



*Almost all aspects of life are engineered at the molecular level, and without understanding molecules we can only have a very sketchy understanding of life itself.* (Francis Harry Compton Crick)

## 7.1 Introduction

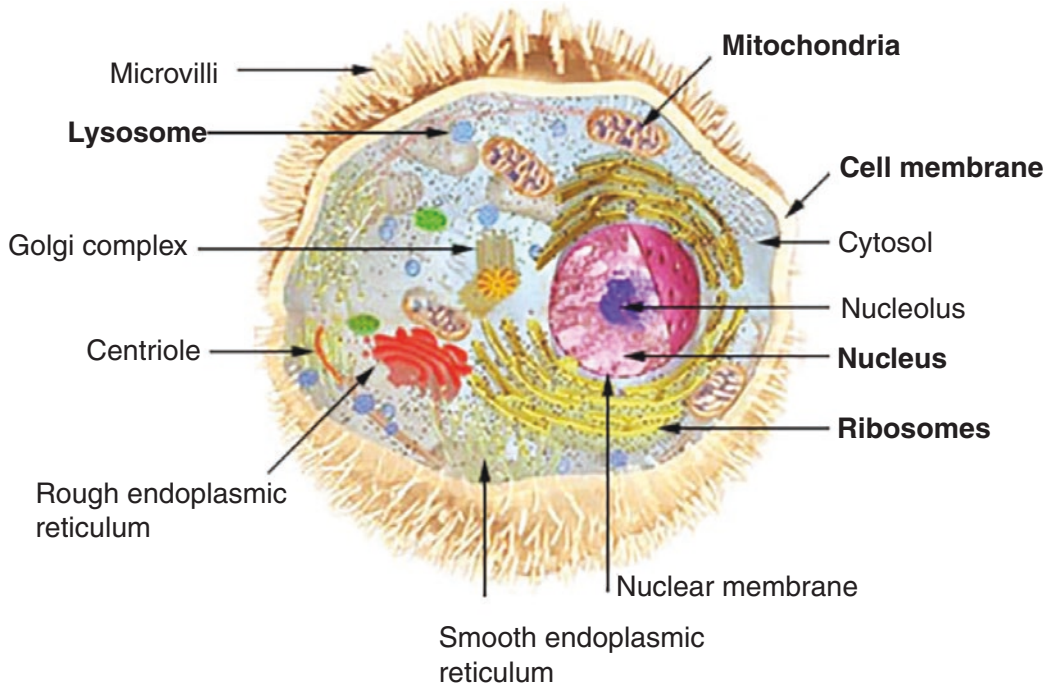
The cell is the basic unit of life in all forms of living organisms, from the smallest bacterium to the most complex animal. On the basis of microscopic and biochemical differences, living cells are divided into two major classes: *prokaryotes*, which include bacteria, blue–green algae, and rickettsiae, and *eukaryotes*, which include yeasts, and plant and animal cells. Eukaryotic cells are far more complex internally than their bacterial ancestors and the cells are organized into compartments or *organelles*, each delineated by a membrane. The DNA of the cell is packaged with protein into compact units called *chromosomes* that are located within a separate organelle, the *nucleus*. In addition, all eukaryotic cells have an internal skeleton, the *cytoskeleton* of protein filaments that gives the cell its shape, and its ability to arrange its organelles and provides the machinery for the movement.

The entire human body contains about 100 trillion cells, which are generated by repeated division from a single precursor cell. As proliferation continues, some of the cells become *differentiated* from others, adopting a different

structure, chemistry, and function. In the human body, more than 200 distinct *cell types* are assembled into a variety of types of tissues, such as epithelia, connective tissue, muscle, and nervous tissue. Each organ in the body is an aggregate of many different cells held together by intercellular supporting structures. Although the many cells of the body often differ markedly from one another, all of them have certain common basic characteristics. Each cell is a complex structure whose purpose is to maintain an intracellular environment favorable for complex metabolic reactions, to reproduce it when necessary, and to protect itself from the hazards of its surrounding environment.

## 7.2 Cell Structure and Function

The different substances that make up the cell are collectively called *protoplasm*, which is composed mainly of water, electrolytes, proteins, lipids, and carbohydrates. The two major parts of the cell (Fig. 7.1) are the *nucleus* and the *cytoplasm*. The nucleus is separated from the cytoplasm by a nuclear membrane, while the cytoplasm is separated from the extracellular fluid (ECF) by a cell membrane. The major organelles in the cell are of three general types: organelles derived from membranes, organelles involved in gene expression, and organelles involved in energy produc-



**Fig. 7.1** A schematic drawing of an animal cell clearly depicting an intricate network of interconnecting, intracellular membrane structures such as the mitochondria,

the nucleus, lysosomes, and the endoplasmic rough and smooth reticulum ([facstaff.gpc.edu/~jaliff/anacell.htm](http://facstaff.gpc.edu/~jaliff/anacell.htm))

tion. The important subcellular structures of the cell and their functions are summarized in Table 7.1.

### 7.2.1 The Plasma Membrane

The plasma membrane encloses the cell, defines its boundaries, and maintains the essential difference between the cytosol and the extracellular environment. The cell membrane is an organized sea of lipid in a fluid state, a nonaqueous dynamic compartment of cells. The cell membranes are assembled from four major components: a lipid bilayer, membrane proteins, sugar residues, and a network of supporting fibers.

The basic structure of a cell membrane is a lipid bilayer of phospholipid molecules. The fatty acid portions of both the molecules are hydrophobic and occupy the center of the membrane, while the hydrophilic phosphate portions form the two surfaces in contact with intracellular fluid

(ICF) and ECF. This lipid bilayer of 7–10 nm thickness is a major barrier impermeable to water-soluble molecules, such as ions, glucose, and urea. The three major classes of membrane lipid molecules are phospholipids (phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, sphingomyelin), cholesterol, and glycolipids. The lipid composition of different biological membranes varies depending on a specific function of the cell or cell membrane, as summarized in Table 7.2.

The cell surface often has a loose carbohydrate coat called *glycocalyx*. The sugar residues generally occur in combination with proteins (glycoproteins, proteoglycans) or lipids (glycolipids). The oligosaccharide side chains are generally negatively charged and provide the cell with an overall negative surface charge. While some carbohydrates act as receptors for binding hormones, like insulin, others may be involved in immune reactions and cell–cell adhesion events.

**Table 7.1** Cell structures (compartments) and their function

Cell structure	Major functions
Plasma membrane	Cell morphology and movement, transport of ions and molecules, cell-to-cell recognition, cell surface receptors
Endoplasmic reticulum	Formation of compartments and vesicles, membrane synthesis, synthesis of proteins and lipids, detoxification reactions
Lysosomes	Digestion of worn-out mitochondria and cell debris, hydrolysis of proteins, carbohydrates, lipids, and nucleic acids
Peroxisomes	Oxidative reactions involving molecular oxygen, utilization of hydrogen peroxide (H <sub>2</sub> O <sub>2</sub> )
Golgi complex	Modification and sorting of proteins for incorporation into organelles and for export, forms secretory vesicles
Microbodies	Isolation of particular chemical activities from the rest of the cell body
Mitochondria	Cellular respiration, oxidation of carbohydrates, proteins, and lipids, synthesis of urea and heme
Nucleus	DNA synthesis and repair, RNA synthesis, control center of the cell, directs protein synthesis and reproduction
Chromosomes	Contain hereditary information in the form of genes
Nucleolus	RNA processing; assembling ribosomes
Ribosomes	Sites of protein synthesis in cytoplasm
Cytoplasm	Metabolism of carbohydrates, lipids, amino acids, and nucleotides
Cytoskeleton	Structural support, cell movement, cell morphology

**Table 7.2** The specific functions of the cell membrane components

Component	Composition	Function	How it works	Example
Lipid	Phospholipid bilayer	Permeability barrier	Polar molecules excluded	Glucose
Transmembrane protein	Channels	Passive transport	Creates a tunnel	Na <sup>+</sup> , K <sup>+</sup> ions
	Carrier or transporters	Facilitated diffusion	Carrier “flip-flops”	Glucose transport
	Receptors	Transmits information into cell	Following receptor binding, induce activity in the cell	Peptide hormones, Neurotransmitters
Cell surface markers	Glycoprotein (GP)	“Self”-recognition	Shape of GP is characteristic of a cell or tissue	Major histocompatibility complex recognized by immune system
	Glycolipid	Tissue recognition	Shape of carbohydrate chain is characteristic of tissue	A, B, O blood group markers
Interior Protein network	Clathrins	Anchor certain proteins to specific sites	Form network above the membrane to which proteins are anchored	Localization of LDL receptor within coated pits
	Spectrin	Determines cell shape	Forms supporting scaffold by binding to both membrane and cytoskeleton	Red blood cell

The proteins of the membrane are responsible for most membrane functions, such as transport channels, pumps, carriers or transporters, specific receptors, enzymes, cell identity, and cell adhesion. The membrane proteins can be associated

with the lipid bilayer in various ways, depending on the function of the protein. The polypeptide chain may extend across the lipid bilayer (transmembrane proteins) or simply be attached to one or the other side of the membrane.

## 7.2.2 Cytoplasm and Its Organelles

Cytoplasm or *cytosol* is an aqueous solution that fills the cytoplasmic matrix, the space between the nuclear envelope and the cell membrane. The cytosol contains many dissolved proteins, electrolytes, glucose, certain lipid compounds, and thousands of enzymes. In addition, glycogen granules, neutral fat globules, ribosomes, and secretory granules are dispersed throughout the cytosol. Many chemical reactions of metabolism occur in the cytosol where substrates and cofactors interact with various enzymes. The various organelles (Table 7.1) suspended in the cytosol are either surrounded by membranes (nucleus, mitochondria, and lysosomes) or derived from membranous structures (endoplasmic reticulum, Golgi apparatus). Within the cell, these membranes interact as an endomembrane system by being in contact, giving rise to one another, or passing tiny membrane-bound sacs called *vesicles* to one another. All biological membranes are phospholipid bilayers with embedded proteins. The chemical composition of lipids and proteins in membranes varies depending on a specific function of an organelle or a specific cell in a tissue or an organ.

### 7.2.2.1 The Endoplasmic Reticulum

The cytoplasm contains an interconnecting network of tubular and flat membranous vesicular structures called the *endoplasmic reticulum* (ER). Like the cell membrane, walls of the ER are composed of a lipid bilayer containing many proteins and enzymes. The regions of the ER rich in ribosomes are termed rough or granular ER, while the regions of the ER with relatively few ribosomes are called smooth or agranular ER. *Ribosomes* are large molecular aggregates of protein and ribonucleic acid (RNA) that are involved in the manufacture of various proteins by translating the messenger RNA (mRNA) copies of genes. Subsequently, the newly synthesized proteins (hormones and enzymes) are incorporated into other organelles (Golgi complex, lysosomes) or transported or exported to other target areas outside the cell. Enzymes anchored within the

smooth ER catalyze the synthesis of a variety of lipids and carbohydrates. Many of these enzyme systems are involved in the biosynthesis of steroid hormones and in the detoxification of a variety of substances.

### 7.2.2.2 The Golgi Complex

The *Golgi complex* or apparatus is a network of flattened, smooth membranes, and vesicles. It is the delivery system of the cell. It collects, packages, modifies, and distributes molecules within the cell or secretes the molecules to the external environment. Within the Golgi bodies, the proteins and lipids synthesized by the ER are converted to glycoproteins and glycolipids and collected in membranous folds or vesicles called cisternae, which subsequently moves to various locations within the cell. In a highly secretory cell, the vesicles diffuse to the cell membrane and then fuse with it and empty their contents to the exterior by a mechanism called *exocytosis*. The Golgi apparatus is also involved in the formation of intracellular organelles, such as lysosomes and peroxisomes.

