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Cells and Tissues in Health and Disease

Very simply, medicine is the study (and maintenance) of health. Health requires appropriate organ structure and function. Health that has gone awry or out of balance is *disease*. To understand how and why things go wrong in the body, we need to understand what is normal – normal anatomy, normal physiology, and normal function. The starting point and basis for all health and disease is the cell (Cotran et al., 1999). Cells form tissues that form organs that are responsible for an organism's life.

The eukaryotic cell is a remarkable creation! Self-sustaining, it contains all that is needed to survive and reproduce – mechanisms to replicate, create energy, create proteins and molecules to make substrates it needs, a storage depot, a way to import and export signals, and a way to remove and/or destroy waste. Each of these functions is mediated by specific organelles, that is, membrane-bound "factories" that carry out their specific tasks (Figure 1.1).

The cell and each organelle within it are surrounded by a membrane. The primary functions of the membrane are to enclose and protect the integrity of the cell and to mediate movement of molecules and signals in and out of the cell. The membrane is composed of a lipid bilayer with proteins either located within the bilayer and/or protruding out either end. This structure supports the optimal function and flexibility of the cell.

The director of all activities in the cell (and body) lies within the genetic material, which resides in the nucleus. The eukaryotic nucleus houses DNA within genes tightly bound together in structures called chromosomes. When needed, these tightly bound structures will "unwind" to permit cell division or replication (mitosis) and/or protein formation.

Cell division, or mitosis, is simply replication of the cell. DNA normally exists in a diploid state – two copies of the DNA per cell (i.e., two copies of each chromosome with all their genes within). In general, mitosis is preceded by S phase of interphase (during which DNA replication occurs) and is often followed by

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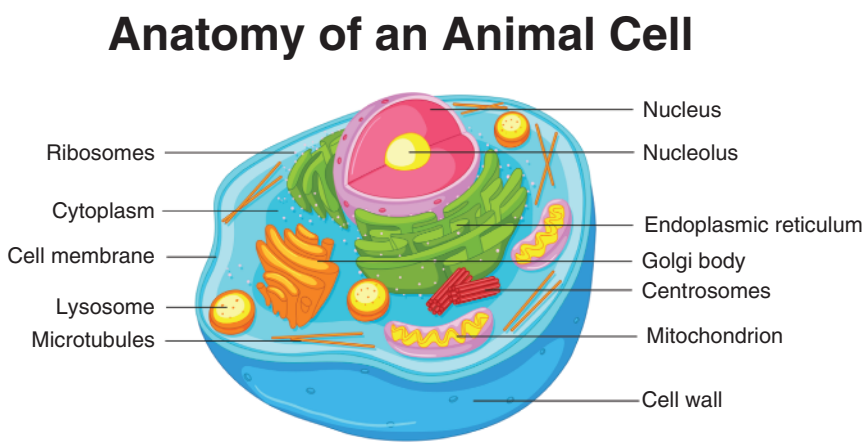

Figure 1.1 Diagram of a normal eukaryotic cell (GraphicsRF/Adobe Stock Photos).

metaphase, telophase (chromosomes split and spread apart), and ultimately cytokinesis. In cytokinesis, division of the cytoplasm, organelles, and cell membrane occurs and two new cells are created, each containing roughly equal shares of these cellular components.

Gamete production occurs by meiosis, a process like mitosis but with distinct differences. In meiosis, the chromosomes duplicate (during interphase) and homologous chromosomes exchange genetic information (chromosomal crossover) during the first division called meiosis I. The daughter cells divide again in meiosis II, splitting up sister chromatids to form haploid gametes. Gametes are haploid, that is, they have only one copy of DNA such that when the gametes from a male and female fuse to form a zygote, the diploid condition is restored. This process only occurs in the organs that produce gametes, i.e., the ovaries and testicles.

Energy, in the form of adenosine triphosphate (ATP), is created inside the mitochondria of cells. Energy is produced by oxidative phosphorylation (aka aerobic respiration), which requires oxygen. Mitochondria have a double membrane system where there is an outer membrane surrounding the mitochondria and an inner membrane within the mitochondria that forms the substrate where ATP is produced. Mitochondria also have a function in cell cycle regulation and regulate some other essential processes. Unique to this organelle is the presence of its own mitochondrial DNA (mtDNA), which is distinct from nuclear DNA (nDNA). Mitochondrial DNA is passed down by the females (matrilineal).

