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Mitochondria contain several proteins that are capable of inducing apoptosis, including cytochrome c. When mitochondrial membranes become permeable, cytochrome c leaks into the cytoplasm, triggering caspase activation and apoptotic death. The permeability of mitochondria is controlled by a family of more than 20 proteins, the prototype of which is BCL-2. In healthy cells, BCL-2 and the related protein BCL-X_L are produced in response to growth factors and other stimuli that keep cells viable. These antiapoptotic proteins maintain the integrity of mitochondrial membranes, in large part by holding two proapoptotic members of the family, BAX and BAK, in check. When cells are deprived of growth factors and survival signals, are exposed to agents that damage DNA, or accumulate unacceptable amounts of misfolded proteins, a number of sensors are activated. The most important of these sensors are called BH3-only proteins because they contain the third homology domain of the BCL-2 family. These sensors shift the balance in favor of BAK and BAX, which dimerize, insert into the mitochondrial membrane, and form channels through which cytochrome c and other mitochondrial proteins escape into the cytosol. At the same time, the deficiency of survival signals leads to decreased levels of BCL-2 and BCL-X_L, further compromising mitochondrial permeability. Once in the cytosol, cytochrome c interacts with certain cofactors and activates caspase-9, leading to the activation of a caspase cascade.

- **The death receptor (extrinsic) pathway of apoptosis.** Many cells express surface molecules, called death receptors, which trigger apoptosis. Most of these are members of the tumor necrosis factor (TNF) receptor family, which contain in their cytoplasmic regions a conserved "death domain," so named because it mediates interaction with other proteins involved in cell death. The prototypic death receptors are the type I TNF receptor and Fas (CD95). Fas ligand (FasL) is a membrane protein expressed mainly on activated T lymphocytes. When these T cells recognize Fas-expressing targets, Fas molecules are cross-linked by FasL and bind adaptor proteins via the death domain (see Fig. 1.12). These recruit and activate caspase-8, which in turn activates downstream caspases. The death receptor pathway is involved in elimination of self-reactive lymphocytes and in killing of target cells by some cytotoxic T lymphocytes that express FasL.
- **Terminal phase of apoptosis.** Activated caspase-8 and caspase-9 act through a final common series of reactions that first involve the activation of additional caspases, which through numerous substrates ultimately activate enzymes that degrade the cell's proteins and nucleus. The end result is the characteristic cellular fragmentation of apoptosis.
- **Clearance of apoptotic cells.** Apoptotic cells and their fragments entice phagocytes by producing a number of "eat-me" signals. For instance, in normal cells phosphatidylserine is present on the inner leaflet of the plasma membrane, but in apoptotic cells this phospholipid "flips" to the outer leaflet, where it is recognized by tissue macrophages. Cells that are dying by apoptosis also secrete soluble factors that recruit phagocytes. Numerous macrophage receptors are involved in the binding and engulfment of apoptotic cells. This process is so efficient that the dead cells disappear without leaving a trace, and there is no accompanying inflammation.

MORPHOLOGY

In H&E-stained tissue sections, the nuclei of apoptotic cells show various stages of chromatin condensation, aggregation, and, ultimately, karyorrhexis (Fig. 1.13). At the molecular level this is reflected in fragmentation of DNA into nucleosome-sized pieces. The cells rapidly shrink, form cytoplasmic buds, and fragment into apoptotic bodies that are composed of membrane-bound pieces of cytosol and organelles (eFig. 1.2; also see Fig. 1.11). Because these fragments are quickly shed and phagocytosed without eliciting an inflammatory response, even substantial apoptosis may be histologically undetectable.

Other pathways of cell death, in addition to necrosis and apoptosis, have been described. *Necroptosis* is a form of cell death caused by the cytokine tumor necrosis factor (TNF) that shows features of both necrosis and apoptosis, hence its name. *Pyroptosis* (*pyro*, fever) is induced by activation of inflammasomes (Chapter 5), which releases the cytokine interleukin-1 (IL-1), which cause inflammation and fever. *Ferroptosis* depends on levels of cellular iron. The roles of these mechanisms of cell death in normal physiology and pathologic states are not clearly established and remain topics of investigation.

