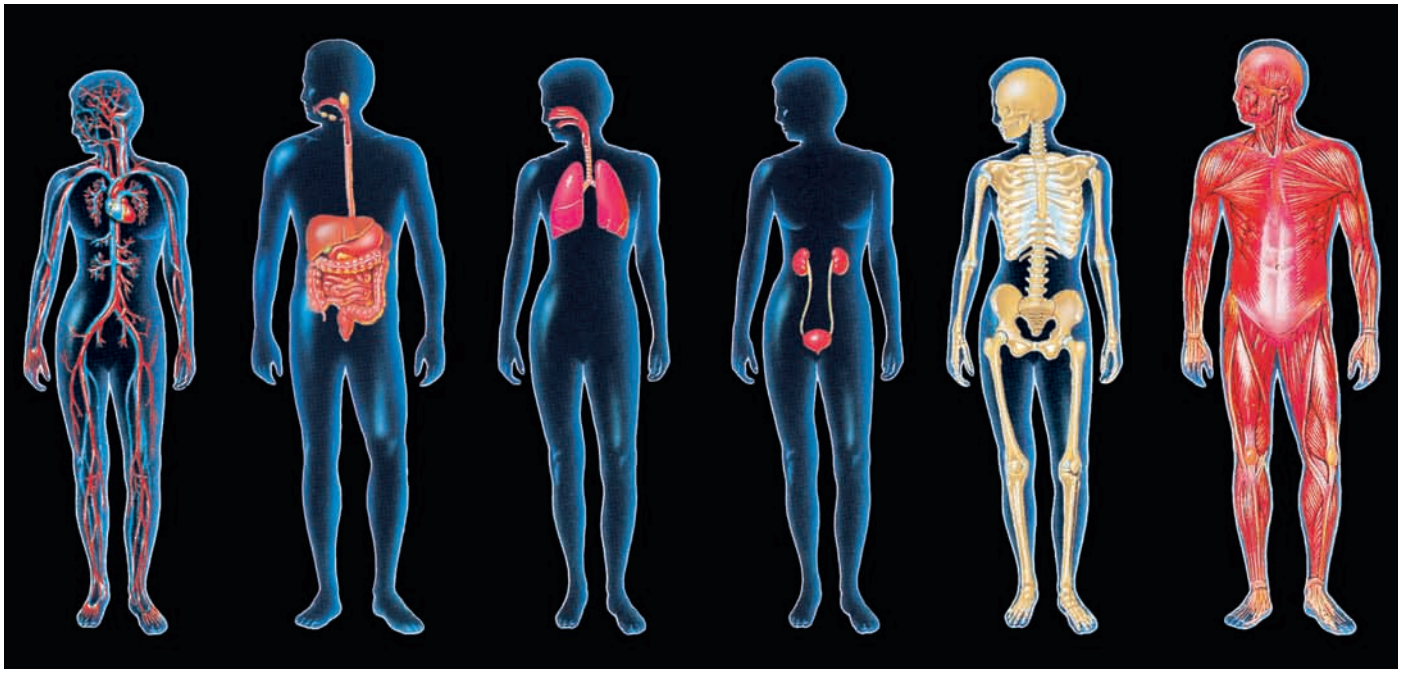


Circulatory system
heart, blood vessels, blood

Digestive system
mouth, pharynx, esophagus, stomach, small intestine, large intestine, salivary glands, exocrine pancreas, liver, gallbladder

Respiratory system
nose, pharynx, larynx, trachea, bronchi, lungs

Urinary system
kidneys, ureters, urinary bladder, urethra

Skeletal system
bones, cartilage, joints

Muscular system
skeletal muscles

Figure 1-5 Components of the body systems.

Body cells are in contact with a privately maintained internal environment.

The fluid collectively contained within all body cells is called **intracellular fluid (ICF)**. The fluid outside the cells is called **extracellular fluid (ECF)**. Note that the ECF is outside the cells but inside the body. Thus, the ECF is the internal environment of the body. You live in the external environment; your cells live in the body's internal environment.