The endoplasmic reticulum in concert with the Golgi apparatus is involved in the production and movement of cellular products out of the cell. The rough

endoplasmic reticulum (RER) contains ribosomes that are used to produce proteins targeted for release out of the cell. The smooth endoplasmic reticulum (SER) has enzymes that metabolize steroids, lipids, some drugs, and glycogen. When the cellular products are ready to be released or excreted from the cell, they merge with the Golgi vesicles which then fuse with the cell membrane and discharge the contents outside the cell (Figure 1.2).

Lysosomes are organelles that serve as waste receptacles for the cell. These organelles contain enzymes that can degrade molecules and other waste products. After degradation of waste, these secondary lysosomes fuse with the membrane and discharge their contents ("empty the garbage") out of the cell (Figure 1.2). Membrane integrity is critical for this organelle to prevent the enzymes within them from leaking out and degrading all other components of the cell.

The cell cytoskeleton is formed by microfilaments, microtubules, and intermediate filaments. Each of these has a separate role in cell movement and shape. Microtubules are involved in mitosis when the cell divides into half and moves apart. Intermediate filaments help certain cell types to move. For example, desmin is an intermediate

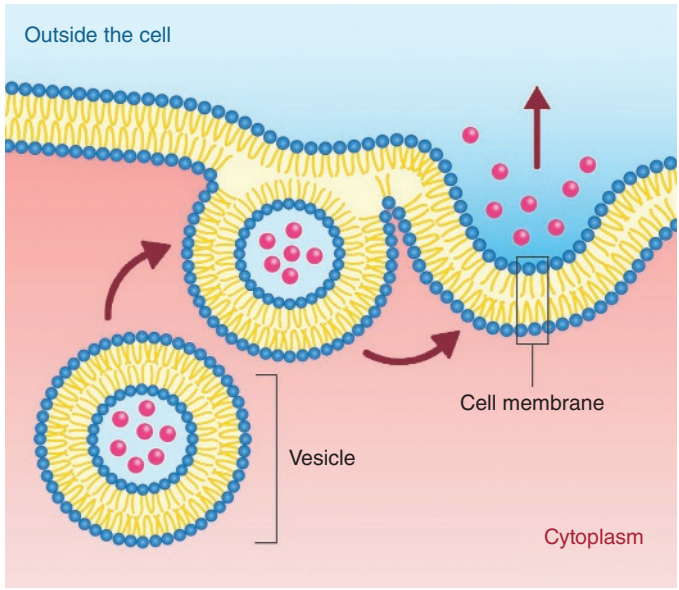

Figure 1.2 Diagram of an animal cell indicating the processes for excreting molecules and waste out of the cell. Molecules tagged for export out of the cell leave the Golgi vesicles, which merge with the membrane and expel their contents. Secondary lysosomes filled with waste also expel their contents after merging with the membrane. *Source:* Fancy Tapis/Shutterstock.

filament involved in skeletal muscle contraction. In addition to proteins that reside on the outer surface, the cell may have "appendages," which stick out of the cell surface. These are small structures, such as cilia, which can help the cell sense the environment or move. Within the limits of the cell membrane is a watery, gel-like substrate (the cytoplasm) in which the filaments and organelles reside.

When the cell processes are all working well, the cell is in *homeostasis*. Homeostasis is the range of conditions wherein all cellular processes are functioning normally. Cells, tissues, organs, the organism, and the environment all have their own homeostatic parameters. When conditions change, which challenge the organism's or the cells' homeostasis, it must respond to restore balance. It all starts with the cell.

The cell responds to challenges or stimuli by adapting and changing to restore homeostatic balance. These adaptations are often reversible, and the cell can change back once the imposing challenge/stimulus has resolved and/or ceases. In situations where the challenging stimulus does not immediately resolve, the cell can exist in this altered "homeostatic" state. Should the challenging stimulus persist, the cell may undergo irreversible changes that may ultimately lead to its death. In this latter situation, the greater the number of cells that die, the more damage the tissue/organ will incur.

Reversible Cell Adaptations

Reversible changes of the cell vary according to the cell type that is affected. There are four basic types of reversible cellular changes: hypertrophy, hyperplasia, atrophy, and metaplasia. *Hypertrophy* is the increase of size or function of the cell, which results ultimately in enlarged organ size. The enlarged cell size is due to the synthesis of more structural components of the cell. This type of response is seen in cells that do not regularly divide, such as muscle, nerve, etc. The stimulus for hypertrophy is increased functional demand (by pathologic or physiologic causes) and/or by stimulation from hormones or growth factors. An example of pathologic hypertrophy would be cardiac hypertrophy; the heart muscle increases in size to increase pumping force to overcome a downstream blockage (e.g., faulty valve). An example of "physiologic" hypertrophy in humans would be weightlifting. Lifting weights puts a stressor on the arm muscles (e.g., biceps and triceps) to increase force to lift the weights. The net effect of the former is an enlarged heart; the net effect of the latter are thicker, bulging arm muscles.