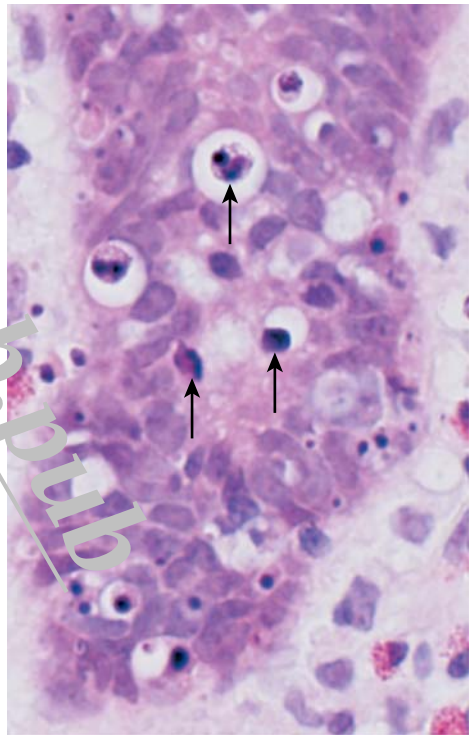
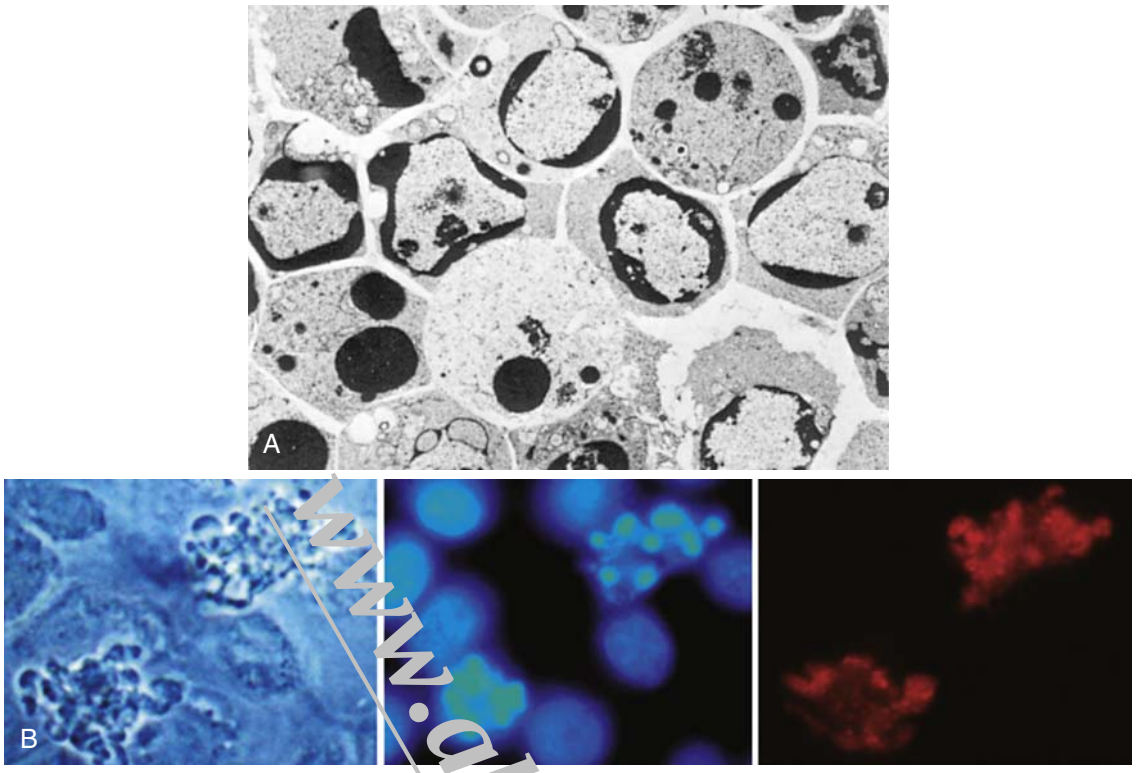


FIG. 1.13 Morphologic appearance of apoptotic cells. Apoptotic cells (some indicated by *arrows*) in a normal crypt in the colonic epithelium are shown. (The preparative regimen for colonoscopy frequently induces apoptosis in epithelial cells, which explains the abundance of dead cells in this normal tissue.) Note the fragmented nuclei with condensed chromatin and the shrunken cell bodies, some with pieces falling off. (Courtesy of Dr. Sanjay Kakar, Department of Pathology, University of California San Francisco, San Francisco, CA.)



