CHAPTER 1

Mechanisms and Morphology of Cellular Injury, Adaptation, and Death[a]

Margaret A. Miller, L. Tiffany Lyle, and James F. Zachary

Key Readings Index

The goal of this chapter is to explain and illustrate how the structure and function of cells are altered by their response (e.g., adaptation, degeneration, or death) to injury. This information will serve as the underpinnings for materials presented in the remaining chapters covering general pathology (Section I, Cellular and Molecular Mechanisms of Disease) and for comprehending materials presented on disease mechanisms and pathogeneses in subsequent chapters that cover systemic pathology (Section II, Pathology of Organ Systems).

Normal Cell

Knowledge of anatomy and of normal structural variations in cells, tissues, and organs is prerequisite to developing the skills necessary to recognize and interpret lesions (see the Introduction and Appendix C, Postmortem Examination (Autopsy) of Domestic Animal Species; Appendix D, Recognition and Interpretation of Macroscopic (Gross) Lesions; and E, Diagnoses in Veterinary Pathology). The focus of this chapter is on the structure of the normal cell and cellular responses to injury. Cell and tissue structure of each organ system is covered briefly at the beginning of each chapter in Section II, Pathology of Organ Systems.

Components of Normal Cells and Their Vulnerabilities

A clear understanding of normal cell structure and function is essential to the study of cellular responses to injury. The cell can be visualized simplistically as a membrane-enclosed structure, subdivided into smaller functional units (organelles) by these membranes (Fig. 1.1). This interconnecting system of membrane-bound compartments is termed the *cytocavitary network*. The function of individual organelles depends in great part on the biochemistry of their membrane and intracellular matrix (i.e., gel component of the cytoplasm that supports the functions of the organelle). Cell membranes and organelles are targets for injury by various microbial, genetic, metabolic, and toxic diseases that are addressed in greater detail in Section II, Pathology of Organ Systems.

Cell Membranes (Cytocavitary Network)

Cell membranes are fluidic phospholipid bilayers that enclose cells and their organelles (Fig. 1.2). Two major functions of these membranes are (1) to serve as selective barriers (i.e., barrier systems [see Chapter 4, Mechanisms of Microbial Infections]) and (2) to form a structural base for the membrane-associated proteins (enzymes and receptors) that determine cell function. The term fluidic indicates that proteins and lipids in the membrane are not immovable but can travel as part of the *cytocavitary network* (Fig. 1.3) throughout the physical extent of the cell. As an example of this process of "fluidic" movement, transmembrane proteins used as cell surface receptors are synthesized and assembled in the rough endoplasmic reticulum (rER), inserted into membranes in the Golgi complex, and moved (fluidic) to the cell's surface at the plasma membrane via the cytocavitary network (see Fig. 1.3).

The *plasma membrane* encloses the entire cell and thus is its first contact with harmful substances, such as toxins or infectious microbes. Microvilli and cilia (see Fig. 1.1) are specialized areas of the plasma membrane that are often altered in disease. Plasma membranes separate the interior of the cell from the external environment, neighboring cells, or the extracellular matrix (ECM). Surface proteins, such as fibronectin, play a role in cell-to-cell and cell-to-ECM interactions. *Transmembrane proteins* embedded in the phospholipid bilayer serve in a variety of essential structural, transport, and enzymatic functions (Fig. 1.4). Ligand-receptor interactions play key roles in these functions. Ligands are signaling molecules (also known as first messengers) (i.e., autocrine, paracrine, and endocrine signals [see Fig. 12.1]) that bind to receptors in the plasma membrane (cell surface receptors), cytoplasm (cytoplasmic receptors), or nucleus (nuclear receptors). Ligands may be cell associated, such as those on the surface of infectious

[a]For a glossary of abbreviations and terms used in this chapter, see E-Glossary 1.1.