### 7.2.2.3 Lysosomes

*Lysosomes* are small vesicles (0.2–0.5  $\mu\text{m}$ ), formed by the Golgi complex and have a single limiting membrane. Lysosomes maintain an acidic matrix (pH 5 and below) and contain a group of glycoprotein digestive enzymes (hydrolases) that catalyze the rapid breakdown of proteins, nucleic acids, lipids, and carbohydrates into small basic building molecules. The enzyme content within lysosomes varies and depends on the specific needs of an individual tissue. Through a process of endocytosis, a number of cells either remove extracellular particles (phagocytosis), such as microorganisms, or engulf ECF with the unwanted substances (pinocytosis). Subsequently, the lysosomes fuse with the endocytotic vesicles and form secondary lysosomes or digestive vacuoles. Products of lysosomal digestion are either reutilized by the cell or removed from the cell by exocytosis. Throughout the lives of cells, lysosomes break down the organelles and recycle their component proteins and other molecules at

a fairly constant rate. However, in metabolically inactive cells, the hydrolases digest the lysosomal membrane and release the enzymes resulting in the digestion of the entire cell. By contrast, metabolically inactive bacteria do not die, since they do not possess lysosomes. Programmed cell death (apoptosis) or selective cell death is one of the principal mechanisms involved in the removal of unwanted cells and tissues in the body. In this process, lysosomes release the hydrolytic enzymes into the cytoplasm to digest the entire cell.

#### 7.2.2.4 Peroxisomes

Peroxisomes are small membrane-bound vesicles or microbodies (0.2–0.5  $\mu\text{m}$ ), derived from the ER or Golgi apparatus. Many of the enzymes within the peroxisomes are oxidative enzymes that generate or utilize hydrogen peroxide ( $\text{H}_2\text{O}_2$ ). Some enzymes produce hydrogen peroxide by oxidizing D-amino acids, uric acid, and various 2-hydroxy acids using molecular oxygen, while other enzymes, such as catalase, convert hydrogen peroxide to water and oxygen. Peroxisomes are also involved in the oxidative metabolism of long-chain fatty acids and different tissues contain different complements of enzymes depending on the cellular conditions.

#### 7.2.2.5 Mitochondria

*Mitochondria* are tubular or sausage-shaped organelles (1–3  $\mu\text{m}$ ). They are composed mainly of two lipid bilayer-protein membranes. The outer membrane is smooth and derived from the ER. The inner membrane contains many infoldings or shelves called *cristae* which partition the mitochondrion into an inner matrix called *mitosol* and an outer compartment. The outer membrane is relatively permeable but the inner membrane is highly selective and contains different transporters. The inner membrane contains various proteins and enzymes necessary for oxidative metabolism, while the matrix contains dissolved enzymes necessary to extract energy from nutrients. Mitochondria contain a specific DNA. However, the genes that encode the enzymes for oxidative phos-

phorylation and mitochondrial division have been transferred to the chromosomes in the nucleus. The cell does not produce brand new mitochondria each time the cell divides. Instead, mitochondria are self-replicative. Each mitochondrion divides into two and these are partitioned between the new cells. The mitochondrial reproduction, however, is not autonomous and is controlled by the cellular genome. The total number of mitochondria per cell depends on the specific energy requirements of the cell and may vary from less than 100 to up to several thousand. Mitochondria are called the “power-houses” of the cell, where oxidative phosphorylation of various substrates derived from glucose and fatty acid enter the Krebs cycle to generate ATP molecules.

#### 7.2.2.6 Ribosomes

*Ribosomes* are large complexes of RNA and protein molecules and are normally attached to the outer surfaces of endoplasmic reticulum. The major function of ribosomes is to synthesize proteins. Each ribosome is composed of one large and one small subunit, with a mass of several million daltons.

### 7.2.3 Cytoskeleton

The cytoplasm contains a network of protein fibers called cytoskeleton that provides a shape to the cell and anchors various organelles suspended in cytosol. The fibers of the cytoskeleton are made up of different proteins of different sizes and shapes, such as actin (actin filaments), tubulin (microtubules), vimentin, and keratin (intermediate filaments). The exact composition of the cytoskeleton varies depending on the cell type and function. Centrioles are small organelles that occur in pairs within the cytoplasm, usually located near the nuclear envelope, and are involved in the organization of microtubules. Each centriole is composed of nine triplets of microtubules (long hollow cylinders of about 25 nm length) and plays a major role during cell division.

## 7.2.4 Nucleus

The nucleus is the largest membrane-bound organelle in the cell and occupies about 10% of the total cell volume. The nucleus is composed of a double membrane called *nuclear envelope* that encloses the fluid-filled interior called *nucleoplasm*. The outer membrane is contiguous with the ER. The nuclear envelope has numerous pores called nuclear pores which are about 90 Å in diameter and 50–80 nm apart and permit certain molecules to pass into and out of the nucleus.

The primary functions of the nucleus are cell division and the control of the phenotypic expression of genetic information that directs all of the activities of a living cell. The cellular DNA is located in the nucleus as DNA–histone protein complex known as *chromatin* that is organized into *chromosomes*. The total genetic information stored in the chromosomes of an organism is said to constitute its *genome*. The human genome consists of 24 chromosomes (22 different chromosomes and two different sex chromosomes) and contains about  $3 \times 10^9$  nucleotide pairs. The smallest unit of DNA that encodes a protein product is called a gene and consists of an ordered sequence of nucleotides located in a particular position on a particular chromosome. There are approximately 30,000 genes per human genome and only a small fraction (15%) of the genome is being actively expressed in any specific cell type. The genetic information is transcribed into RNA, which subsequently is translated into a specific protein on the ribosome. The nucleus contains a subcompartment called *nucleolus* that contains large amounts of RNA and protein. The main function of nucleolus is to form granular subunits of ribosomes, which are transported into the cytoplasm where they play an essential role in the formation of cellular proteins.

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## 7.3 Cell Reproduction

All the cells in the human body are derived from a single cell, the fertilized egg, which undergoes trillions of cell divisions in order to become a

new individual human being. Cells reproduce by duplicating their contents and then dividing into two equal halves. The reproduction of a somatic cell involves two sequential phases: *mitosis* (the process of nuclear division) and *cytokinesis* (cell division). In gametes, the nuclear division occurs through a process called *meiosis*. The life cycle of the cell is the period of time from one cell division to the next. The duration of the *cell cycle*, however, varies greatly from one cell type to another and is controlled by the DNA-genetic system.

### 7.3.1 The Cell Cycle

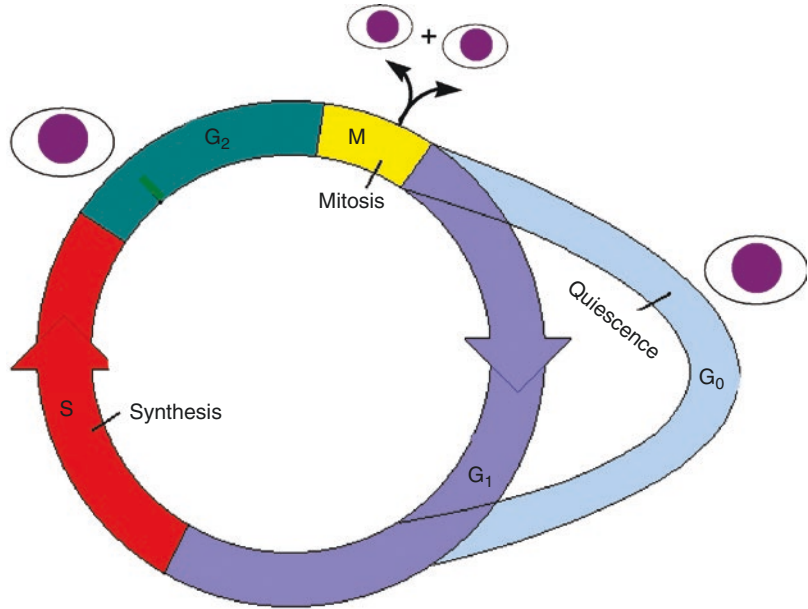
In all somatic cells, the cell cycle (Fig. 7.2) is broadly divided into the *M phase* (or *mitosis*) and the *interphase* (growth phase). In most cells, the M phase takes only a small fraction of the total cycle, when the cell actually divides. The cell is in *interphase* during the rest of the time, which is subcategorized into three phases:  $G_1$ , S, and  $G_2$ . During the  $G_1$  phase, most cells continue to grow, until they are committed to divide. If they are not ready to go into the S-phase, they may remain for a long time in a resting state known as  $G_0$ , before they are ready to resume proliferation. During the  $G_2$  phase, cells synthesize RNA and proteins and continue to grow until they enter into the M-phase.

The reproduction of the cell really begins in the nucleus itself, where the synthesis and replication of the total cellular genome occur during the S-phase. Every somatic cell is in a diploid phase, where the nucleus contains 23 pairs of chromosomes. Following replication, the nucleus has a total of 46 pairs of chromosomes. The chromosome pairs are attached at a point called *centromere* and are called *chromatids*.

#### 7.3.1.1 Mitosis and Cytokinesis

One of the first events of mitosis takes place in the cytoplasm. A pair of *centrioles* is duplicated just before DNA replication. Toward the end of interphase, the two pairs of centrioles move to the opposite poles of the cell. A complex of *microtu-*

**Fig. 7.2** The cell division cycle is generally represented by four successive phases (G<sub>1</sub>, Synthesis, G<sub>2</sub>, and Mitosis)



*bules* (spindle) pushes the centrioles farther apart creating the so-called mitotic apparatus. It is very important to note that mitochondria in the cytoplasm are also replicated before mitosis starts, as they have their own DNA. On the basis of specific events during nuclear division, mitosis is subcategorized into four phases. During the *prophase*, the nuclear envelope breaks down, chromosome condensation continues further, and the centromere of the chromatids is attached to opposite poles of the spindle. During the early *metaphase*, the spindle fibers pull the centromeres to the center forming an equatorial plate. At the end of the metaphase, the centromeres divide the chromatids into equal halves. During the *anaphase*, the sister chromatids are pulled apart, physically separated, and drawn to opposite poles, thus completing the accurate division of the replicated genome. By the end of the anaphase, 23 identical pairs of chromosomes are on the opposite sides of the cell. The *telophase*, the mitotic apparatus is disassembled, the nuclear envelope is reestablished around each group of 23 chromosomes, the nucleolus reappears, and finally the chromosomes begin to uncoil into a more extended form to permit expression of rRNA genes. Cytokinesis is the physical division

of the cytoplasm and the cell into two daughter cells, which inherit the genome as well as the mitochondria.

### 7.3.2 Rates of Cell Division

For many mammalian cells, the standard cell cycle is generally quite long and may be 12–24 h for fast-growing tissues. Many adult cells, such as nerve cells, lens of the eye, and muscle cells lose their ability to reproduce. Certain epithelial cells of the intestine, lungs, and skin divide continuously and rapidly in less than 10 h. The early embryonic cells do not grow but divide very rapidly with a cell cycle time of less than an hour. In general, the mitosis requires less than an hour, while most of the cell cycle time is spent during the G<sub>1</sub> or G<sub>0</sub> phase. It is possible to estimate the duration of the S-phase by using tracers, such as <sup>3</sup>H-thymidine or bromodeoxyuridine (BrdU).

Control system regulating the cell division: The essential processes of cell reproduction such as the DNA replication and the sequence of cell cycle events are governed by a cell cycle control system that is based on two key families of proteins: cyclin-dependent protein *kinases* (Cdk),

and activating proteins called *cyclins*. These two protein complexes regulate the normal cell cycle at the end of the G<sub>1</sub> and G<sub>2</sub> phases. The key component of the control system is a protein kinase known as *M-phase-promoting factor* (MPF), whose activation by phosphorylation drives the cell into mitosis. The mechanisms that the control cell division of mammalian cells in various tissues and organs depend on the social control genes and protein growth factors, as survival of the entire organism is the key, not the proliferation of individual cells. Growth factors, such as *platelet-derived growth factor* (PDGF), *fibroblast growth factor* (FGF), and *interleukin-2*, regulate cell proliferation through a complex network of intracellular signaling cascades, which ultimately regulate gene transcription and the activation of cell cycle control system.