Hyperplasia is the increase in numbers of cells that can also result in larger organ size. The mechanism of increased cell numbers is by the stimulation of stem cells or the proliferation of mature cells. This adaptation is common in

cell types that normally continually divide (e.g., epithelium of the gastrointestinal tract). As in hypertrophy, hyperplasia can be induced by physiologic or pathologic stressors. Physiologic hypertrophy occurs under hormonal influence in certain organs, such as in the mammary gland, during pregnancy. Approaching parturition (birth), mammary gland cells divide and increase in number for milk production, resulting in mammary gland enlargement. Pathologic hyperplasia can be caused by excess of hormones or growth factors resulting in pathologic conditions, such as endometrial hyperplasia or prostatic hyperplasia.

Atrophy is the reduction in cell size or function (often due to underutilization), which results in a reduction in organ size. The decreased cell size can be due to decreased protein synthesis and/or increased protein degradation, as the cells are not in use and have much lower metabolic demand. As in the adaptations above, causes can be physiologic or pathologic, and atrophy is a common mechanism employed during embryo/fetal development. When a muscle has a reduced workload, such as when one has a cast over a broken bone, the decreased workload to the associated muscles results in disuse atrophy. When the bone mends and the arms/legs resume normal functioning, the muscle undergoes hypertrophy to return to normal size/function.

The last reversible adaptation is *metaplasia*. Metaplasia is a reversible change in the phenotype of a cell – one differentiated cell type is replaced by a different differentiated cell type. This is basically an adaptive substitution of cell type that will be more tolerant and less sensitive to the imposing stimulus. The new cell type originates from stem cells that receive a message to produce a different cell type. One example of this adaptation is in the respiratory tract. Normally, the cells in the upper respiratory tract are columnar in shape and have cilia on their apical/luminal surface. In situations where the tract is chronically irritated from inhaling air with particles, the columnar cells with cilia will be damaged easily. The body will respond by reprogramming the stem cells to produce squamous cells (instead of columnar cells), which are more robust and can better handle the irritation. This must be a temporary change, as the squamous cell type cannot replace the cilia and the normal respiratory cell type's function.

Nonreversible Cell Injury and Cell Death

There are many causes of cell injury, but the ultimate mechanism of cell injury is the same. Depletion of ATP from decreased production in the mitochondria can be induced by many etiologies, all ultimately resulting from a decrease of oxygen (*hypoxia*). Even a slight, 5–10% decrease in ATP from hypoxia can lead

to decreased activity of membrane ion pumps, which results in a net gain of water into the cell and cell swelling. Altered metabolic pathways, calcium pump function, protein synthesis, and structural disruption also occur. If the extent of ATP decrease is very severe, the mitochondrial damage worsens. When this happens and the calcium pumps fail to keep calcium out of the cell, the injury becomes irreversible. Free radicals can build up inside the cell and intensify the already existing damage to the membranes, mitochondria, etc., leading to cell death.

If the injury or stimulus is very prolonged or severe, irreversible cellular changes will be observed, which ultimately lead to cell death. If too many cells die, then organ function can be compromised. Cell death is a normal and essential process during embryogenesis, organ development, and maintenance of homeostasis. There are two mechanisms by which cells can die: necrosis and apoptosis. The distinction between these two mechanisms has clinical relevance.

Let us start with *necrosis*. Cell death by necrosis involves cell membrane rupture and release of cellular contents and lysosomal enzymes out of the cell, which can digest adjacent cells/tissues (Figure 1.3). The dying cells cannot maintain cellular membrane integrity and contents leak out into the surrounding tissue. In necrosis, an inflammatory process is always incited. Necrosis is always a pathologic response to severe injury or pathology. Cellular necrosis can be seen using light microscopy as early as 4–12 hours after inception and earlier using electron microscopy. There are different patterns of necrosis depending on the etiologic agent and tissue affected, which can lead to its etiology. In coagulative necrosis (often bacterial in origin), the "ghosts" of cells can be seen under the microscope for a few days. In liquefactive necrosis (often viral, or toxic in origin), all that is observed is a liquid mass of dead cells and debris. Caseous necrosis includes friable white tissue (grossly looking like cottage cheese) that is well circumscribed (encapsulated) by connective tissue and inflammation caused by acid-fast bacteria. Finally, in affected blood vessels, fibrin and immune cell deposition occur in the vessel walls and this is known as fibrinoid necrosis.