E-Glossary 1.1 Glossary of Abbreviations and Terms

AA	Amyloid A protein
AIF	Apoptosis-inducing factor
AL	Amyloid protein composed of immunoglobulin light chains
Apaf-1	Apoptosis protease activating factor 1
Atg	Autophagy-related gene products
ATP	Adenosine triphosphate
Bak	Bcl-2 antagonist/killer, a proapoptotic protein
Bax	Bcl-2–associated X protein, a proapoptotic protein
Bcl-2	B lymphocyte lymphoma 2 family of regulatory proteins
Bid	BH3-interacting domain death agonist
BMP3	Bone morphogenetic protein 3
C5	Complement component 5
C5b	Complement fragment 5b
C6	Complement component 6
C7	Complement component 7
C8	Complement component 8
C9	Complement component 9
cAMP	Cyclic adenosine monophosphate
CD3	Cluster of differentiation (classification determinant) protein 3
CD59	Cluster of differentiation glycoprotein 59
CDK	Cyclin-dependent kinase
cGMP	Cyclic guanosine monophosphate
CHS	Chediak-Higashi syndrome
CNS	Central nervous system
CYP	Member of the cytochrome P450 family
DD	Death domain
DDR	DNA damage response
DISC	Death-inducing signaling complex
DNA	Deoxyribonucleic acid
DOPA	Dihydroxyphenylalanine
DR	Death receptor
ECM	Extracellular matrix
ER	Endoplasmic reticulum
FAD	Flavin adenine dinucleotide
FADD	Fas-associated death domain
FasL	Fas ligand
FasR	Fas receptor (also known as Fas)
FGF4	Fibroblast growth factor 4
FLIP	(FADD-like interleukin-1 β-converting enzyme)-inhibitory protein, an antiapoptotic protein
FOXO	Forkhead box protein O
H&E	Hematoxylin and eosin
IGF-1	Insulin-like growth factor-1
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-10	Interleukin-10
LC	Light chain
LYST	Lysosomal trafficking regulator gene
MAC	Membrane attack complex
MAPK	Mitogen-activated protein kinase
MDR1	Multidrug resistance 1 gene
MLKL	Mixed lineage kinase domain-like
MOMP	Mitochondrial outer membrane permeabilization
MPT	Mitochondrial permeability transition
mRNA	Messenger ribonucleic acid
mtDNA	Mitochondrial DNA
mTOR	Mammalian target of rapamycin
NAD	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate
NFκB	Nuclear factor κ B
NK	Natural killer
NO	Nitric oxide
NOR	Nucleolar organizing region
p53	Protein 53, product of the tumor protein *TP53* gene
PAS	Periodic acid–Schiff
PCR	Polymerase chain reaction
PFK1	Phosphofructokinase 1
PPARγ	Peroxisome proliferator-activated receptor γ
PTH	Parathyroid hormone
PUMA	p53-upregulated modulator of apoptosis
rER	Rough endoplasmic reticulum
RIPK	Receptor-interacting protein-serine/threonine kinase
RNA	Ribonucleic acid
ROS	Reactive oxygen species
rRNA	Ribosomal ribonucleic acid
SASP	Senescence-associated secretory phenotype
sER	Smooth endoplasmic reticulum
SMAC	Second mitochondrial activator of caspases
SNARE	Soluble NSF (*N*-ethylmaleimide–sensitive fusion protein) attachment protein receptor
SOD	Superoxide dismutase
spp.	Species (plural)
TCA cycle	Tricarboxylic acid cycle, also known as citric acid cycle or Krebs cycle
TERC	Telomerase RNA subunit template component
TERT	Telomerase reverse transcriptase
TGF-α	Transforming growth factor-α
TGF-β	Transforming growth factor-β
TNF-α	Tumor necrosis factor-α
TNFR	Tumor necrosis factor receptor
TRADD	TNF receptor–associated death domain
TRAILR	TNF-related apoptosis-inducing ligand receptor
tRNA	Transfer ribonucleic acid
UBL	Ubiquitin-like
ULK1	UNC-51–like autophagy-activating kinase 1
VEGF	Vascular endothelial growth factor
VMP1	Vacuolar membrane protein 1
VPS34	Vacuolar protein sorting 34