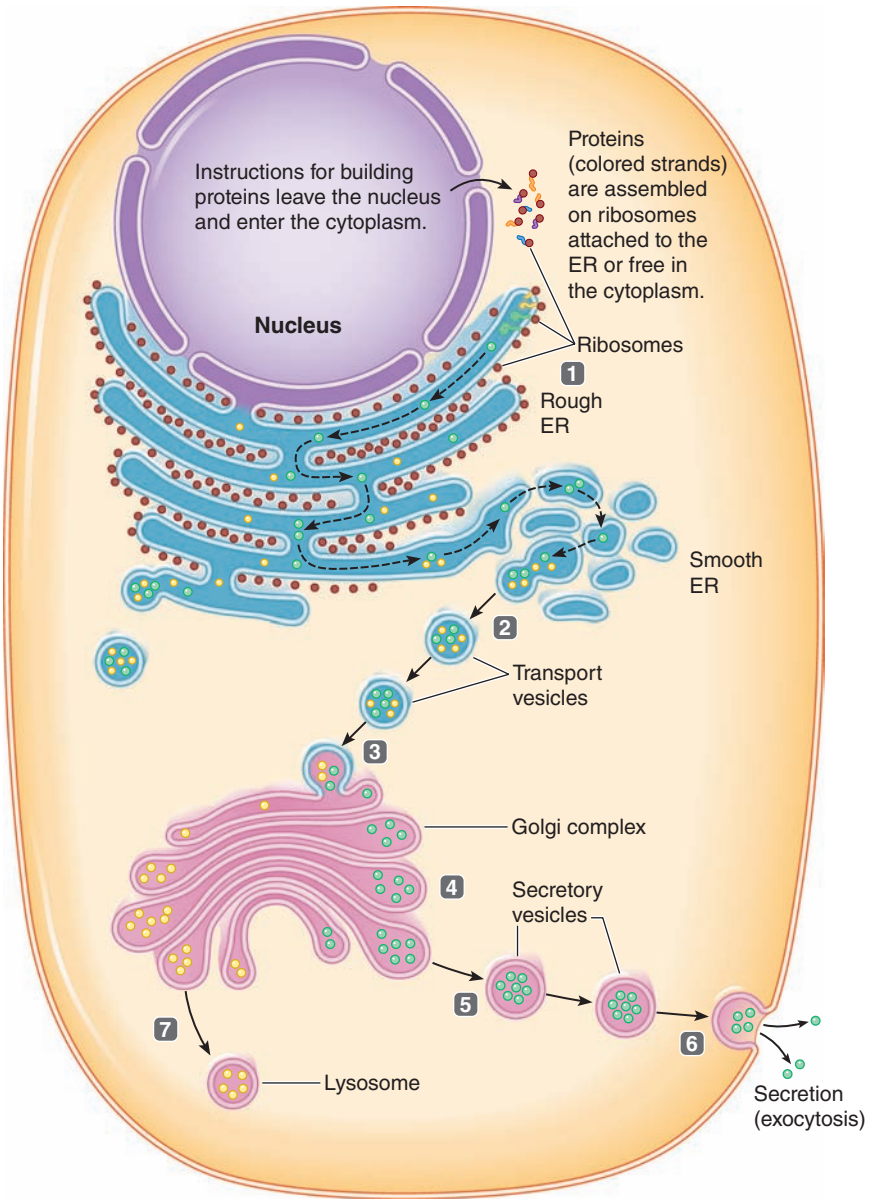
ECF is made up of two components: the **plasma**, the fluid portion of the blood, and the **interstitial fluid**, which surrounds and bathes the cells (*inter* means "between"; *stitial* means "that which stands") (Figure 1-6).

No matter how remote a cell is from the external environment, it can make life-sustaining exchanges with its surrounding fluid. Particular body systems accomplish the transfer of materials between the external environment and the internal environment so that the composition of the internal environment is appropriately maintained to support the life and functioning of the cells. The digestive system transfers the nutrients required by all body cells from the external environment into the plasma, and the respiratory system transfers O_2 from the external environment into the plasma. The circulatory system distributes these nutrients and O_2 throughout the body. Materials are thoroughly mixed and exchanged between the plasma and the interstitial fluid across the capillaries, the smallest and thinnest of blood vessels. As a result, the nutrients and O_2 originally obtained from the external environment are delivered to the interstitial fluid, from which the body cells pick up these needed supplies. Similarly, wastes produced by the cells are released into the interstitial fluid, picked up by the plasma, and transported to the organs that specialize in eliminating these wastes from the internal environment to the external environment. The lungs remove CO_2 from the plasma and blow out this waste, and the kidneys remove other wastes for elimination in the urine.

