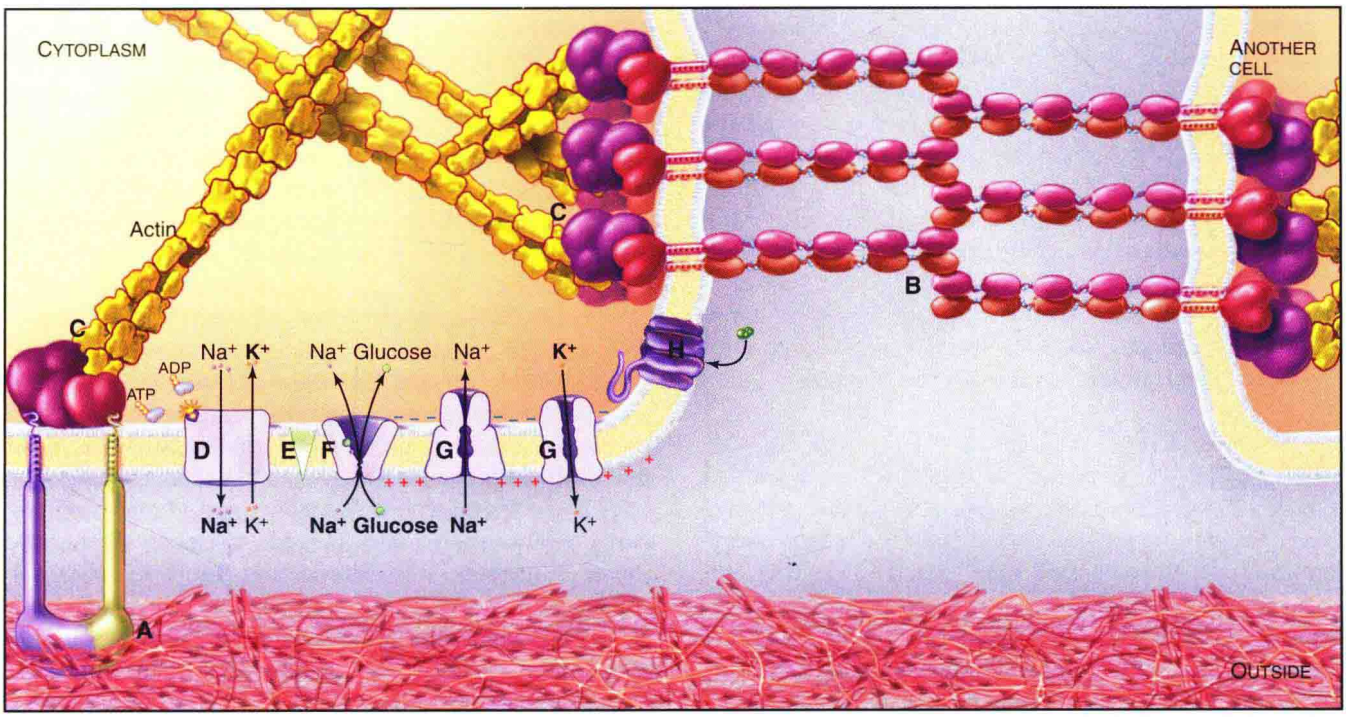


**Figure 1–12** Drawing illustrating the structure and functions of an animal cell plasma membrane. The lipid bilayer forms a permeability barrier between the cytoplasm and the extracellular environment. Transmembrane adhesion proteins anchor the membrane to the extracellular matrix (*A*) or to like receptors on other cells (*B*) and transmit forces to the cytoskeleton (*C*). ATP-driven enzymes (*D*) pump $Na^+$ out and $K^+$ into the cell against concentration gradients (*E*) to establish an electrical potential across the lipid bilayer. Other transmembrane carrier proteins (*F*) use these ion concentration gradients to drive the transport of nutrients into the cell. Selective ion channels (*G*) open and shut transiently to regulate the electrical potential across the membrane. A large variety of receptors (*H*) bind specific extracellular ligands and send signals across the membrane to the cytoplasm.

molecules. Consequently, they only cross the membrane through transmembrane channels, carriers, and pumps, which provide the cell with nutrients, control internal ion concentrations, and establish a transmembrane electrical potential. A single amino acid change in one plasma membrane pump and $Cl^-$ channel causes cystic fibrosis.