The other mechanism of cell death is called *apoptosis* (Figure 1.3, top pathway). In apoptosis, the cell membrane remains intact and the dead cell fragments are formed into small, membrane-bound structures called "apoptotic bodies." Because the membranes remain intact, apoptotic cell death does *not* incite inflammation. Apoptosis is actually a very complex and tightly orchestrated process of "cell suicide." When damage is so severe to the cell proteins and DNA, the cell basically "signals" the process that results in death by apoptosis. This process is normal during fetal development but can also be induced by severe damage to the cell. The apoptotic bodies are visible under light and electron microscopy.

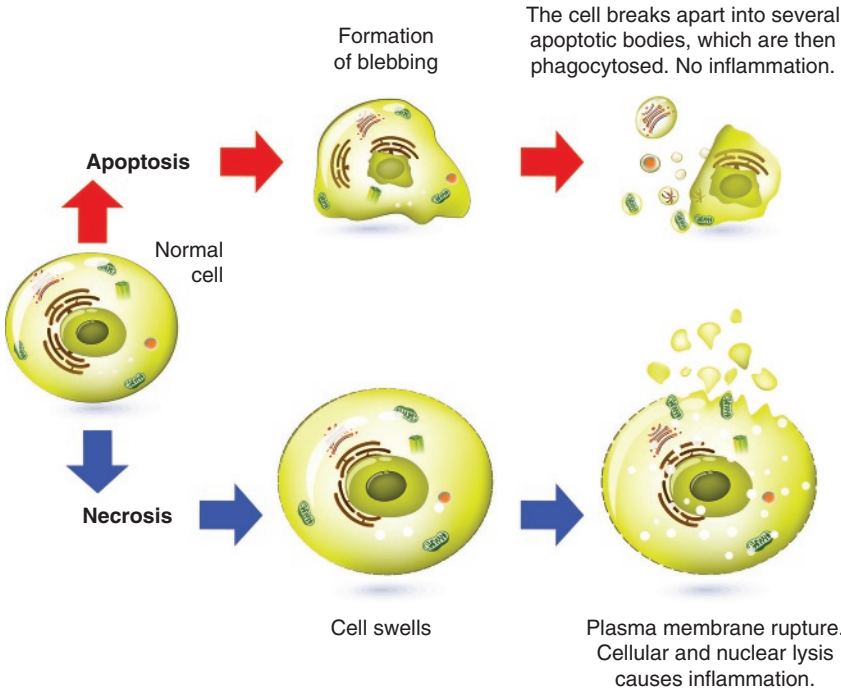

Figure 1.3 Pathways of cell death – necrosis and apoptosis. Details discussed in text (Designua/Shutterstock).

However, the lack of cellular leakage and lack of an inflammatory process makes clinical diagnosis of this phenomenon *clinically* difficult.

From a clinical diagnostic perspective, necrotic cell death provides us with a mechanism to diagnose disease and the organs affected. When the cell membranes break open, all the enzymes within the cell come pouring out. They get absorbed into the blood circulation. By assaying the enzyme levels in the blood, we can identify the organ(s) affected. For example, when there is suspicion of a heart attack in people, the hospital will assay the blood for the appropriate cardiac enzyme. If the enzyme levels are high, then this indicates heart muscle damage. Since the major mechanism of cell damage is lack of oxygen, this suggests a "heart attack" (cardiac infarct; reduced blood supply to the heart muscle). Additionally, when a sick individual presents to the clinic, blood work may show evidence of inflammation (increased white blood cell count). Combining evidence of inflammation with elevations of certain organ system enzymes can help narrow down the source of the inflammation (e.g., liver or kidney). More information on this issue will be provided later.

In summary, cell pathology underlies disease. Cell death by necrosis underlies our ability to clinically diagnose disease due to release of organ-specific enzymes into circulation and by inciting an inflammatory response – further details of which will be discussed in the following chapters.

Reference

Cotran, R.S., Kumar, V., and Collins, T. (1999). *Robbin's Pathologic Basis of Disease*, 6e. 3–42. Philadelphia, PA: W.B. Saunders Company.