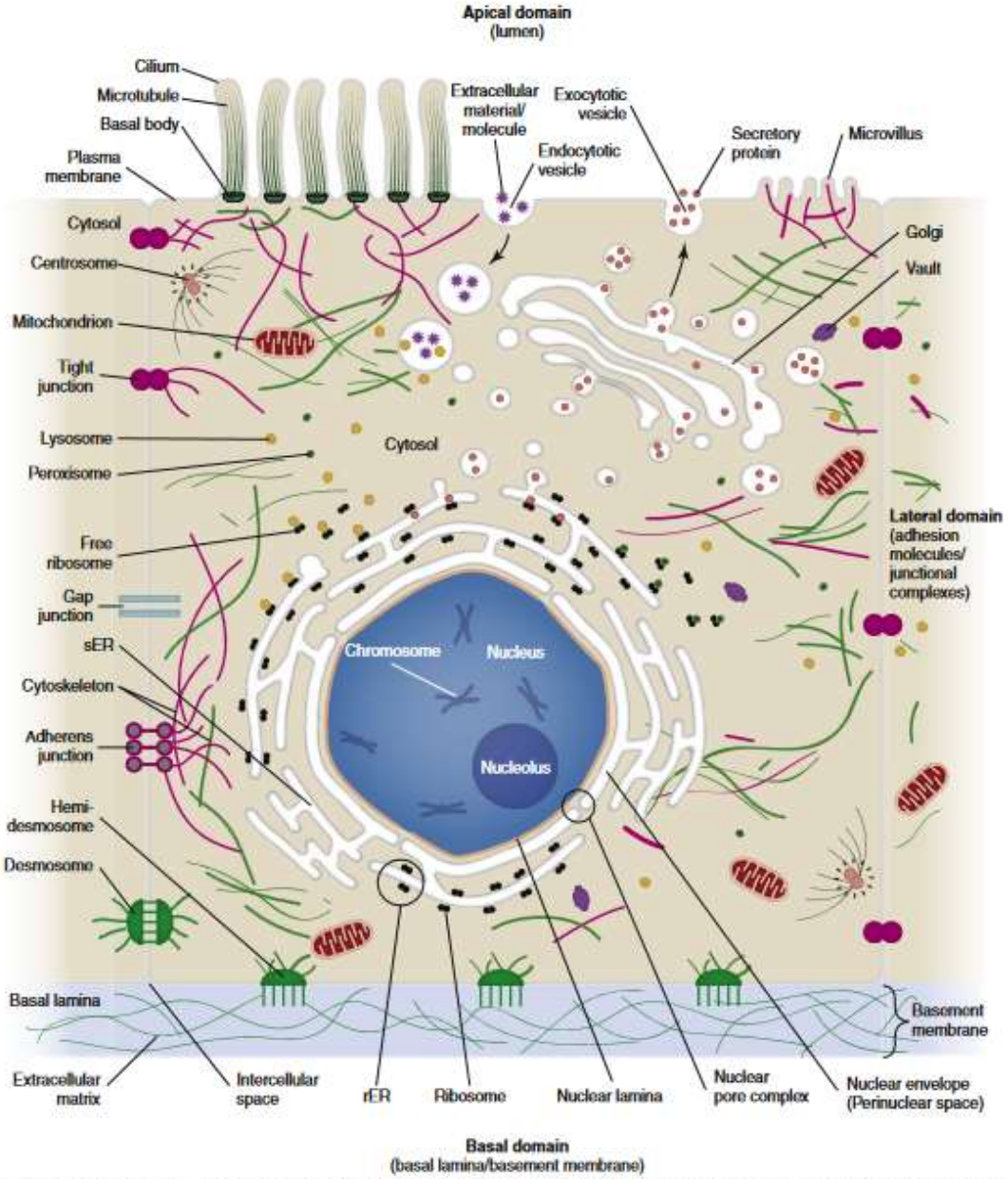


Figure 1.1 Cell Structure and the Organization of Organelles, Cytoskeleton, and Membrane Enhancements. The lateral domain is present on all lateral sides of the cell. *rER*, Rough endoplasmic reticulum; *sER*, smooth endoplasmic reticulum. (Courtesy Dr. M.A. Miller, College of Veterinary Medicine, Purdue University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