Thus, a body cell takes in essential nutrients from its watery surroundings and eliminates wastes into these same surroundings, just as an amoeba does. The main difference is that each body cell must help maintain the composition of the internal environment so that this fluid continuously remains suitable to support the existence of all body cells. In contrast, an amoeba does nothing to regulate its surroundings.

Body systems maintain homeostasis, a dynamic steady state in the internal environment.

Body cells can live and function only when the ECF is compatible with their survival; thus, the chemical composition and physical state of this internal environment must be maintained within narrow limits. As cells take up nutrients and O_2 from the internal environment, these essential materials must constantly be replenished. Likewise, wastes must constantly be removed from the internal environment so that they do not reach toxic



1 The rough ER synthesizes proteins to be secreted to the exterior or to be incorporated into plasma membrane or other cell components.

2 The smooth ER packages the secretory product into transport vesicles, which bud off and move to the Golgi complex.

3 The transport vesicles fuse with the Golgi complex, open up, and empty their contents into the closest Golgi sac.

4 The newly synthesized proteins from the ER travel by vesicular transport through the layers of the Golgi complex, which modifies the raw proteins into final form and sorts and directs the finished products to their final destination by varying their wrappers.

5 Secretory vesicles containing the finished protein products bud off the Golgi complex and remain in the cytosol, storing the products until signaled to empty.

6 On appropriate stimulation, the secretory vesicles fuse with the plasma membrane, open, and empty their contents to the cell's exterior. Secretion has occurred by exocytosis, with the secretory products never having come into contact with the cytosol.

7 Lysosomes also bud from the Golgi complex.

Figure 2-3 Overview of the secretion process for proteins synthesized by the endoplasmic reticulum. **FIGURE FOCUS:** *Compare the contents of a transport vesicle and a secretory vesicle.*

pinches off a transport vesicle. Transport vesicles move to the Golgi complex, described in the next section, for further processing of their cargo.

In contrast to the sparseness of the smooth ER in most cells, some specialized cell types have an extensive smooth ER, which has additional functions as follows:

- The smooth ER is abundant in cells that specialize in lipid metabolism—for example, cells that secrete lipid-derived steroid hormones. The membranous wall of the smooth ER, like that of the rough ER, contains enzymes for synthesis of lipids. These cells have an expanded smooth-ER compartment that houses the additional enzymes necessary to keep pace with demands for hormone secretion.
- In liver cells, the smooth ER contains enzymes specialized for detoxifying harmful substances produced within the body by metabolism or substances that enter the body from the outside in the form of drugs or other foreign compounds.
- Muscle cells have an elaborate, modified smooth ER known as the *sarcoplasmic reticulum,* which stores calcium used in the process of muscle contraction (see p. 258).

Misfolded proteins are destroyed by the ubiquitin–proteasome pathway.

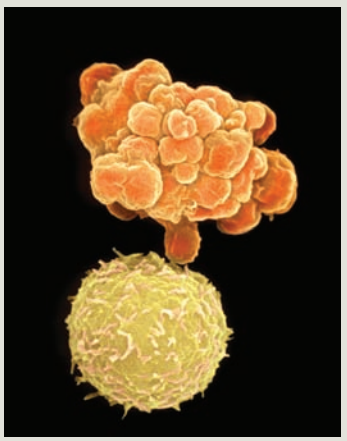
Like any good factory, the rough ER has a quality control system in place to remove defective products. Misfolded proteins are tagged with **ubiquitin**, a small protein "doom tag" that labels those flawed proteins for destruction. Ubiquitin directs the tagged protein out of the ER to one of many proteasomes located throughout the cell. A **proteasome**, a nonmembranous organelle, is a protein degradation machine: It is a cylinder-shaped complex about the size of a ribosomal subunit that contains multiple protein-digesting enzymes that break down ubiquinated proteins into recyclable building blocks (Figure 2-4). A proteasome consists of a hollow *core particle* capped at

tially harmful intracellular contents characteristic of necrosis. No inflammatory response is triggered, so no neighboring cells are harmed. Instead, cells in the vicinity swiftly engulf and destroy the apoptotic cell fragments by phagocytosis. The breakdown products are recycled for other purposes as needed. The tissue as a whole has continued to function normally, while the targeted cell has unobtrusively killed itself.