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## 7.4 Cell Transformation and Differentiation

The zygote and blastomeres resulting from the first couple of cleavage divisions are *totipotent*, meaning that they are capable of forming any cell in the body. As the development progresses, certain decisions are made that narrow the developmental options of cells. At the decision point where cells become committed, a restriction event has occurred. The commitment of cells during cleavage to become either inner cell mass or *trophoblast* and the segregation of embryonic cells into the three germ layers are the early restriction events in the mammalian embryo. When a cell has passed its last decision point, its fate is fixed, and it is said to be *determined*. A cell is determined, if it has undergone a self-perpetuating change of internal character that distinguishes it and its progeny from other cells in the embryo and commits them to a specialized course of development. The determined cell may pass through many developmental stages but can-

not move onto another developmental track. For example, a muscle cell cannot become a nerve cell. Restriction and determination signify the progressive limitation of the development capacities in the embryo. Differentiation refers to the actual morphological or functional expression of the portion of genome that remains available to a determined cell or group of cells, and characterizes the phenotypic specialization of cells. Therefore, differentiation is the process of acquiring specific new characteristics resulting in observable changes in cellular function. By contrast, cells within a developing embryo display the least amount of differentiation. In the adult, undifferentiated cells are known as *pluripotent cells*, which are precursor cells or *stem cells* that are not totally committed to a specific function.

The three germ layers *ectoderm*, *mesoderm*, and *endoderm* have different fates. The endoderm forms a tube, the *primordium* of the digestive tract. It gives rise to the pharynx, esophagus, stomach, intestines, and several other associated organs such as liver, pancreas, and lungs. While the endoderm forms the epithelial components of these structures, the supporting muscular and fibrous elements arise from the mesoderm. In general, the mesoderm gives rise to the muscles and connective tissues of the body. The mesoderm first gives rise to *mesenchyme* and ultimately to cartilage, bone, fibrous tissue, and the dermis (the inner layer of the skin). In addition, the tubules of the urogenital system, vascular system, and the blood cells also develop from the mesoderm. The ectoderm forms the epidermis and the entire nervous system. In a process known as *neurulation*, a central portion of the ectoderm creates a neural tube that pinches off from the rest of the ectoderm and will form the brain and spinal cord. Some of the ectodermal cells develop into a *neural crest* and form all of the peripheral nervous system as well as the pigment cells of the skin.

Cells differentiate through several mechanisms. A cell and its progeny may contain suf-



ficient intrinsic information to determine their phenotypic character. Cell differentiation generally depends on changes in gene expression rather than on gene loss, as the genome of a differentiated cell has the entire DNA content of the undifferentiated parent cell. In order to regulate the expression of genes, the most important point of control is the initiation of RNA transcription. These gene regulatory proteins can switch the transcription of individual genes on or off by recognizing short stretches of the DNA double helix of defined sequence and thereby determining which of the thousands of genes in a cell will be transcribed. Each cell may have a specific combination or different combinations of gene regulatory proteins. According to environmental models, cells respond to external signals and differentiate accordingly. For example, after exposure to 5-azacytidine, fibroblasts from a standard tissue culture line differentiate into skeletal muscle, cartilage, or adipose tissue.

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## 7.5 Normal Growth

### 7.5.1 Cell Types

The human body is an ordered clone of cells, all containing the same genome but specialized in different ways. There are approximately 200 different cell types that represent, for the most part, discrete and distinctly different categories based on histological and morphological characteristics and cellular function. Recent subtler techniques involving immunohistology and mRNA expression are even revealing new subdivisions of cell types within the traditional classification. The different cell types, such as the neuron and lymphocyte, have the same genome, but the structural and functional differences are so extreme

that it is difficult to imagine that they came from the same cell.

Different cell types synthesize different sets of proteins. However, many processes are common to all cells and have many proteins in common. However, some proteins are unique in the specialized cells, in which they function, and cannot be detected anywhere else. The genome of a cell contains in its DNA sequence, the information to make many thousands of different proteins and RNA molecules. A cell typically expresses only a fraction of these genes and the different types of cells in a human body arise because different sets of genes are expressed. Moreover, cells can change the pattern of genes they express in response to signals from other cells or environment. Different cells perform different functions. The most important cellular functions are movement, conductivity, metabolic absorption, secretion, excretion, respiration, and reproduction.

### 7.5.2 Tissue Types

In the human body, specialized cells of one or more types are organized into cooperative assemblies called *tissues* that perform one or more unique functions. Different types of tissues combine to form organs, which in turn are integrated to perform complex functions.

The major types of tissues are epithelial, muscle, connective, nerve, blood, and lymphoid tissues that are further divided into many subtypes (Table 7.3). All cells are in contact with a network of extracellular macromolecules, known as *extracellular matrix*, that holds cells and tissues together and provides an organized latticework within which cells can migrate and interact with one another.

**Table 7.3** Tissue types

Tissue	Tissue type	Location	Function
Epithelial	Simple squamous	Lines major organs	Absorption, filtration, and secretion
	Simple cuboidal	Lines tubules and ducts of glands	Absorption and secretion
	Simple columnar	Lines GI tract	Secretion and absorption
	Stratified Squamous	Lines interior of mouth, tongue, and vagina	Protection
	Transitional	Lines urinary bladder	Permits stretching
Connective	Loose connective	Deep layers of skin, blood vessels, and organs Tendons, and ligaments	Support, and elasticity Attaches structures together, and provides strength
	Dense connective		
	Elastic connective	Lungs, arteries, trachea, and vocal cords	Provides elasticity
	Reticular connective	Spleen, liver, and lymph nodes	Provides internal scaffold for soft organs
	Cartilage	Ends of long bones, trachea, and tip of nose	Provides flexibility and support
	Bone	Bones	Protection, support, and muscle attachment
	Vascular connective tissue	Within blood vessels	Transport of gases, and blood clotting
Muscle	Adipose tissue	Deep layers of skin, surrounds heart, and kidney	Support, protection, and heat conservation
	Smooth muscle	GI tract, uterus, blood vessels, and u. bladder	Propulsion of materials
	Cardiac muscle	Heart	Contraction
Neural	Skeletal muscle	Attached to bones	Movement
	Different types of Neurons	Brain and spinal cord	Conduction of electrical impulse, and neurotransmission

## 7.6 Cell-to-Cell Communication

Cells in the human body are programmed to communicate with each other and to respond to a specific set of signals in order to regulate their growth, replication, development, and organization into tissues, and coordinate their overall biochemical behavior. Cells communicate with one another in three ways: (a) through physical contact with one another by forming cells junctions, (b) by secreting chemical signaling molecules that help communication at a distance, and (c) by cellular receptors which bind to specific signaling molecules and respond by generating intracellular messengers.

### 7.6.1 Cell-Cell Interaction

Cells in tissues are in physical contact with neighboring cells and extracellular matrix at spe-

cialized contact sites, called cell junctions (communicating, occluding, and anchoring), which allow transport of molecules between cells or provide a barrier to passage of molecules between cells. Gap or communicating junctions are composed of clusters of channel proteins that create an intercellular gap (1.5 nm wide) to allow small molecules to pass directly from cell to cell. Cells connected by gap junctions are electrically and chemically coupled, since the cells share ions and small molecules. Occluding or tight junctions exist primarily in epithelial sheets. The tight junctions form a continuous, impermeable, or semipermeable barrier to diffusion and play an important part in maintaining the concentration differences of small hydrophilic molecules across epithelial sheets and restrict the diffusion of membrane transport proteins. Anchoring junctions such as *adherens*, *desmosomes*, and *hemidesmosomes* are most abundant in tissues that are subjected to severe mechanical stress and

connect the cytoskeletal elements (actin or intermediate filaments) of a cell to those of another cell or to the extracellular matrix. To form an anchoring junction, cells must first adhere. Such a selective cell adhesion or tissue-specific recognition process is mediated by two distinct classes of cell–cell adhesion molecules (CAMs). Cadherins, the transmembrane glycoproteins, mediate  $\text{Ca}^{2+}$ -dependent cell–cell adhesion, while the neural cell adhesion molecule (N-CAM) mediates the  $\text{Ca}^{2+}$ -independent cell–cell adhesion systems.

A substantial part of the tissue volume is the extracellular space that is filled by an extracellular matrix which is composed of proteins and polysaccharides that are secreted locally by the cells in the matrix. The extracellular matrix not only binds the cells together but, also, influences their development, polarity, and behavior. The two main classes of macromolecules that make up the matrix are glycosaminoglycans (GAGs) and fibrous proteins.

### 7.6.2 Cell Signaling and Cellular Receptors

Cells communicate by means of hundreds of types of intercellular signaling molecules that include amino acids, peptides, proteins, steroids, nucleotides, fatty acid derivatives, and dissolved gases. The four primary modes of chemical signaling are *endocrine*, *paracrine*, *autocrine*, and *synaptic*. Endocrine signaling involves specialized endocrine cells that secrete the signaling molecules (hormones) into the blood stream, which are transported to distant target cells distributed throughout the body in order to produce a response in different cells and tissues. In paracrine signaling, the signal molecules that a cell secretes may act as local mediators, affecting only the neighboring cells. In autocrine signaling, the signal molecules secreted by a cell act on the same cell that generates them. In synaptic signaling, the signal molecules (neurotransmitters) secreted by a cell (neuron) bind to the receptors on a target cell at a specialized cell junction, called *synapse*.

The cellular receptors are very specific protein molecules on the plasma membrane, in the cytoplasm, or in the nucleus, that are capable of recognizing and binding the extracellular signaling molecules, also called *ligands*. As a consequence of ligand–receptor interaction, the cell may generate a cascade of intracellular signals that alter the pattern of gene expression and the behavior of the cell. One of the final steps in the signal transduction pathway is the phosphorylation of an effector protein by a protein kinase. Through cascades of highly regulated protein phosphorylation, elaborate sets of interacting proteins relay most signals from the cell surface to the nucleus, thereby altering the cell's pattern of gene expression and, as a consequence, its behavior.

Small hydrophobic signal molecules, including the thyroid and steroid hormones, diffuse into the cell and activate receptor proteins that regulate gene expression. Some dissolved gases, such as nitric oxide and carbon monoxide, activate an intracellular enzyme (guanyl cyclase), which produces cyclic GMP in the target cell. Most of the extracellular signal molecules are hydrophilic and activate transmembrane receptor proteins on the surface of the cell membrane. The ligands that bind with membrane receptors include hormones, neurotransmitters, lipoproteins, antigens, infectious agents, drugs, and metabolites.