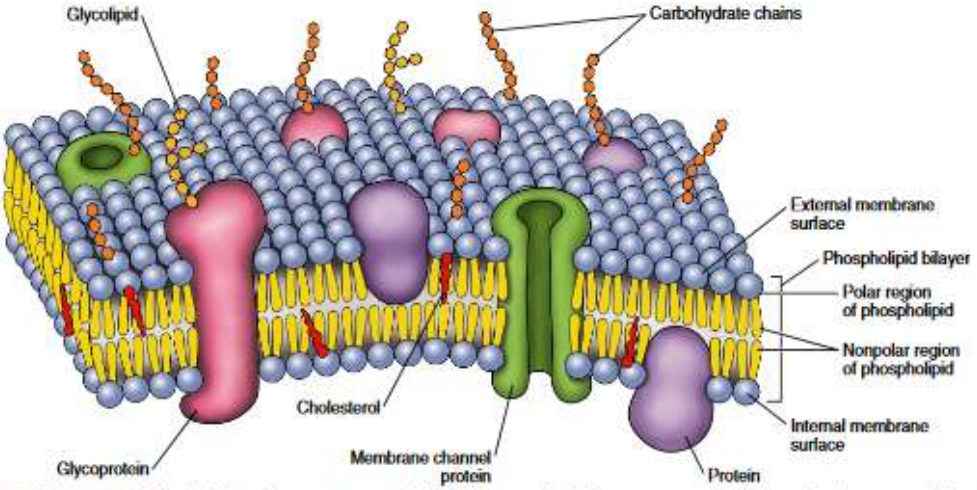


Figure 1.2 Fluid Mosaic Model of Cell Membrane Structure. The lipid bilayer provides the basic structure and serves as a relatively impermeable barrier to most water-soluble molecules.

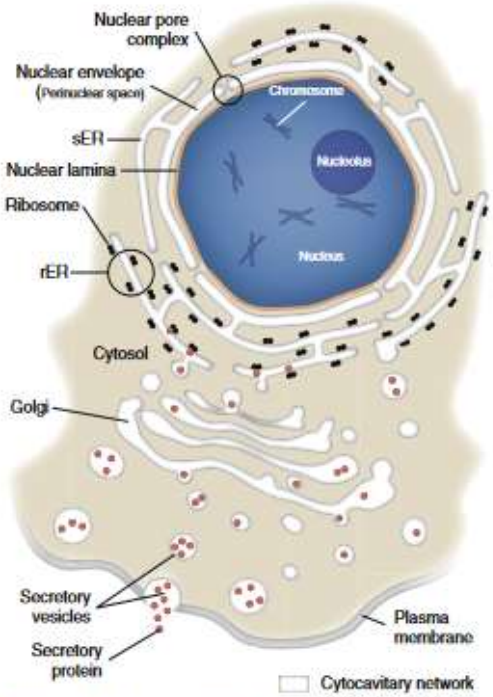


Figure 1.3 Cytocavitary Network. The rough endoplasmic reticulum (rER) and Golgi complex function in synthesis of proteins and glycoproteins used in and secreted from cells. Transcription, translation, assembly, modification, and packaging of these molecules occur in an orderly sequence from the nucleus to the plasma membrane as shown. Smooth endoplasmic reticulum (sER) is involved in the synthesis of lipids, steroids, and carbohydrates and in the metabolism of exogenous substances. (Courtesy Dr. M.A. Miller, College

microbes (see Figs. 4.34 and 4.37), or extracellular, such as hormones, growth factors, cytokines, cell recognition molecules, and neurotransmitters.

Cytoplasmic and nuclear receptors, through control of gene expression, regulate cellular development, homeostasis,[b] metabolism, and aging. Ligands that bind these receptors include lipophilic substances, such as steroid hormones, vitamins, and xenobiotic endocrine disruptors that cross plasma and nuclear membranes by passive diffusion.

Cell surface receptors are central to the pathogenesis of many disorders discussed throughout this book. As an extension of a transmembrane protein, cell surface receptors receive and interpret extracellular signals (i.e., ligands) from the environment. When a ligand binds to an appropriate surface receptor, conformational changes in the transmembrane protein result in a process called signal transduction (signaling molecule → specific receptor protein on the plasma membrane → second messenger transmits the signal into the cell → physiologic response) and the activation (i.e., second messenger system [see later discussion]) or inhibition of the receptor's biochemical pathway. There are hundreds of different types of glycoprotein and lipoprotein transmembrane receptors; each type is linked to a specific intracellular biochemical pathway, and individual cells contain many of these receptors based on their function as determined by their genome. *Transmembrane receptors* are often used by infectious microbes to invade cells or use cell systems during their life cycles, thus initiating a process that can injure the host cell. These receptors and their roles in the mechanisms of infectious disease are discussed in detail in Chapter 4, Mechanisms of Microbial Infections.