eFIG. 1.2 Morphologic features of apoptosis. (A) This electron micrograph of cultured cells undergoing apoptosis shows some nuclei with peripheral crescents of compacted chromatin, and others that are uniformly dense or fragmented. (B) These images of cultured cells undergoing apoptosis show blebbing and formation of apoptotic bodies (*left panel*, phase contrast micrograph), a stain for DNA showing nuclear fragmentation *(middle panel)*, and activation of caspase-3 (*right panel*, immunofluorescence stain with an antibody specific for the active form of caspase-3, revealed as red color). (A, From Kerr JFR, Harmon BV: Definition and incidence of apoptosis: a historical perspective. In Tomei LD, Cope FO, editors: *Apoptosis: The Molecular Basis of Cell Death*. Cold Spring Harbor, NY, 1991, Cold Spring Harbor Laboratory Press, pp 5–29; B, Courtesy Dr. Zheng Dong, Medical College of Georgia, Augusta, GA.)

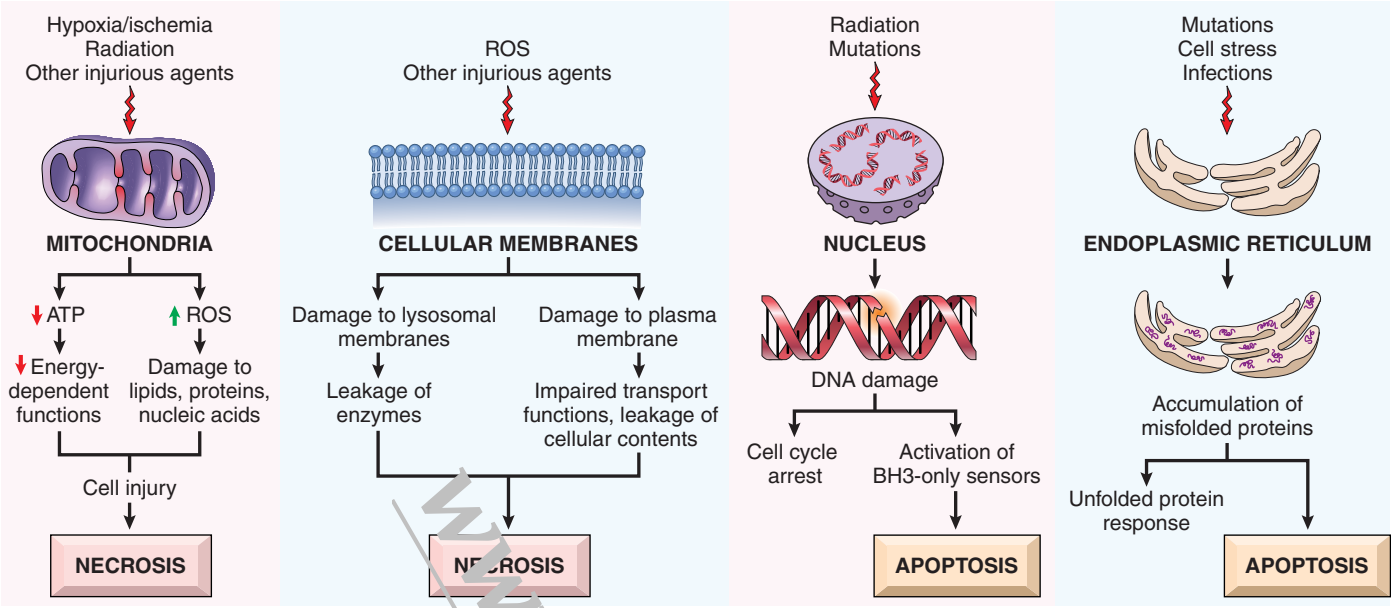


FIG. 1.15 The principal biochemical mechanisms and sites of damage in cell injury. Note that causes and mechanisms of cell death by necrosis and apoptosis are shown as being independent but there may be overlap; for instance, both may occur as a result of ischemia, oxidative stress, and radiation-induced cell death. *ATP,* Adenosine triphosphate; *ROS,* reactive oxygen species.

Although necrosis is the principal form of cell death caused by hypoxia, apoptosis by the mitochondrial pathway is also thought to contribute.

- Abnormal oxidative phosphorylation also leads to the formation of *reactive oxygen species*, described later.
- Damage to mitochondria is often associated with the formation of a high-conductance channel in the mitochondrial membrane, called the mitochondrial permeability transition pore. The opening of this channel leads to the loss of mitochondrial membrane potential and pH changes, further compromising oxidative phosphorylation.