Generally, receptors are classified on the basis of their location and function. Three main families of cell surface receptors (Table 7.4) have been identified. Following the binding of a specific signal, ion-channel-linked receptors open or close briefly to allow transport of molecules into the cell. G-protein-linked receptors activate or inactivate plasma membrane-bound enzymes or ion channels via trimeric GTP-binding proteins (G proteins). Some G-protein-linked receptors activate or inactivate adenylyl cyclase and alter the intracellular concentration of cyclic AMP, while some others generate inositol triphosphate ( $\text{IP}_3$ ), which increases intracellular  $\text{Ca}^{2+}$  levels. A rise in cyclic AMP or  $\text{Ca}^{2+}$  levels stimulates a number of kinases and phosphorylates target proteins on serine or threonine residues. Enzyme-linked receptors, such as protein kinases phosphorylate specific proteins in the target cell. There are five

**Table 7.4** Cell surface receptors

Receptor family	Enzyme	Second messenger	Signaling molecule
<b>A. Ion-channel-linked</b>			
G-protein-linked	Activate adenylyl cyclase	Increase cyclic AMP	TSH, ACTH, LH, Adrenaline, glucagon, and vasopressin
	Inhibit adenylyl cyclase	Decrease cyclic AMP	Cholera toxin, pertussis toxin
	Activate phosphoinositide-specific phospholipase C	Inositol triphosphate (IP3) increases Ca <sup>2+</sup>	Vasopressin, acetylcholine, and thrombin
	Activate or inactivate ion channels		Acetylcholine (nicotinic Ach receptors)
<b>B. Enzyme-linked</b>			
Receptor guanylyl cyclases	Activate guanylyl cyclase	Increase Cyclic GMP	Atrial natriuretic peptides (ANPs)
Receptor tyrosine kinases	Activate tyrosine kinase	Phosphorylate-specific tyrosine residues	Growth factors (PDGF, FGF, VEGF, M-CSF), and insulin
Tyrosine-kinase-associated receptors	Receptor dimerization	same as above	Cytokines, interleukin-2, growth hormone, prolactin
Receptor tyrosine phosphatases	Activate tyrosine phosphatase	Remove phosphate groups from tyrosine residues	Extracellular antibodies
Receptor serine/threonine kinases		Phosphorylate serine and threonine residues	

known classes of enzyme-linked receptors (Table 7.4). Among these, receptor tyrosine kinases and tyrosine-kinase-associated receptors are by far the most common. Most of the mutant genes (*Ras*, *Src*, *Raf*, *Fos*, and *Jun*) that encode the proteins in the intracellular signaling cascades that are activated by tyrosine kinases were identified as *oncogenes* in cancer cells, as their inappropriate activation causes a cell to proliferate excessively. By contrast, the normal genes are, therefore, referred to as *protooncogenes*.

## 7.7 Transport Through the Cell Membrane

About 56% of the adult human body is fluid. One third of the fluid is outside the cells and is called *ECF* while the remainder is called *ICF*. The *ECF* (the internal environment) is in constant motion throughout the body and contains the ions (sodium, chloride, and bicarbonate) and nutrients (oxygen, glucose, fatty acids, and amino acids) needed by cells for the maintenance of life. Cells secrete various intracellular signal molecules and expel metabolites and waste products into the

*ECF*. The cellular intake or output of different molecules occurs by different transport mechanisms of the plasma membrane, depending on the chemical and biochemical characteristics of the solute molecules.

The cell membrane consists of a lipid bilayer that is not miscible with either the *ECF* or the *ICF* and provides a barrier for the transport of water molecules and water-soluble substances across the cell membrane. Water and small molecules diffuse through the membrane via gaps or transitory spaces in the hydrophobic environment created by the random movement of fatty acyl chains of lipids.

The transport proteins within the lipid bilayer, however, provide different mechanisms for the transport of molecules across the membrane. Membranes of most cells contain pores or specific *channels* that permit the rapid movement of solute molecules across the plasma membrane. Examples of pores are plasma membrane gap junctions and nuclear membrane pores. Channels are selective for specific inorganic ions, whereas pores are not selective. Voltage-gated channels, such as the sodium channel, control the opening or closing of some channels by changes in the

transmembrane potential. Chemically regulated channels, such as the nicotinic–acetylcholine channel, open or close on the basis of the binding of a chemical to the channel.

Plasma membranes contain transport systems (transporters) that involve intrinsic membrane proteins and actually translocate the molecule or ion across the membrane by binding and physically moving the substance. Transporters have an important role in the uptake of nutrients, maintenance of ion concentrations, and control of metabolism. Some carrier proteins transport a single solute or molecule across a membrane, and these are called *uniporters*. With some other carrier proteins (coupled transporters), transfer of one solute depends on the simultaneous or sequential transfer of a second solute, either in the same direction (*symport*) or in the opposite direction (*antiport*). Transporters are classified

on the basis of their mechanism of translocation of a substance and the energetics of the system. Transporters have specificity for the substance to be transported, have defined reaction kinetics, and can be inhibited by both, competitive and noncompetitive inhibitors. Membranes of all cells contain highly specific transporters for the movement of inorganic anions and cations ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ ), and uncharged and charged organic compounds (amino acids, sugars).

Transport through the lipid bilayer or through the transport proteins involves simple diffusion, passive transport (facilitated diffusion), or active transport mechanisms. Certain macromolecules may also be transported by vesicle formation involving either endocytosis or exocytosis mechanisms. The major transport systems in mammalian cells are summarized in Table 7.5.

**Table 7.5** Transport mechanisms across plasma cell membrane

Mechanism	Transport process	Example
A. Nonspecific processes		
Simple diffusion	Direct through the membrane and is dependent on concentration gradient	Oxygen movement into cells
Osmosis	Direct diffusion of water molecules across a semipermeable membrane	Movement of water into cells, when placed in hypotonic solution
Endocytosis		
Phagocytosis	Particles are engulfed by membrane through vesicle formation	Ingestion of bacteria or particles by leukocytes
Pinocytosis	Fluid is engulfed by membrane through vesicle formation	Transport of nutrients by human egg cells
Exocytosis	Extrusion of material from a cell involves membrane vesicles	Secretion of proteins by cells via small membrane vesicles
B. Specific processes		
Facilitated diffusion	Transport of molecules into the cells involve protein channels or transporters and is dependent on concentration gradient	Movement of glucose into most cells
Primary active transport	Transport of molecules against concentration gradient involves carrier protein and requires energy derived by hydrolysis of ATP	$\text{Na}^+$ , $\text{K}^+$ , $\text{Ca}^{2+}$ , $\text{H}^+$ and $\text{Cl}^-$ ions
Secondary active transport	As a consequence of primary active transport, sodium ions can pull other solutes into the cell (cotransport)	Glucose and amino acids
Receptor-mediated endocytosis	Endocytosis is triggered by the binding of a molecule to a specific receptor on the cell surface followed by internalization of vesicles	Cholesterol (LDL) and transferrin uptake by cells

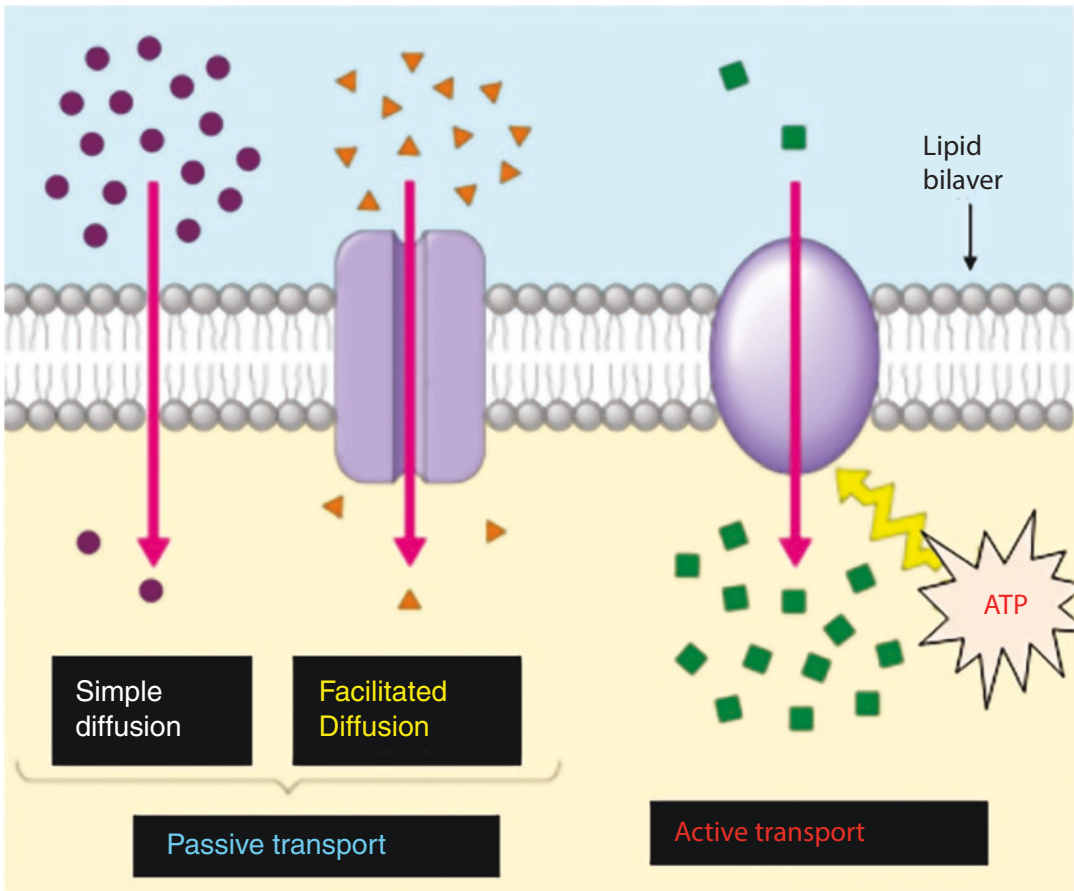
### 7.7.1 Diffusion

Body fluids are composed of two types of solutes: electrolytes, which ionize in solution and exhibit polarity (cations and anions), and non-electrolytes, such as glucose, creatinine, and urea, that do not ionize in solution. The continuous movement of solute molecules among one another in liquids or in gases is called *diffusion*. The solute molecules in the ECF or in the cytoplasm can spontaneously diffuse across the plasma membrane. However, the direction of movement of solutes by diffusion is always from a higher to a lower concentration and Fick's first law of diffusion describes the rate. The overall effect of diffusion is the passive movement of

molecules down a concentration until the concentration on each side is at chemical equilibrium. Diffusion through the cell membrane is divided into two separate subtypes called simple diffusion and facilitated diffusion (Fig. 7.3).

#### 7.7.1.1 Simple Diffusion

Simple diffusion can occur through the cell membrane either through the intermolecular interstices of the lipid bilayer or through transport proteins (watery channels). The diffusion rate of a solute depends on its size (diffusion coefficient) and its lipid solubility. In addition, the diffusion rate is influenced by the differences in electrical potential across the membrane. Diffusion of small uncharged molecules (water, urea, glycol-



**Fig. 7.3** Membrane transport mechanisms of small molecules; simple diffusion is simply dependent on the concentration gradient while facilitated diffusion involves

specific membrane transporters, such as channel proteins or carrier proteins. Active transport requires expenditure of energy

erol) and hydrophobic molecules, such as gases ( $O_2$ ,  $N_2$ ,  $CO_2$ ,  $NO$ ), occurs rapidly and depends entirely on the concentration gradient. Uncharged lipophilic molecules (fatty acids, steroids) diffuse relatively rapidly but, hydrophilic substances (glucose, inorganic ions) diffuse very slowly. *Osmosis* is a special case of diffusion in which free passage of water molecules (but not that of solute molecules) across a cell membrane is permitted.

### 7.7.1.2 Facilitated Diffusion

Passive transport or facilitated diffusion (also known as carrier-mediated diffusion) involves the translocation of a solute through a cell membrane down its concentration gradient, as in simple diffusion, without expenditure of metabolic energy. However, facilitated diffusion requires the interaction of a carrier protein (transporter) with the solute molecules. Upon entering the protein channel, the solute chemically binds to the transporter and induces a conformational change in the carrier protein, so that the channel is open on the intracellular side and releases the molecule (Fig. 7.3). The rate of diffusion is dependent on the concentration gradient and approaches a maximum, called  $V_{max}$ , as the concentration of solute increases. It is very important to recognize that in facilitated diffusion, the transporters are very specific for a solute and exhibit saturation kinetics. Transport of D-glucose is facilitated and a family of transporters (glucose permeases or GLUT 1–6) has been identified. Similarly, an anion transporter ( $Cl^-HCO_3^-$  exchanger) in erythrocytes involves antiport (two molecules in opposite directions) movement of  $Cl^-$  and  $HCO_3^-$  ions.