A unique transmembrane protein receptor is involved in the *notch-signaling pathway*. Ligand activation of notch signaling results in the formation of a cytoplasmic second messenger that enters the nucleus and modifies gene expression during embryonic

[b]The existence of cells, tissues, and organs/organ systems in a physiologic condition that is considered normal for each type of cell, tissue, and organ/organ system (i.e., the structural and functional characteristics of cells that allow them to maintain and regulate the stability and consistency of their

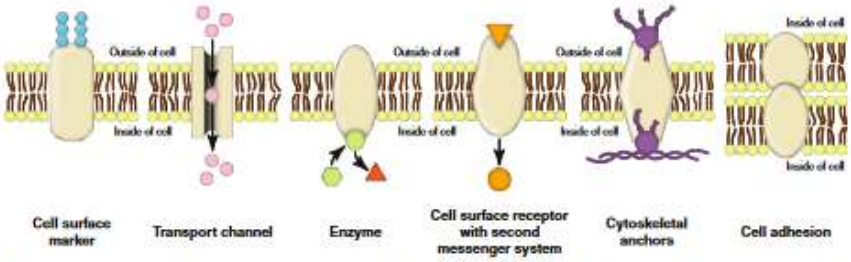


Figure 1.4 Functions of Transmembrane Proteins. Transmembrane proteins that span the phospholipid bilayer of cell membranes serve a variety of structural, transport, signaling, and enzymatic functions. (Courtesy Dr. M.A. Miller, College of Veterinary Medicine, Purdue University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

development and homeostasis. During development, notch signaling allows specific types of cells and tissues to develop, organize, and grow. If a specific cell type expresses a trait essential for the development of a specific tissue type, ligands are released from the "essential" cell that bind notch receptors on adjacent cells. Signal transduction and second messenger systems are activated, leading to the inhibition of division and development of affected "bystander" cells. This outcome allows specific types of cells to increase in number during development, while inhibiting other less essential cell types. Notch-signaling pathways are involved in the development of neural tissues, blood vessels, heart, pancreas, mammary gland, T lymphocytes, hematopoietic lineages, and other cell types. Notch-signaling pathways also play a role in mature animals. They appear to determine, for example, whether enteric stem cells differentiate into villous enterocytes with secretory or absorptive functions. Diseases that kill or injure enteric crypt stem cells (e.g., certain parvoviruses) or villous enterocytes (e.g., coronaviruses) probably disrupt notch-signaling pathways, leading to a lack of secretory or absorptive enterocytes during healing with failure to return to "normal" function (see Chapter 7, Alimentary System and the Peritoneum, Omentum, Mesentery, and Peritoneal Cavity).

Second Messenger Systems. Cells are in continuous contact with a wide variety of extracellular molecules (see first messengers earlier). Examples of first messenger molecules include microbial ligands (also see Chapter 4, Mechanisms of Microbial Infections), hormones, growth factors, neurotransmitters, and xenobiotics. First messenger interactions typically involve the binding of a ligand to its transmembrane protein receptor, which activates a second messenger system (E-Fig. 1.1). Examples of second messenger molecules include Ca^{2+}, cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), inositol triphosphate, diacylglycerol, arachidonic acid, and nitric oxide (NO). The second messenger initiates an intracellular signal transduction cascade that stimulates or alters a metabolic pathway. Thus, second messenger systems translate "first messages" from the plasma membrane into specific actions within the cell and its organelles to maintain homeostasis or defend against infection or other injury.

Cytosol versus Cytoplasm

Whereas the term cytoplasm refers to the light microscopically visible portion of the cell that is inside the plasma membrane and outside the nuclear envelope (see next section), the term cytosol specifies the cytoplasmic matrix (i.e., the gel portion of the cytoplasm that surrounds organelles). The cytosol contains water, dissolved ions, and macromolecules, such as proteins.