As discussed earlier, mitochondria contain proteins such as cytochrome c that, when released into the cytoplasm, alert the cell to internal injury and activate apoptosis. The leakage of these proteins is regulated by other proteins and is a response to loss of survival signals and other proapoptotic triggers. Thus, mitochondria are life sustaining when healthy yet capable of activating numerous protective and pathologic reactions when damaged.

Oxidative Stress

Oxidative stress refers to cellular damage induced by the accumulation of reactive oxygen species (ROS), a form of free radical. Cell injury in many circumstances involves damage by free radicals; these situations include chemical and radiation injury, hypoxia, cellular aging, tissue injury caused by inflammatory cells, and ischemia-reperfusion injury (discussed later). Free radicals are chemical species with a single unpaired electron in an outer orbital. Such chemical species are extremely unstable and readily react with inorganic and organic compounds, such as nucleic acids, proteins, and lipids. During this reaction, the molecules that are "attacked" by free radicals are often themselves converted into other types of free radicals, thereby propagating the chain of damage.

Generation and Removal of Reactive Oxygen Species

The accumulation of ROS is determined by their rates of production and removal (Fig. 1.16). The properties and pathologic effects of the major ROS are summarized in Table 1.3.

ROS are normally produced by two major pathways.

- **ROS are produced in small amounts in all cells during the reduction-oxidation (redox) reactions that occur during energy generation.** In this process, molecular oxygen is reduced in mitochondria by the sequential addition of four electrons to produce water. This reaction is imperfect, however, and when oxygen is only partially reduced, small amounts of highly reactive, short-lived toxic intermediates are generated. These intermediates include superoxide (O_2^-), which is converted to hydrogen peroxide (H_2O_2) spontaneously and by the action of the enzyme superoxide dismutase (SOD). H_2O_2 is more stable than O_2^- and can cross biologic membranes. In the presence of metals, such as Fe^{2+}, H_2O_2 is converted to the highly reactive hydroxyl radical •OH. Ionizing radiation and high doses of ultraviolet light can increase the production of ROS by hydrolyzing water into hydroxyl (•OH) and hydrogen (H•) free radicals.
- **ROS are produced in phagocytic leukocytes, mainly neutrophils,** as a weapon for destroying ingested microbes and other substances during inflammation (Chapter 2). ROS are generated in the phagolysosomes of leukocytes by a process that is similar to mitochondrial respiration and is called the *respiratory burst* (or oxidative burst). In this process, the enzyme phagocyte oxidase, located in the membranes of phagolysosomes, catalyzes the generation of superoxide, which is converted to H_2O_2. H_2O_2 is in turn converted to the highly reactive compound hypochlorite (the major component of household bleach) by the enzyme myeloperoxidase, which is abundant in leukocytes, especially neutrophils. ROS released from neutrophils may injure tissues.