## 7.7.2 Active Transport

Active transport systems or pumps move the solute molecules through a cell membrane against their concentration gradient and require the expenditure of some form of energy (Fig. 7.3). As a result, the concentration of solute molecules on either side of plasma mem-

brane is not equal. For example, the concentration of  $Na^+$  ions in the ECF is 10 times more than the concentration of  $Na^+$  ions in the cytoplasm, while the converse is true with  $K^+$  ions. In active transport, the transporters are very specific for a solute and exhibit saturation kinetics. In addition, the carrier protein imparts energy to the solute to move against electrochemical or concentration gradient. If the energy source is removed or inhibited, the active transport mechanism is abolished. Most of the ions, amino acids, and certain sugars are actively transported across the plasma membrane.

In primary active transport, the energy is derived directly from the hydrolysis of ATP to ADP. The best-known active transport system is the  $Na^+ + K^+$ -dependent ATPase pump (Fig. 7.3) found in virtually all mammalian cells. The transporter protein is an enzyme, ATPase. When three sodium ions bind on the inside and two potassium ions bind on the outside, the ATPase function of the transporter is activated. Following hydrolysis of one molecule of ATP, the liberated energy causes conformational change in the carrier protein, releasing sodium ions to the outside and potassium ions to the inside. The process leads to an electrical potential, with the inside of the cell being more negative than the outside. The excitable tissues (muscle and nerve), kidneys, and salivary glands have a high concentration of the  $Na^+ + K^+$ -dependent ATPase pump. The other important primary active transport pumps are for the transport of  $Ca^{2+}$  and  $H^+$  ions.

The secondary active transport represents a phenomenon called cotransport in which molecules are transported through the plasma membrane using the energy obtained not directly from the hydrolysis of ATP, but from the electrochemical gradient across the membrane. When sodium ions are transported out of the cells, an electrical potential develops which provides energy for the sodium ions to diffuse into the interior. This diffusion energy of sodium ions can pull other molecules into the cell. Glucose and many amino acids are transported into most cells via sodium cotransport system. Following the binding of sodium and glucose molecules to specific sites on the sodium-

glucose transport protein, a conformational change is induced, and both the molecules are transported into the cell.

### 7.7.3 Transport by Vesicle Formation

Transport of macromolecules, such as large proteins, polysaccharides, nucleotides, and even other cells across the plasma membrane, is accomplished by a unique process called *endocytosis* that involves special membrane-bound vesicles. The material to be ingested is progressively enclosed by a small portion of the plasma membrane, which first invaginates and then pinches off to form an intracellular vesicle. Many of the endocytosed vesicles end up in lysosomes, where they are degraded. Endocytosis is subcategorized into two types: *pinocytosis* involves ingestion of fluid and solutes via small vesicles, while *phagocytosis* involves ingestion of large particles such as microorganisms via large vesicles called phagosomes.

Specialized cells that are professional phagocytes, such as macrophages and neutrophils, mainly carry out phagocytosis. For example, more than  $10^{11}$  senescent red blood cells are phagocytosed by macrophages every day in a human body. In order to be phagocytosed, particles must bind to specialized receptors on the plasma membrane. Phagocytosis is a triggered process that requires the activated receptors to transmit signals to the interior of the cell to initiate the response. The Fc receptors on macrophages recognize and bind the Fc portion of antibodies that recognize and bind microorganisms.

Most cells continually ingest bits of their plasma membrane in the form of small pinocytic (endocytic) vesicles that are subsequently returned to the cell surface. The plasma membrane has highly specialized regions, called clathrin-coated pits, that provide an efficient pathway for taking up macromolecules via a process called receptor-mediated endocytosis. Following binding of macromolecules to specific cell surface receptors in these clathrin-coated

pits, the macromolecule-receptor complex is internalized. Most receptors are recycled via transport vesicles back to the cell surface for reuse. More than 25 different receptors are known to participate in receptor-mediated endocytosis of different types of molecules. The low-density lipoprotein (LDL) and transferrin are the most common macromolecules that are transported into the cell via receptor-mediated endocytosis.

The reverse of endocytosis is *exocytosis* that involves transport of macromolecules within vesicles from the interior of a cell to the cell surface or into the ECF. Proteins and certain neurotransmitters can be secreted from the cells by exocytosis in either a constitutive or a regulated process. For example, insulin molecules stored in intracellular vesicles are secreted into the ECF following fusion of these vesicles with the plasma membrane. By contrast, neurotransmitter molecules stored in synaptic vesicles of a presynaptic neuron are released into a synapse only in response to an extracellular signal.

### 7.7.4 Transmission of Electrical Impulses

Nerve and muscle cells are “excitable,” which implies that they are capable of self-generation of electrochemical impulses at their cell membranes. These impulses can be employed to transmit signals, such as nerve signals, from the central nervous system to many tissues and organs throughout the body. There is a difference in the ionic composition of ECF and ICF. Whenever ion channels open or close, there is a change in the movement of ions across a cell membrane. Movement of electrical charges is called a *current*. The flow of the current reflects the charge separation across the membrane, i.e., its voltage or *membrane potential*, and is a measure of the electrical driving force that causes ions to move. When cells are excited, there is a change in current or voltage and information passes along the nerves as electrical currents and associated voltage changes (impulses).

All body cells are electrically polarized, with the inside of the cell being more negatively



charged than the outside. The difference in electrical charge or voltage is known as the *resting membrane potential* and is about  $-70$  to  $-85$  mV. The resting membrane potential is the result of the concentration gradient of ions and differences in the relative permeability of the membrane for different ions. The concentration of  $K^+$  is higher inside the cell than outside, whereas the concentration of  $Na^+$  is low inside cells and high outside. This difference in concentration is maintained by the  $Na^+-K^+$ -ATPase pump. In addition, the cell membrane is more permeable to  $K^+$  than to other ions, such as  $Na^+$  and  $Cl^-$ , and  $K^+$  can diffuse easily from ICF to ECF. Within the cell, there is an excess of anions because of negatively charged proteins that are impermeable.

When a cell, such as a neuron, is stimulated through voltage-regulated channels in sensory receptors or at synapses, ion channels for sodium open and, as a result, there is a net movement of  $Na^+$  into the cell, and the membrane potential decreases making the cell more positively charged. The decrease in resting membrane potential is known as *depolarization*. The point, at which the rapid change in the resting membrane potential reverses the polarity of the cell is referred to as an *action potential* or simply a *nerve impulse*. Immediately following an action potential, the membrane potential returns to the resting membrane potential. The increase in membrane potential is known as *repolarization* that results in the negative polarity of the cell as the voltage-gated sodium channels close and potassium channels open. The  $Na^+-K^+$ -ATPase pump moves  $K^+$  back into the cell and  $Na^+$  out of the cell. The absolute refractory period is the period of time during which it is impossible to generate another action potential, while the relative refractory period is the period of time in which a second action potential can be initiated by stronger-than-normal stimulus.

*Depolarization*, i.e., the opening of sodium ion channels, generates a nerve impulse and is propagated along the nerve, because the opening of sodium ion channels facilitates the opening of other adjacent channels, causing a wave of depolarization to travel down the membrane of nerve

cell. When a nerve impulse reaches the far end of a nerve cell, the axon tip, the wave of depolarization causes the release of a neurotransmitter. At a neuromuscular junction, the release of acetylcholine depolarizes the muscle membrane and opens the calcium ion channels, permitting the entry of calcium ions into the cell, which triggers muscle contraction. In an excitatory neural synapse, the neurotransmitter (acetylcholine) binds to the receptor in the postsynaptic nerve fiber and opens sodium ion channels that lead to the depolarization and propagation of an impulse. By contrast, in an inhibitory synapse the neurotransmitter ( $\gamma$ -aminobutyric acid or GABA, glycine) binds to the receptor in the postsynaptic nerve fiber and opens the potassium ion channels or chloride ion channels, resulting in the repolarization and inhibition of the impulse.

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## 7.8 Cellular Metabolism

### 7.8.1 Role of ATP

All of the chemical reactions involved in maintaining essential cellular functions are referred to as cellular metabolism. The life processes are driven by energy; anabolism requires energy, while catabolism releases energy. Atoms can store potential energy by means of electrons at higher energy levels. Energy is stored in chemical bonds when atoms combine to form molecules. Cells extract the chemical energy from nutrients and transfer it to a molecule known as adenosine triphosphate (ATP). Each molecule of ATP has two high-energy phosphate bonds and each of the phosphate bonds contains about 12,000 cal of energy per mole of ATP under physiological conditions. Oxidative cellular metabolism and oxidative phosphorylation reactions result in the formation of ATP that is used throughout the cell to energize all the intracellular metabolic reactions. The function of ATP is not only to store energy but also to transfer it from one molecule to another. The phosphate bond in ATP molecule is very labile and is broken down to form adenosine diphosphate (ADP) and a phosphoric acid radical with the release of

energy. ATP is used to promote three major categories of cellular function: membrane transport of ions such as  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Mg}^{2+}$ , and  $\text{Cl}^-$ , synthesis of biochemicals, such as proteins, enzymes, and nucleotides, and mechanical work, such as muscle contraction.

### 7.8.1.1 Production of ATP

The catabolism of nutrients can be divided into three different phases. Phase 1 represents the process of digestion that happens outside the cells where proteins, polysaccharides, and fats are broken down into their corresponding smaller subunits: amino acids, glucose, and fatty acid. In phase 2, the small molecules are transported into the cell where the major catabolic processes take place with the formation of acetyl-CoA and limited amounts of ATP and NADH. Finally, in phase 3, the acetyl-CoA molecules are degraded in mitochondria to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  with the generation of ATP.

Cellular oxidation–reduction reactions play a key role in energy flow within a cell and electrons transfer the energy from one atom to another, either by oxidation (loss of electrons) or by reduction (gain of electrons). In a biological system, oxidation refers to the removal of a hydrogen atom (proton plus electron) from a molecule, while reduction involves the gain of a hydrogen atom by another molecule. In many of these enzyme-catalyzed oxidation–reduction reactions, involving the formation of ATP, cells employ coenzymes (cofactors) that shuttle energy as hydrogen atoms are transferred from one reaction to another. One of the most important coenzymes is nicotinamide adenine dinucleotide (NAD<sup>+</sup>) that can accept an electron and a hydrogen atom, and gets reduced to form NADH.

### 7.8.1.2 Glycolysis

The most important process in phase 2 of the catabolism is the degradation of glucose in a sequence of ten biochemical reactions, known as glycolysis or oxidative cellular metabolism. Glycolysis can produce ATP in the absence of oxygen. Each glucose molecule is converted into

two pyruvate molecules with a net generation of six ATP molecules. If oxygen is absent, or significantly reduced within the cell, the pyruvate is converted to lactic acid, which then diffuses into ECF. In many of the normal cells, ATP generation by glycolysis accounts for less than 5% of the overall ATP generation within the cell.

### 7.8.1.3 Oxidative Phosphorylation

Phase 3 begins in the mitochondria with a series of reactions called citric acid cycle (also called the tricarboxylic acid cycle or the Krebs cycle), and ends with oxidative phosphorylation. Following glycolysis, in the presence of oxygen, pyruvate molecules enter the mitochondria and are converted to acetyl groups of acetyl coenzyme A (Acetyl-CoA). The amino acid and fatty acid molecules are also converted to Acetyl-CoA.