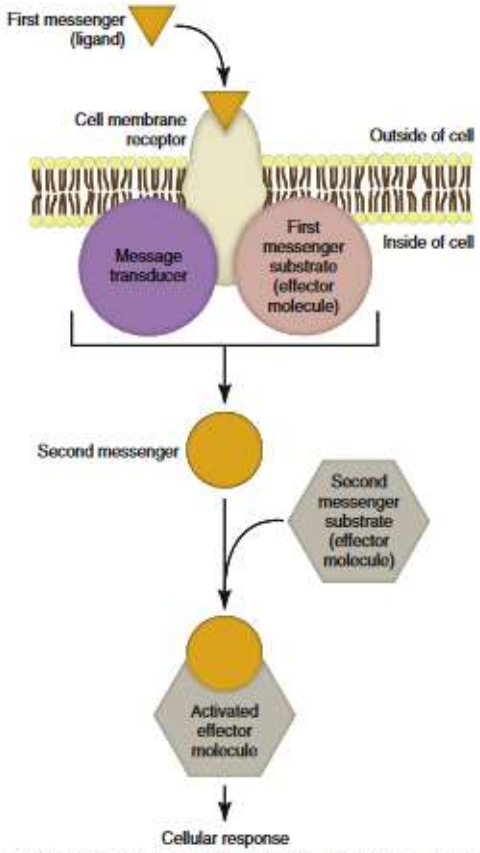
Nucleus

Animals are made of eukaryotic cells, meaning cells that have a nucleus, which, except in mammalian erythrocytes, is retained throughout the life of the cell. The nucleus (see Fig. 1.1) is readily visible by light microscopy because it contains chromatin (DNA complexed with histones), which is well stained by hematoxylin. Uncoiled chromatin is called *euchromatin* and is dispersed throughout the nucleus and actively involved in production of messenger RNA (mRNA). Tightly coiled chromatin is called *heterochromatin* and is clumped around the inner nuclear membrane and is inactive (see also Fig. 1.63). The nucleus is surrounded by an inner and an outer nuclear membrane that together form the nuclear envelope. The inner and outer nuclear membranes merge at the nuclear pore complexes, which allow bidirectional trafficking between the nucleus and the cytosol. The inner nuclear membrane is more "nuclear" in its biochemistry and serves to segregate and maintain the unique biochemistry of the nucleus, whereas the outer nuclear membrane has features more like those of the endoplasmic reticulum (ER), with which it is continuous. This differentiation and arrangement is essential for translation of genetic material (DNA and RNA) into gene products (proteins).

Nucleolus. The nucleolus (see Fig. 1.1) is a non–membrane-bound structure within the nucleus that forms around chromosomal loci of the ribosomal RNA (rRNA) genes known as nucleolar organizing regions (NORs). The nucleolus is the site of transcription and processing of rRNA and of assembly of preribosomal subunits. Thus, it consists of ribosomal DNA, RNA, and ribosomal proteins, including RNA polymerases, imported from the cytosol. At the light microscopic level, the nucleolus can be inconspicuous in inactive cells or quite prominent in cells with high protein production.

Rough Endoplasmic Reticulum

The ER is a membrane-bound network of flattened saclike cisternae (see Figs. 1.1 and 1.3). The membrane of the rER is continuous with the outer nuclear membrane, so the luminal contents of the rER and of the nuclear envelope communicate. The rER is so named because attached ribosomes impart a rough appearance (at the ultrastructural level) to its membrane as opposed to the appearance of the smooth ER (sER), which lacks surface ribosomes. The main function of rER is protein synthesis. Translation of mRNA with assembly of amino acids into peptides begins on ribosomes that are free in the cytosol. When the developing peptide is detected by a signal recognition particle, translation pauses until the ribosomal peptide–mRNA complex is attached to the outer surface of the rER. Protein formation continues in the membrane or lumen of the rER until a signal peptidase removes the signal peptide, at which time the newly



E-Figure 1.1 **Messenger Systems in Cells.** (Courtesy Dr. M.A. Miller, College of Veterinary Medicine, Purdue University; and Dr. J.F. Zachary, College of Veterinary Medicine, University of Illinois.)

formed protein can be transported to the cellular or extracellular site where it is needed or to the Golgi complex for further processing (see Fig. 1.3). Transmission electron microscopy is generally required to visualize the rER; however, cells that produce abundant protein and thus have abundant rER tend to have more basophilic cytoplasm because of the ample nucleic acid (RNA) in ribosomes.

Ribosomes. Ribosomes facilitate the synthesis of proteins in cells (i.e., translation) (see Figs. 1.1 and 1.3). Their function is to "translate" information encoded in mRNA into polypeptide chains of amino acids that make up proteins. There are two types of ribosomes, free and fixed (also known as membrane bound). They are identical in structure but differ in intracellular location. Free ribosomes are located in the cytosol and are able to move throughout the cell, whereas fixed ribosomes are attached to the rER. Free ribosomes synthesize proteins that are released into the cytosol and used within the cell. Fixed ribosomes synthesize proteins that are (1) inserted into the cell membrane (transmembrane proteins) at the rER and subsequently moved (fluid mosaic membrane model) to their final destinations usually within the plasma membrane or (2) placed in membrane-bound vesicles and moved through the Golgi complex (see next paragraph) to the plasma membrane and released via exocytosis into the extracellular environment.