Other plasma membrane proteins mediate the interaction of the cell with its immediate environment. Transmembrane receptors bind extracellular signaling molecules, such as hormones and growth factors, and transduce their presence into chemical or electrical signals that influence the activity of the cell. Genetic defects in signaling proteins, which turn on signals for growth in the absence of appropriate extracellular stimuli, cause some human cancers.

**Adhesive glycoproteins** of the plasma membrane allow cells to bind specifically to each other or to the **extracellular matrix.** These selective interactions allow cells to form multicellular structures, like epithelia. Similar interactions allow white blood cells to bind bacteria, so that they can be ingested and digested in lysosomes. In cells subjected to mechanical forces, like muscle and epithelia, the adhesive proteins of the plasma membrane are reinforced by association with cytoskeletal filaments inside the cell. In skin, defects in these attachments cause blistering diseases.

ER synthesizes phospholipids and proteins for the plasma membrane (see Fig. 1–6). After insertion into the lipid bilayer of the ER, proteins move through the Golgi apparatus by vesicular transport to the plasma membrane. Many components of the plasma membrane are not permanent residents; receptors for extracellular molecules, including nutrients and some hormones, can recycle from the plasma membrane to endosomes and back to the cell surface many times before they are degraded. Defects in the receptor for low-density lipoproteins cause arteriosclerosis.

### Mitochondria

Mitochondrial enzymes convert most of the energy released from the breakdown of nutrients into the synthesis of ATP, the common currency for most energy-requiring reactions in cells (see Fig. 1–11). This efficient mitochondrial system uses molecular oxygen to complete the oxidation of fats, proteins, and sugars to carbon dioxide and water. A less efficient glycolytic system in the cytoplasm extracts energy from the partial breakdown of glucose to make ATP. Mitochondria cluster near sites of ATP utilization, such as sperm tails, membranes engaged in active transport, nerve terminals, and the contractile apparatus of muscle cells.

Mitochondria also have a key role in cellular responses to toxic stimuli from the environment. In response to drugs such as many used in cancer chemotherapy, mitochondria release into the cytoplasm a toxic cocktail of enzymes and other proteins that brings about the death of the cell. Defects in this form of cellular suicide, known as **apoptosis,** lead to autoimmunity, cancer, and some neurodegenerative diseases.

Mitochondria form in a fundamentally different way from the ER, Golgi apparatus, and lysosomes (see Fig. 1–6). Free ribosomes synthesize most of the mitochondrial proteins, which are released into the cytoplasm. Receptors on the surface of mitochondria recognize and bind signal sequences on mitochondrial proteins. Energy-requiring processes transport these proteins into the lumen or insert them into the outer or inner mitochondrial membranes.

DNA, ribosomes, and messenger RNAs located inside mitochondria produce a small number of the proteins that contribute to the assembly of the organelle. This machinery is left over from an earlier stage of evolution when mitochondria arose from symbiotic Eubacteria (see Fig. 1–1). Defects in the maternally inherited mitochondrial genome cause several diseases, including deafness, diabetes, and ocular myopathy.

### Peroxisomes

Peroxisomes are membrane-bound organelles containing enzymes that participate in oxidative reactions (see Fig. 1–11). Like mitochondria, peroxisomal enzymes oxidize fatty acids, but the energy is not used to synthesize ATP. Peroxisomes are particularly abundant in plants, as well as some animal cells. Peroxisomal proteins are synthesized in the cytoplasm and imported using the same strategy, but different targeting sequences and transport machinery, as mitochondria (see Fig. 1–6). Genetic defects in peroxisomal biogenesis cause several forms of mental retardation.

### Cytoskeleton and Motility Apparatus

A cytoplasmic network of three protein polymers—actin filaments, intermediate filaments, and microtubules (Fig. 1–13)—maintains the shape of a cell. Each polymer has distinctive properties and dynamics. The ability of skin cells to resist mechanical forces illustrates the cytoskeletal function of these polymers.

Actin filaments and microtubules also provide tracks for the ATP-powered motor proteins that produce most cellular movements (Fig. 1–14), including cellular locomotion, muscle contraction, transport of organelles through the cytoplasm, mitosis, and the beating of **cilia** and **flagella.** The specialized forms of motility exhibited by muscle and sperm are exaggerated, highly organized versions of the motile processes used by most other eukaryotic cells.

Networks of cross-linked actin filaments anchored to the plasma membrane reinforce the surface of the