The citric acid cycle begins with the interaction of acetyl-CoA and oxaloacetate to form the tricarboxylic acid molecule called citric acid which, subsequently, is oxidized to generate two molecules of  $\text{CO}_2$  and oxaloacetate. The energy liberated from the oxidation reactions is utilized to produce three molecules of NADH and one molecule of reduced flavin adenine nucleotide ( $\text{FADH}_2$ ). Oxidative phosphorylation is the last step in the catabolism, in which NADH and  $\text{FADH}_2$  transfer the electrons to a series of carrier molecules, such as cytochromes (the electron-transport chain), on the inner surfaces of the mitochondria with the release of hydrogen ions. Subsequently, the molecular oxygen picks up electrons from the electron-transport chain to form water, releasing a great deal of chemical energy that is used to make the major portion of the cellular ATP. The energy released in the electron-transfer steps causes the protons to be pumped outward. The resulting electrochemical proton gradient across the inner mitochondrial membrane induces the formation of ATP from ADP and phosphoric acid radical. The aerobic oxidation of glucose results in a maximal net production of 36 ATP molecules, all but four of them produced by oxidative phosphorylation.

## 7.9 DNA and Gene Expression

### 7.9.1 DNA: The Genetic Material

The ability of cells to maintain a high degree of order depends on the hereditary or genetic information that is stored in the genetic material, the DNA. Within the nucleus of all mammalian cells, a full complement of genetic information is stored and the entire DNA is packaged into 23 pairs of chromosomes. A chromosome is formed from a single enormously long DNA molecule that consists of many small subsets called genes each of which represents a specific combination of DNA sequence designed for a specific cellular function. The three most important events in the existence of a DNA molecule are replication, repair, and expression.

The chromosomes can undergo self-replication that permits DNA to make copies of itself, as the cell divides and transfers the DNA (23 pairs of chromosomes) to daughter cells, which can, thus, inherit every property and characteristic of the original cell. There are approximately 30,000 genes per human genome which control every aspect of cellular function, primarily through protein synthesis. The sequence of amino acids in a particular protein or enzyme is encoded in a specific gene. Most of the chromosomal DNA, however, does not code for proteins or RNAs. The central dogma of molecular biology is that the overall process of information transfer in the cell involves transcription of the DNA into RNA molecules, which subsequently generate specific proteins on ribosomes by a process known as translation.

A major characteristic of DNA is its ability to encode an enormous quantity of biological information. Only a few picograms ( $10^{-12}$  g) of DNA are sufficient to direct the synthesis of as many as 100,000 distinct proteins within a cell. This supreme coding effectiveness of DNA is because of its unique chemical structure.

#### 7.9.1.1 DNA Structure

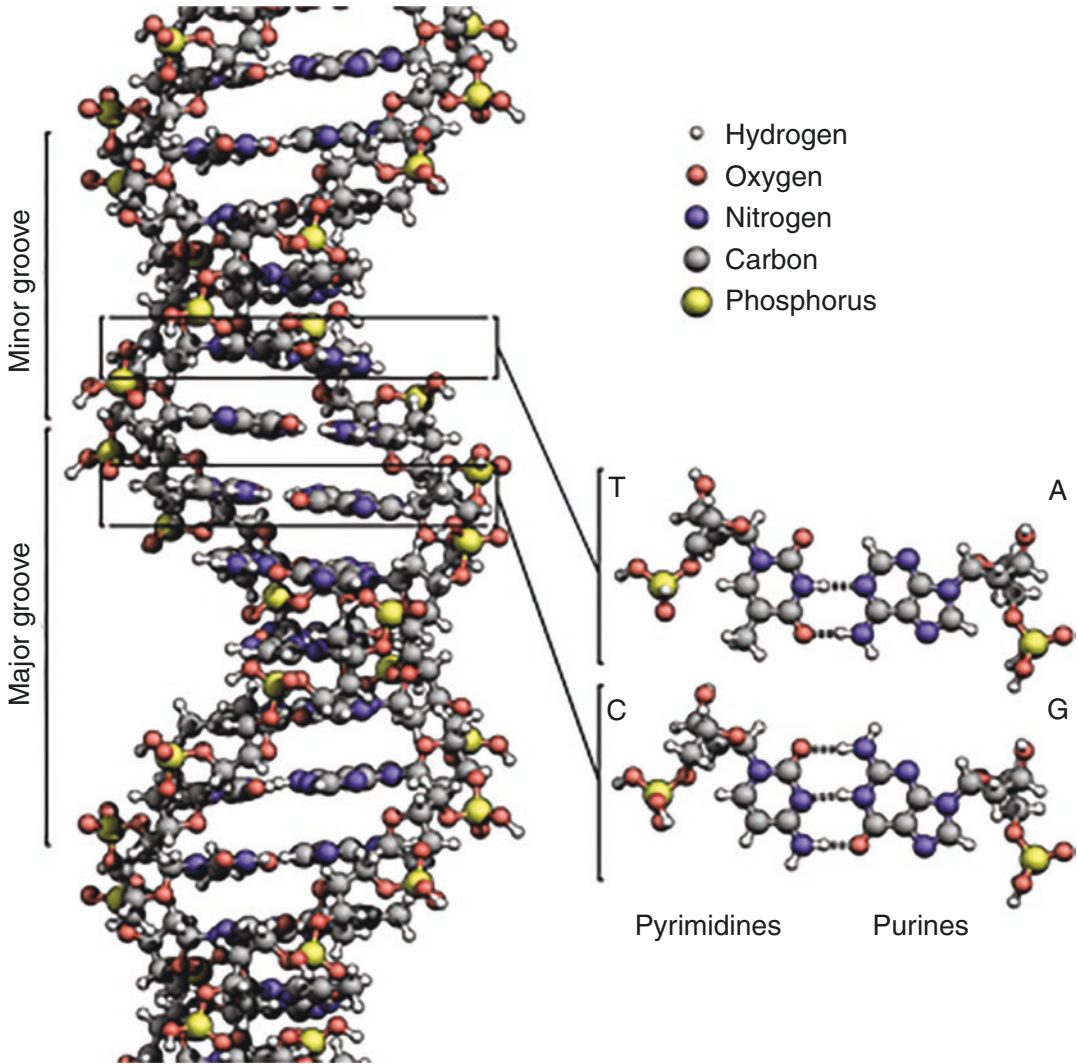
As described previously, DNA was first discovered in 1869 by the chemist, Friedrich Miescher who extracted a white substance from the cell nuclei of

human pus and called it “nuclein.” Because nuclein is slightly acidic, it is known as nucleic acid. In the 1920s, the biochemist, Levine identified two types of nucleic acids: DNA and RNA. Levine also concluded that the DNA molecule is a polynucleotide formed by the polymerization of nucleotides. Each nucleotide subunit of a DNA molecule is composed of three basic elements: a phosphate group, a five-carbon sugar (deoxyribose), and one of the four types of nitrogen-containing organic bases. Two of the bases, thymine and cytosine, are called pyrimidines, while the other two bases, adenine and guanine, are called purines. Their first letters commonly represent the four bases: T, C, and A, G.

The presence of the 5'-phosphate and the 3'-hydroxyl groups in the deoxyribose molecule allows the DNA to form a long chain of polynucleotides by joining nucleotides through phosphodiester bonds. Any linear strand of DNA will always have a free 5'-phosphate group at one end and a free 3'-hydroxyl group at the other; therefore, the DNA molecule has an intrinsic directionality (5' → 3' direction). Although some forms of cellular DNA exist as single-stranded structures, the most widespread DNA structure discovered by Watson and Crick, in 1953, represents the DNA as a double helix containing two polynucleotide strands that are complementary mirror images of each other (Fig. 7.4). The “backbone” of DNA molecule is composed of deoxyribose sugars joined by phosphodiester bonds to phosphate groups, while the bases are linked in the middle of the molecule through hydrogen bonds. The relationship between bases in the double helix is described as complementary, because adenine always bonds with thymine and guanine always bonds with cytosine. As a consequence, the double-stranded DNA contains equal amounts of purines and pyrimidines. An important structural characteristic of the double-stranded DNA is that its strands are antiparallel meaning that the two strands are aligned in opposite directions.

#### 7.9.1.2 DNA Replication

In order to serve as the basic genetic material, all the chromosomes in the nucleus duplicate their

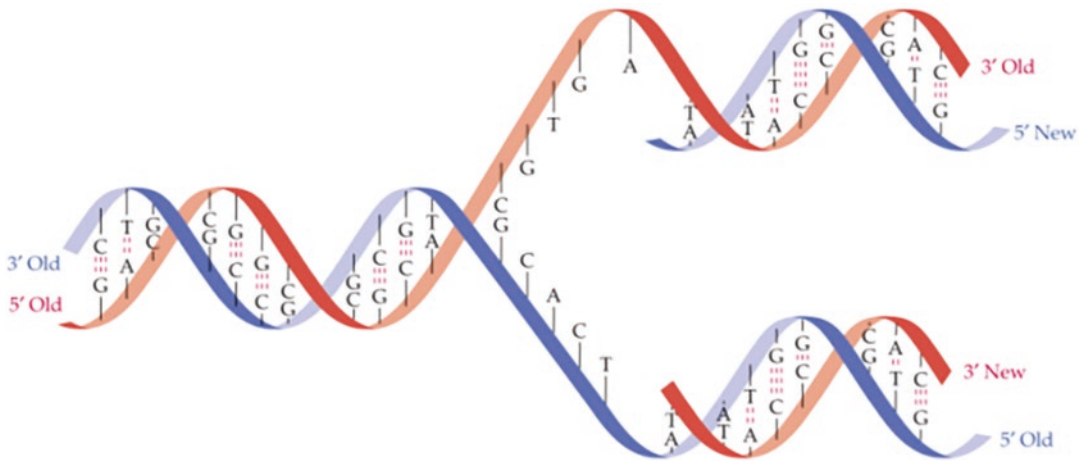


**Fig. 7.4** DNA double helix (DNA—Wikipedia)

DNA before every cell division. When a DNA molecule replicates, the double-stranded DNA separates or unzips at one end, forming a replication fork (Fig. 7.5). The principle of complementary base pairing dictates that the process of replication proceeds by a mechanism in which a new DNA strand that matches each of the original strands that serve as a template, is synthesized. If the sequence of the template is ATTGCAT, the sequence of the new strand in the duplicate must be TAACGTA. Replication is semiconservative in the sense that at the end of each round of replication, one of the parental

strands is maintained intact, and combines with one newly synthesized complementary strand.

DNA replication requires the cooperation of many proteins and enzymes. While DNA helicases and single-strand binding proteins help unzip the double helix and hold the strands apart, a self-correcting DNA polymerase moves along in a  $5' \rightarrow 3'$  direction on a single strand (leading strand) and catalyzes nucleotide polymerization or base pairing. Because the two strands are antiparallel, this  $5' \rightarrow 3'$  DNA synthesis can take place continuously on the leading strand only, while the base pairing on the lagging strand is



**Fig. 7.5** DNA replication

discontinuous and involves synthesis of a series of short DNA molecules that are subsequently sealed together by the enzyme DNA ligase. In mammals, DNA replication occurs at a polymerization rate of about 50 nucleotides per second. At the end of the replication, a repair process known as DNA proofreading is catalyzed by DNA ligase and DNA polymerase enzymes, which cut out the inappropriate or mismatched nucleotides from the new strand and replace these with the appropriate complementary nucleotides. The replication process occurs with few mistakes being made; thus, the DNA sequences are maintained with very high fidelity. For example, a mammalian germline cell with a genome of  $3 \times 10^9$  base pairs is subjected on average to only about 10–20 base pair changes per year. However, genetic change has great implications for evolution and human health and is the product of mutation, and recombination.