Golgi Complex

The Golgi complex, also commonly called the Golgi apparatus, is a series of flattened membrane-bound sacs with its inner face (*cis* or entry face) near the rER in a paranuclear position (see Fig. 1.3). Proteins made in the rER are delivered to the entry face of the Golgi complex by transport vesicles. As the proteins traverse the Golgi complex, they are processed (e.g., carbohydrate moieties added through glycosylation) and packaged into secretory vesicles to be released from the outer (*trans*) face of the Golgi complex into the cytosol, either for use by the cell that produced them, as in the case of lysosomal enzymes, or (more commonly) for delivery to the plasma membrane for export. Transmission electron microscopy is usually required to visualize the Golgi complex. However, an active Golgi complex, such as that needed for processing and packaging of immunoglobulin molecules, is large enough to impart a paranuclear eosinophilic pallor to plasma cells in a hematoxylin and eosin (H&E)-stained histologic section.

Smooth Endoplasmic Reticulum

sER is a membrane-bound network of tubules (see Figs. 1.1 and 1.3) without surface ribosomes. sER is not involved in protein synthesis. Its main function is the synthesis of lipids, steroids, and carbohydrates, as well as the metabolism of exogenous substances, such as drugs or toxins. Cells, such as hepatocytes, that are important for synthesis of lipids and metabolism of drugs or toxins have abundant sER, as do cells that produce steroid hormones, such as adrenocortical cells and certain testicular or ovarian cells. Cells with abundant sER have pale eosinophilic, finely vacuolated cytoplasm.

Mitochondria

Mitochondria are dynamic organelles that can change shape, undergo fission and fusion, and move about within the cell. They can be large enough (up to 1 μm) to resolve with the light microscope, especially in muscle from athletic animals such as racehorses. Because most cellular processes require "energy," a major mitochondrial function is the generation of energy as adenosine triphosphate (ATP) through oxidative phosphorylation. Mitochondria are also involved in programmed cell death (e.g., apoptosis), signaling, cell differentiation, and cell growth. Mitochondria contain their own genome (see later section on the Genetic Basis of Disease), which consists mainly of circular DNA that encodes transfer and rRNAs as well as some mitochondrial proteins. However, most of the genes that encode mitochondrial proteins are located in the nucleus of the cell. Mitochondria have a biochemically distinct inner and outer membrane. The inner membrane is folded into cristae that project into the central matrix of the mitochondrion (see Figs. 1.1 and 1.5).

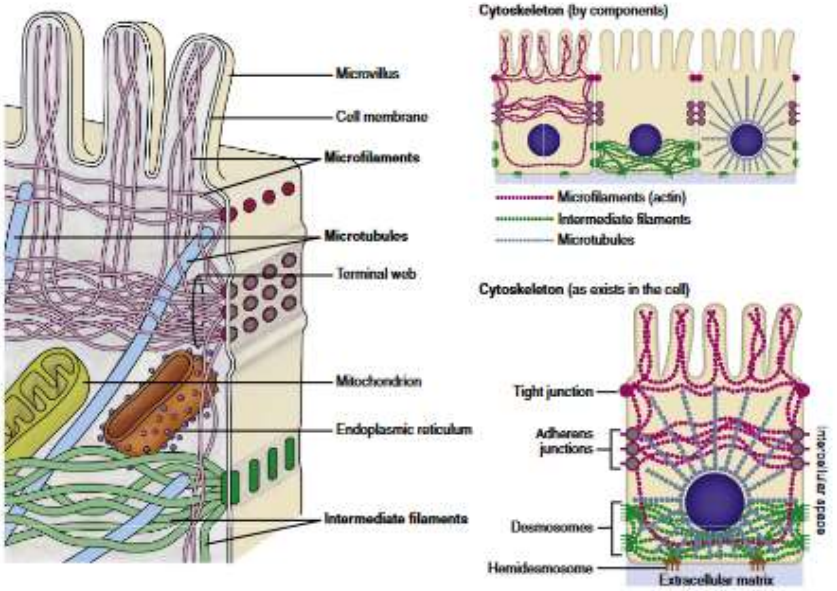


Figure 1.5 Cytoskeleton. The complexity and interrelations of microfilaments, intermediate filaments, and microtubules with the plasma membrane and other organelles are depicted.