By comparison to apoptosis and necrosis, both means of cell death, the self-eating process of autophagy (see p. 31) actually promotes cell survival by removing outdated or damaged cell components, thus permitting the cell to refresh itself with healthy new replacement parts.

Control of Apoptosis

If every cell contains caspases, what normally keeps these powerful self-destructive enzymes under control (that is, in inactive form) in cells that are useful to the body and deserve to live? Likewise, what activates the death-wielding caspases in unwanted cells destined to eliminate themselves? Given the importance of these life-or-death decisions, it is not surprising that multiple internal control pathways tightly regulate whether a cell is "to be or not to be." A cell normally receives a constant stream of "survival signals," which reassure the cell that it is useful to the body, that all is right in the internal environment surrounding the cell, and that everything is in good working order within the cell. These signals include tissue-specific growth factors, certain hormones, and appropriate contact with neighboring cells and surrounding connective tissue. These extracellular survival signals trigger intracellular pathways that block activation of the caspases, thus restraining the cell's death machinery. Most cells are programmed to commit suicide if they do not receive their normal reassuring survival signals. With the usual safeguards removed, the lethal protein-snipping enzymes are unleashed. For example, withdrawal of growth factors or detachment from the surrounding connective tissue causes a cell to promptly execute itself.



Dr. Gopal Murti/Science Source

A normal cell (bottom) and a cell undergoing apoptosis (top).

Furthermore, cells display "death receptors" in their outer plasma membrane that receive specific extracellular "death signals," such as a particular hormone or a specific chemical messenger from white blood cells that arrive at the cell via the blood. Activation of death pathways by these signals can override the life-saving pathways triggered by the survival signals. The death-signal pathway swiftly ignites the internal apoptotic machinery, driving the cell to its demise. Likewise, the self-execution machinery is set in motion when a cell suffers irreparable intracellular damage. Thus, some signals block apoptosis and others promote it. Whether a cell lives or dies depends on which of these competing signals dominates at any given time. Although all cells have the same death machinery, they vary in the specific signals that induce them to commit suicide.

Considering that every cell's life hangs in delicate balance at all times, it is not surprising that faulty control of apoptosis—resulting in either too much or too little cell suicide—appears to participate in many major diseases. Excessive apoptotic activity is believed to contribute to the brain cell death associated with Alzheimer's disease, Parkinson's disease, and stroke and to the premature demise of important infection-fighting cells in AIDS. Conversely, too little apoptosis most likely plays a role in cancer. Evidence suggests that cancer cells fail to respond to the normal extracellular signals that promote cell death. Because these cells neglect to die on cue, they grow in unchecked fashion, forming a chaotic, out-of-control mass.

Apoptosis is currently one of the hottest topics of investigation in the field. Researchers are scrambling to sort out the multiple factors involved in the mechanisms controlling this process. Their hope is to find ways to tinker with the apoptotic machinery to find badly needed new therapies for treating a variety of big killers.

Enzymatic Regulation of Intermediary Metabolism

The term **intermediary metabolism** refers collectively to the large set of chemical reactions inside the cell that involve the degradation, synthesis, and transformation of small organic molecules such as simple sugars, amino acids, and fatty acids. These reactions are critical for ultimately capturing the energy used for cell activities and for providing the raw materials needed to maintain the cell's structure, function, and growth. Intermediary metabolism occurs in the cytoplasm, with most of it being accomplished in the cytosol. The cytosol contains thousands of enzymes involved in intermediary biochemical reactions.

Ribosomal Protein Synthesis Also dispersed throughout the cytosol are the free ribosomes, which synthesize proteins for use in the cytosol itself. In contrast, recall that the rough-ER ribosomes synthesize proteins for secretion and for construction of new cell components.

Storage of Fat, Glycogen, and Secretory Vesicles

Excess nutrients not immediately used for ATP production are converted in the cytosol into storage forms that are readily visible under a light microscope. Such nonpermanent masses of stored material are known as **inclusions**. Inclusions are not surrounded by membrane, and they may or may not be present,