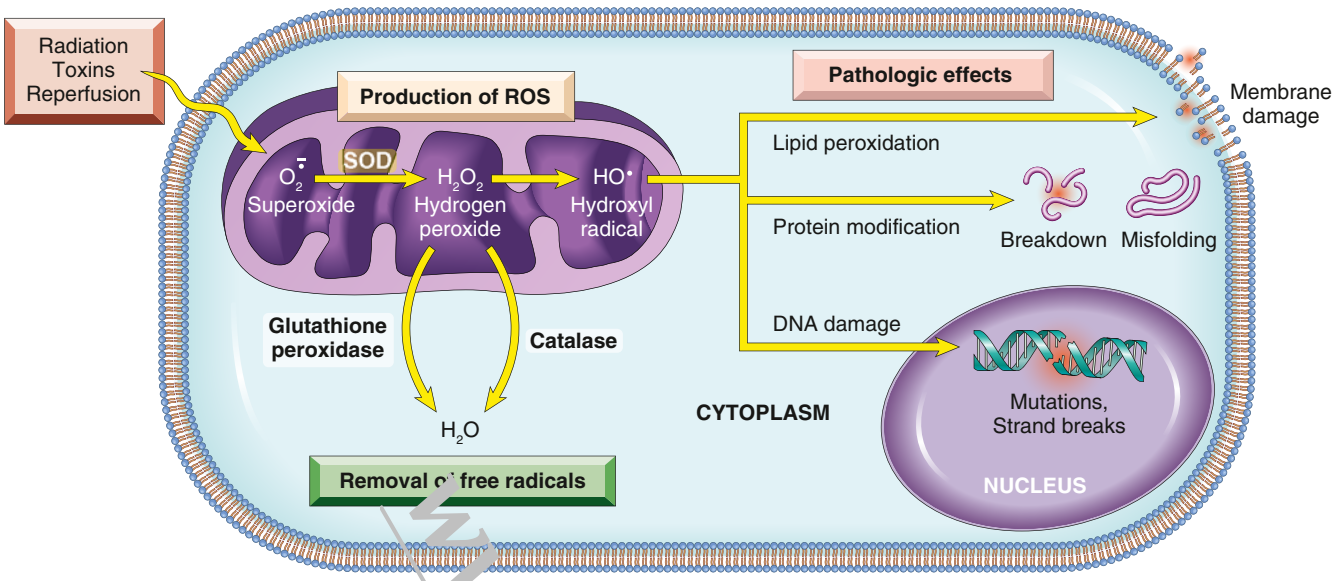


FIG. 1.16 The generation, removal, and role of reactive oxygen species (ROS) in cell injury. The production of ROS is increased by many injurious stimuli. These free radicals are removed by spontaneous decay and by specialized enzymatic systems. Excessive production or inadequate removal leads to accumulation of free radicals in cells, which may damage lipids (by peroxidation), proteins, and DNA, resulting in cell injury. *SOD*, Superoxide dismutase.

Table 1.3 Principal Free Radicals Involved in Cell Injury

Free Radical	Mechanisms of Production	Mechanisms of Removal	Pathologic Effects
Superoxide ($O_2^{\cdot-}$)	Incomplete reduction of O_2 during mitochondrial oxidative phosphorylation; by phagocyte oxidase in leukocytes	Conversion to H_2O_2 and O_2 by superoxide dismutase	Direct damaging effects on lipids (peroxidation), proteins, and DNA
Hydrogen peroxide (H_2O_2)	Mostly from superoxide by action of SOD	Conversion to H_2O and O_2 by catalase, glutathione peroxidase	Can be converted to •OH and ClO^-, which destroy microbes and cells
Hydroxyl radical (•OH)	Produced from H_2O, H_2O_2, and $O_2^{\cdot-}$ by various chemical reactions	Conversion to H_2O by glutathione peroxidase	Direct damaging effects on lipids, proteins, and DNA
Peroxynitrite ($ONOO^-$)	Interaction of $O_2^{\cdot-}$ and NO mediated by NO synthase	Conversion to nitrite by enzymes in mitochondria and cytosol	Direct damaging effects on lipids, proteins, and DNA

ClO^-, Hypochlorite; *NO*, nitric oxide; *SOD*, superoxide dismutase.

Cells have evolved mechanisms that remove free radicals and thereby minimize their injurious effects. Free radicals are inherently unstable and decay spontaneously. There are also nonenzymatic and enzymatic systems, sometimes called free radical scavengers, that serve to inactivate free radicals (see Fig. 1.16):

- *Superoxide dismutases (SODs)*, found in many cell types, convert superoxide into H_2O_2, which is degraded by catalase (see below).
- *Glutathione peroxidases* are a family of enzymes whose major function is to protect cells from oxidative damage. The most abundant member of this family, glutathione peroxidase 1, is found in the cytoplasm of all cells. It catalyzes the breakdown of H_2O_2 to H_2O.
- *Catalase*, present in peroxisomes, catalyzes the decomposition of hydrogen peroxide into O_2 and H_2O. It is highly efficient, being capable of degrading millions of molecules of H_2O_2 per second.
- *Endogenous or exogenous antioxidants* (e.g., vitamins E, A, and C and β-carotene) may either block the formation of free radicals or scavenge them once they have formed.

Cell Injury Caused by Reactive Oxygen Species

Reactive oxygen species cause cell injury by damaging multiple components of cells (see Fig. 1.16):

- *Peroxidation of membrane lipids.* ROS damage plasma membranes as well as mitochondrial and lysosomal membranes because the double bonds in membrane lipids are vulnerable to attack by free radicals. The lipid–radical interactions yield peroxides, which are themselves unstable and reactive, and an autocatalytic chain reaction ensues.
- *Crosslinking and other changes in proteins.* Free radicals promote sulfhydryl-mediated protein crosslinking, resulting in enhanced degradation or loss of functional activity. Free radical reactions