### 7.9.1.3 Gene Mutation

A mutation is any inherited change in the genetic material involving irreversible alterations in the sequence of DNA nucleotides. These mutations may be phenotypically silent (hidden) or expressed (visible). Mutations may be classified into two categories: base substitutions and frameshift mutations. Point mutations are base substitutions involving one or a few nucleotides in the coding sequence and may include replacement of

a purine–pyrimidine base pair by another base pair (transitions) or a pyrimidine–purine base pair (transversions). Point mutations cause changes in the hereditary message of an organism and may result from physical or chemical damage to the DNA or from spontaneous errors made during replication. Frameshift mutation involves spontaneous mispairing and may result from the insertion or deletion of a base pair. Mutational damage to the DNA is generally caused by three sources: (a) ionizing radiation causes breaks in the DNA double strand as a result of the action of free radicals on phosphodiester bonds, (b) ultraviolet radiation creates DNA cross-links because of the absorption of UV energy by pyrimidines, and (c) chemical mutagens modify the DNA bases and alter the base pairing behavior. Mutations in germline tissue are of enormous biological significance, while somatic mutations may cause cancer.

### 7.9.1.4 DNA Recombination

DNA can undergo important and elegant exchange events through recombination. These change events refer to a number of distinct processes of rearranging the genetic material. Recombination is defined as the creation of new gene combinations and may include the exchange of an entire chromosome or rearrangement of the position of a gene or a segment of a gene on a chromosome. Homologous or general recombina-

nation produces an exchange between a pair of distinct DNA molecules, usually located on two copies of the same chromosome. Sections of DNA may be moved back and forth between chromosomes but, the arrangement of genes on a chromosome is not altered. An important example is the exchange of sections of homologous chromosomes in the course of meiosis that is characteristic of gametes. As a result, homologous recombination generates new combinations of genes that can lead to genetic diversity. In a site-specific recombination, DNA homology is not required; it involves the alteration of the relative positions of short and specific nucleotide sequences in either one or both of the two participating DNA molecules. Transpositional recombination involves the insertion of viruses, plasmids, and transposable elements or transposons into the chromosomal DNA. Gene transfer in general represents a unidirectional transfer of genes from one chromosome to another. The acquisition of an AIDS-bearing virus by a human chromosome is an example of a gene transfer.

## 7.9.2 Gene Expression and Protein Synthesis

### 7.9.2.1 DNA Transcription

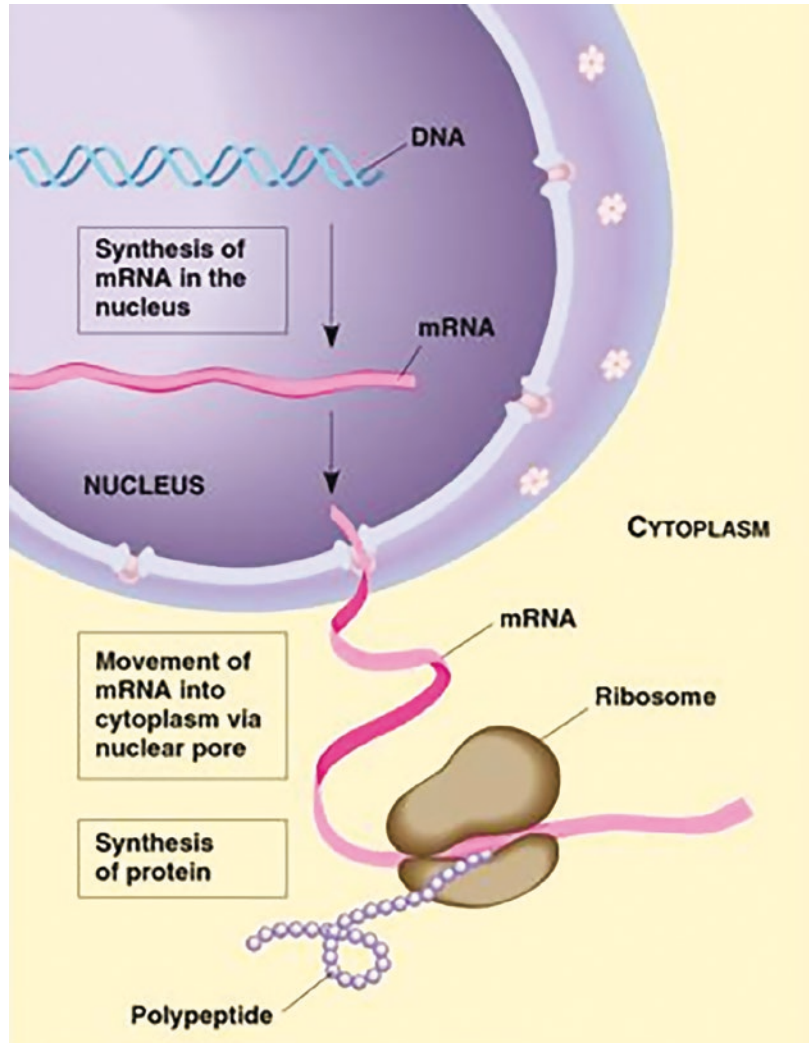
Proteins are the tools of heredity. The essence of heredity is the ability of the cell to use the information in its DNA to control and direct the synthesis of all proteins in the body. The production of RNA is called transcription and it is the first stage of gene expression (Fig. 7.6). The result is the formation of messenger RNA (mRNA) from the base sequence specified by the DNA template. All types of RNA molecules are transcribed from the DNA. An enzyme called RNA polymerase first binds to a promoter site (beginning of a gene), unwinds the two strands of the DNA double helix, moves along the DNA strand, and synthesizes the RNA molecule by binding complementary RNA nucleotides with the DNA strand. Upon reaching the termination sequence, the enzyme breaks away from the DNA strand

and at the same time a RNA molecule is released into the nucleoplasm. It is important to note that only one strand (the sense strand) of the DNA helix contains the appropriate sequence of bases to be copied into an RNA sense strand. This is accomplished by maintaining the 5' → 3' direction in producing the RNA molecule. As a result, the RNA chain is complementary to the DNA strand and is called the primary RNA transcript of the gene. This primary RNA transcript consists of long stretches of noncoding nucleotide sequences called introns that intervene between the protein coding nucleotide sequences called exons. In order to generate mRNA molecules, all the introns are cut out and the exons are spliced together. Further modifications to stabilize the transcript include 5-methylguanine capping at the 5' end and polyadenylation at the 3' end. The spliced, stabilized mRNA molecules are finally transported to the endoplasmic reticulum in the cytoplasm where proteins are synthesized.

### 7.9.2.2 RNA Structure

Both transcription and translation are mediated by a RNA molecule, which is an unbranched linear polymer of ribonucleoside 5'-monophosphates. RNA is chemically similar to DNA. The main difference between RNA and DNA is that the RNA molecule contains ribose sugar and another pyrimidine, uracil, in place of thymine. RNAs are classified according to the different roles they play in the course of the protein synthesis. The length of the molecules varies from approximately 65 to 200,000 nucleotides depending on the role they play. There are many types of RNA molecules within a cell and some RNAs contain modified nucleotides which provide greater metabolic stability. mRNA molecules carry the genetic code to the ribosomes where they serve as templates for the synthesis of proteins. A transfer RNA (tRNA) molecule, also generated in the nucleus, transfers specific amino acids from the soluble amino acid pool to the ribosomes and ensures the alignment of these amino acids in a proper sequence. Ribosomal RNA (rRNA) forms the structural framework of

**Fig. 7.6** Transcription and translation. [http://fajerpc.magnet.fsu.edu/Education/2010/Lectures/26\\_DNA\\_Transcription\\_files/image006.jpg](http://fajerpc.magnet.fsu.edu/Education/2010/Lectures/26_DNA_Transcription_files/image006.jpg)



ribosomes where most proteins are synthesized. All RNA molecules are synthesized in the nucleus. While the enzyme, RNA polymerase II, is mainly responsible for the synthesis of mRNA, RNA polymerase I and III mediate the synthesis of rRNA and tRNA.

### 7.9.2.3 Genetic Code

The genetic code in a DNA sense strand consists of a specific nucleotide sequence that is coded in successive “triplets” that will eventually control the sequence of amino acids in a protein molecule. A complementary code of triplets in mRNA molecules, called codons, is synthesized during the transcription. For example, the successive triplets

in a DNA sense strand are represented by bases, GGC, AGA, and CTT. The corresponding complementary mRNA codons, CCG, UCU, and GAA, represent the three amino acids proline, serine, and glutamic acid, respectively. Each amino acid is represented by a specific mRNA codon. The various mRNA codons for the 20 amino acids and the codons for starting and stopping of protein synthesis are summarized in Table 7.6. The genetic code is regarded as degenerate, because most of the amino acids are represented by more than one codon. An important feature of the genetic code is that it is universal; all living organisms use precisely the same DNA code to specify the sequence of amino acids in proteins.

**Table 7.6** Amino acids and the genetic code

Amino acid	Abbreviation	Lettercode		RNA	codons	
<b>Neutral amino acids</b>						
Glycine	gly	G	GGU	GGA	GGG	
Alanine	ala	A	GCU	GCA	GCG	
Valine	val	V	GAU	GUA	GUG	
Leucine	leu	L	CUU	CUA	CUG	UUA
Isoleucine	ile	I	AUU	AUA		UUG
Proline	pro	P	CCU	CCA	CCG	
Phenylalanine	phe	F	UUU			
Tyrosine	tyr	Y	UAU			
Tryptophan	try	W	UGG			
Serine	ser	S	UCU	UCA	UCG	AGU
Threonine	thr	T	ACU	ACC	ACG	
Cysteine	cys	C	UGU			
Methionine	met	M	AUG			
Asparagine	asn	D	AAU	AAC		
Glutamine	gin	Q	CAA	CAG		
<b>Acidic amino acids</b>						
Aspartic acid	asp	N	GAU	GAC		
Glutamic acid	glu	E	GAA	GAG		
<b>Basic amino acids</b>						
Lysine	lys	K	AAA	AAG		
Arginine	arg	R	CGC	CGG	AGA	AGG
Histidine	his	H	CAU	CAC		



#### 7.9.2.4 DNA Translation: Protein Synthesis

More than half of the total dry mass of a cell is made up of proteins. The second stage of gene expression is the synthesis of proteins, which requires complex catalytic machinery. The process of mRNA-directed protein synthesis by ribosomes is called translation and is dependent on two other RNA molecules, rRNA and tRNA. Ribosomes are the physical structures in which proteins are actually synthesized and are composed of two subunits: a small subunit with one rRNA molecule and 33 proteins, and a large subunit with four rRNAs and 40 proteins. Proteins that are transported out of the cell are synthesized on ribosomes that are attached to the ER, while most of the intracellular proteins are made on free ribosomes in the cytoplasm. A tRNA molecule contains about 80 nucleotides and has a site for attachment of an amino acid. Because tRNA needs to bind to mRNA to deliver a specific amino acid, tRNA molecules consist of a complementary triplet of nucleotide bases, called anticodon. Each tRNA acts as a carrier to transport a specific amino acid to the ribosomes and for each of the 20 amino acids, there are 20 different tRNA molecules.

Protein biosynthesis is a complex process and involves bringing together mRNA, ribosomal subunits, and the tRNAs. Such an ordered process requires a complex group of proteins, known as initiation factors, that help initiate the synthesis of the protein. The first step in the translation is the recognition of mRNA by ribosomes and its binding to mRNA molecule at the 5' end. Immediately, the appropriate tRNA that carries a particular amino acid (methionine) to the 3' end of mRNA is attached to the ribosome and binds mRNA at the start codon (AUG). The process of translation then begins by bringing in tRNAs that are specified by the codon–anticodon interaction. The ribosome exposes the codon, immediately adjacent to the AUG, on the mRNA to allow a specific anticodon to bind to the codon. At the same time, the amino acids (methionine and the incoming amino acid) are linked together by a

peptide bond and the tRNA carrying methionine is released. Next, the ribosome moves along the mRNA molecule to the next codon, when the next tRNA binds to the complementary codon, placing the amino acid adjacent to the growing polypeptide chain. The process is continued until the ribosome reaches a chain-terminating nonsense stop codon (UAA, UAG, UGA). In other words, the process stops when a release factor binds to the nonsense codon, stops the synthesis of protein, and releases the protein from the ribosome. Some proteins emerging from the ribosome are ready to function, while others undergo a variety of posttranslational modifications to convert the proteins to functional forms, or to facilitate the transport to intracellular or extracellular targets.

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## 7.10 Disease and Pathophysiology

### 7.10.1 Homeostasis

The term *homeostasis* is used by physiologists to describe the maintenance of static, or constant conditions in the internal environment by means of positive and negative feedback of information. About 56% of the adult human body is fluid. Most of the fluid is ICF and about one-third is ECF that is in constant motion throughout the body and contains the ions (sodium, chloride, and bicarbonate) and nutrients (oxygen, glucose, fatty acids, and amino acids) needed by the cells for the maintenance of life. Claude Bernard (1813–1878) defined ECF as the internal environment of the body and hypothesized that the same biological processes that make life possible are also involved in disease (Wagner 1995b). The laws of disease are the same as the laws of life. All the organs and tissues of the body perform functions that help maintain homeostasis. As long as the organs and tissues of the body perform functions that help maintain homeostasis, the cells of the body continue to live and function properly.

### 7.10.2 Disease Definition

At the present time, precisely defining what disease is, is as complex as defining what exactly life is. It may be relatively easier to define disease at a cellular and molecular level than at the level of an individual. Throughout the history of medicine, two main concepts of disease have been dominant. The *ontological* concept views a disease as an entity that is independent, self-sufficient, and running a regular course with a natural history of its own. The physiological concept defines disease as a deviation from the normal physiology or biochemistry; the disease is a statistically defined deviation of one or more functions in a patient from those of healthy people of the same age and sex under very similar circumstances.

At birth, molecular blueprints collectively make up a person's genome or genotype that will be translated into cellular structures and functions. A single gene defect can lead to biochemical abnormalities that produce many different clinical manifestations of disease, or phenotypes, a process called *pleiotropism*. Many different gene abnormalities can result in the same clinical manifestations of disease; this process is called genetic heterogeneity. Thus, diseases can be defined as abnormal processes as well as abnormalities in the molecular concentrations of different biological markers, signaling molecules, and receptors.

### 7.10.3 Pathophysiology

In 1839, Theodor Schwann discovered that all the living organisms are made up of discrete cells. In 1858, Rudolph Virchow observed that a disease could not be understood unless it is realized that the ultimate abnormality must lie in the cell. He correlated disease with cellular abnormalities as revealed by chemical stains, thereby founding the field of cellular pathology. Consequently, he defined pathology as physiology with obstacles.

Most diseases begin with a cell injury that occurs if the cell is unable to maintain homeosta-

sis. Since the time of Virchow, gross pathology and histopathology have been a foundation of the diagnostic process and the classification of disease. Traditionally, the four aspects of a disease process that form the core of pathology are etiology, pathogenesis, morphologic changes, and clinical significance. The altered cellular and tissue biology, and all forms of loss of function of tissues, and organs are, ultimately, the result of cell injury and cell death. Therefore, knowledge of the structural and functional reactions of cells and tissues to injurious agents, including genetic defects, is the key for understanding the disease process.

Currently diseases are defined and interpreted in molecular terms and not just with general descriptions of altered structures. Pathology is evolving into a bridging discipline that involves both basic science and clinical practice and is devoted to the study of the structural and, functional changes in cells, tissues, and organs that underlie disease. The molecular, genetic, microbiologic, immunologic, and morphologic techniques help to understand both, the ontological and the physiological causes of disease.

#### 7.10.3.1 Altered Cellular and Tissue Biology

The normal cell is able to handle normal physiologic and functional demands, so-called normal homeostasis. However, physiologic and morphologic cellular adaptations normally occur in response to excessive physiologic conditions or some adverse, or pathologic stimuli. The cells adapt in order to escape and protect themselves from injury. An adapted cell is neither normal nor injured but has an altered steady state and preserves the viability of the cell. If a cell cannot adapt to severe stress or pathologic stimuli, the consequence may be *cellular injury* that disrupts cell structures or deprives the cell of oxygen and nutrients. Cell injury is reversible up to a certain point, but irreversible (lethal) cell injury ultimately leads to cell death, generally known as *necrosis*. By contrast, an internally controlled suicide program, resulting in cell death, is called *apoptosis*.

### Cellular Adaptations

Some of the most significant physiologic and pathologic adaptations of cells involve changes in cellular size, growth, or differentiation. These include (a) *atrophy*, a decrease in size and function of the cell, (b) *hypertrophy*, an increase in cell size, (c) *hyperplasia*, an increase in cell number, and (d) *metaplasia*, an alteration of cell differentiation. The adaptive response may also include the intracellular accumulation of normal and abnormal endogenous substances (lipids, protein, glycogen, bilirubin, and pigments), or abnormal exogenous products. Cellular adaptations are a common and central part of many disease states. The molecular mechanisms leading to cellular adaptations may involve a wide variety of stimuli and various steps in the cellular metabolism. Increased production of cell signaling molecules, alterations in the expression of cell surface receptors, and overexpression of intracellular proteins are typical examples.

#### 7.10.3.2 Cellular Injury

Cellular injury occurs if the cell is unable to maintain homeostasis. The causes of cellular injury may be *hypoxia* (oxygen deprivation), infection, or exposure to toxic chemicals. In addition, immunologic reactions, genetic derangements, and nutritional imbalances may also cause cellular injury. In hypoxia (oxygen deprivation), glycolytic energy production may continue but, *ischemia* (loss of blood supply) compromises the availability of metabolic substrates and may injure tissues faster than hypoxia. Various types of cellular injuries and their responses are summarized in Table 7.7.

#### Biochemical Mechanisms

Regardless of the nature of the injurious agents, there are a number of common biochemical themes or mechanisms responsible for cell injury.

1. ATP depletion: It is one of the most common consequences of ischemic and toxic injury. ATP depletion induces cell swelling, decreases protein synthesis, decreases membrane transport, and increases membrane permeability.

**Table 7.7** Progressive types of cell injury and responses

Type	Responses
Adaptation	Atrophy, hypertrophy, hyperplasia, and metaplasia
Active cell injury	Immediate response of “entire cell”
Reversible	Loss of ATP, cellular swelling, detachment of ribosomes, and autophagy of lysosomes
Irreversible	“Point of no return” structurally when vacuolization occurs of the mitochondria and calcium moves into the cell.
Necrosis	Common type of cell death with severe cell swelling and breakdown of organelles
Apoptosis	Cellular self-destruction for elimination of unwanted cell population
Chronic cell injury (subcellular alterations)	Persistent stimuli response may involve only specific organelles or cytoskeleton, e.g., phagocytosis of bacteria
Accumulations or Infiltrations	Water, pigments, lipids, glycogen, and proteins
Pathologic calcification	Dystrophic and metastatic calcification

The above table modified from reference (McCance and Huether 1998)

2. Oxygen and oxygen-derived free radicals: Ischemia causes cell injury by reducing blood supply and cellular oxygen. Radiation, chemicals, and inflammation generate oxygen free radicals that cause the destruction of the cell membrane and cell structure.
3. Intracellular  $\text{Ca}^{2+}$  and loss of calcium homeostasis: Most of the intracellular calcium is in the mitochondria and endoplasmic reticulum. Ischemia and certain toxins increase the concentration of  $\text{Ca}^{2+}$  in the cytoplasm resulting in the activation of a number of enzymes, which causes intracellular damage, and increases the membrane permeability.
4. Mitochondrial dysfunction: A variety of stimuli (free  $\text{Ca}^{2+}$  levels in cytosol, oxidative stress) cause mitochondrial permeability transition (MPT) in the inner mitochondrial membrane, resulting in the leakage of cytochrome c into the cytoplasm.

5. Defects in membrane permeability: All forms of cell injury, as well as many bacterial toxins and viral proteins, damage the plasma membrane. As a result, there is an early loss of selective membrane permeability.

### Intracellular Accumulations

Normal cells generally accumulate certain substances such as electrolytes, lipids, glycogen, proteins, calcium, uric acid, and bilirubin that are involved in normal metabolic processes. As a manifestation of injury and metabolic derangements in cells, abnormal amounts of various substances, either normal cellular constituents or exogenous substances, may accumulate in the cytoplasm or nucleus, either transiently or permanently. One of the major consequences of the failure of the transport mechanisms is cell swelling due to excess intracellular water. Abnormal accumulations of organic substances, such as triglycerides, cholesterol and cholesterol esters, glycogen, proteins, pigments, and melanin, may be caused by disorders in which the cellular capacity exceeds the synthesis or catabolism of these substances. Dystrophic calcification occurs mainly in the injured or dead cells, while metastatic calcification may occur in the normal tissues. Hypercalcemia may be a consequence of increased parathyroid hormone, destruction of bone tissue, renal failure, and vitamin D-related disorders. All of these accumulations harm cells by “crowding” the organelles and by causing excessive, and harmful metabolites that may be retained within the cell or expelled into the ECF and circulation.

### 7.10.3.3 Necrosis

Cellular death resulting from the progressive degradative action of enzymes on the lethally injured cells, ultimately leading to the processes of cellular swelling, dissolution, and rupture, is called necrosis. The morphologic appearance of necrosis is the result of denaturation of proteins and enzymatic digestion (autolysis or heterolysis) of the cell. Different types of necrosis occur in different organs or tissues. The most common type, *coagulative necrosis*, resulting from hypoxia and ischemia, is characterized by the

denaturation of cytoplasmic proteins, breakdown of organelles, and cell swelling. It occurs primarily in the kidneys, heart, and adrenal glands. *Liquefactive necrosis* may result from ischemia or bacterial infections. The cells are digested by *hydrolases* and the tissue becomes soft and liquefies. As a result of ischemia, the brain tissue liquefies and forms cysts. In an infected tissue, hydrolases are released from the lysosomes of neutrophils; they kill bacterial cells and the surrounding tissue cells resulting in the accumulation of pus. *Caseous necrosis* (in which the dead tissue maintains a cheese-like appearance) present in the foci of tuberculous infections is a combination of coagulative and liquefactive necrosis. In *fat necrosis*, the *lipase* enzymes break down triglycerides and form opaque chalky necrotic tissue as a result of saponification of free fatty acids with alkali metal ions. In a patient, the necrotic tissue and the debris usually disappear by a combined process of enzymatic digestion, and fragmentation or become calcified.

### 7.10.3.4 Apoptosis

Apoptosis, a type of cell death implicated in both normal and pathologic tissue, is designed to eliminate unwanted host cells in an active process of cellular self-destruction effected by a dedicated set of gene products. Apoptosis occurs during normal embryonic development and is a homeostatic mechanism to maintain cell populations in tissues. It also occurs as a defense mechanism in immune reactions and during cell damage by disease or noxious agents. Various kinds of stimuli may activate apoptosis. These include injurious agents (radiation, toxins, free radicals), specific death signals (TNF and *Fas* ligands), and withdrawal of growth factors, and hormones. Within the cytoplasm, a number of protein regulators (Bcl-2 family of proteins) either promote or inhibit cell death. In the final phase, the execution *caspases* activate the proteolytic cascade that eventually leads to the intracellular degradation, fragmentation of nuclear chromatin, and breakdown of the cytoskeleton. The most important morphologic characteristics are cell shrinkage, chromatin condensation, and formation of cytoplasmic blebs, and apoptotic bodies that are, sub-

sequently, phagocytosed by adjacent healthy cells, and macrophages. Unlike necrosis, apoptosis involves nuclear and cytoplasmic shrinkage, and affects scattered single cells.

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## Further Reading

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