Lec2

General Pathology

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PhD. Oral Pathology

Cell Injury, Cell Death, and Adaptation

Cellular responses to stress and noxious(harmful) stimuli:

The normal cell is restricted to a narrow range of functions and structures ordered by its state of metabolism, differentiation, and specialization. The ability to handle physiologic demands, maintaining a healthy steady state called *homeostasis*.

In response to environmental changes, cells have to adapt in the face of physiological and pathological stimuli that seek to disturb their normal homeostatic environment. This process is called *cellular adaptation.*

***Adaptations* are reversible functional and structural responses to changes in physiologic states that mean normal stimulation by hormones (e.g., pregnancy, enlargement of the breast) and some pathologic stimuli by stress, during which new but altered steady states are achieved, allowing the cell to survive and continue to function. Like Hypertrophy, Hyperplasia, Atrophy and Metaplasia**

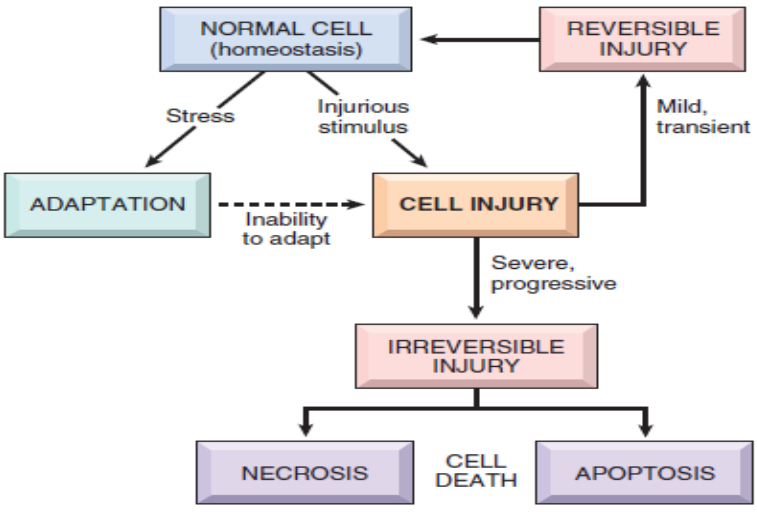


Figure 2.1 Stages of the cellular response to stress and injurious stimuli.

The types of pathological adaptation may consist of:

1. **Hypertrophy: an increase in the size and functional activity of cells that leads to an increase in the size of the organ.**
   a. Physiologic hypertrophy: e.g.: in skeletal muscle cells of a weight lifter.
   b. Pathologic hypertrophy: e.g.: cardiac enlargement that occurs with hypertension or aortic valve disease.
2. **Hyperplasia: an increase in cell number.**

a. **Hormonal hyperplasia e.g.: The proliferation of the glandular epithelium of the female breast at puberty and during pregnancy.**

b. **Compensatory hyperplasia: occurs when a portion of the tissue is removed or diseased e.g.: when a liver is partially resected, mitotic activity in the remaining cells begins to restore the liver to its normal weight**

c. **Pathologic hyperplasia: caused by excessive hormonal or growth factor stimulation.**
   e.g. .1. *Endometrial hyperplasia* occurs due to disturbances in the balance between estrogen and progesterone hormones causing abnormal menstrual bleeding.
   ***2. Connective tissue hyperplasia* in wound healing in which proliferating fibroblasts and blood vessels aid in repair.**

3. **Atrophy: a decrease in the size and metabolic activity of cells.**
   Causes:
   1- Decreased workload, e.g., immobilization of a limb to permit healing of a fracture
   2- Loss of innervation
   3- Diminished blood supply
   4- Inadequate nutrition
   5- Loss of endocrine stimulation
   6- Aging
4. **Metaplasia: (phenotype changing): change in the differentiation of a cell. When there is failure of normal cellular differentiation, this can result in *dysplasia* and *neoplasia*.**
   E.g.: in cigarette smokers, the normal ciliated columnar epithelial cells of the respiratory epithelium is replaced by stratified squamous epithelial cells

Types of cell injuries:

1. **Reversible: If the change in the cellular environment is greater than the capacity of the cell to adapt and then return to its normal environment.**
2. **Irreversible: if the injurious stimulus is persistent or severe, the cell suffers *irreversible injury* and ultimately undergoes *cell death*.**

1. Morphology of reversible injury

1. *Cellular swelling*: is the earliest manifestation of almost all forms of injury to cells. When it affects many cells, it causes pallor, increased turgor, and increased weight of the affected organ.

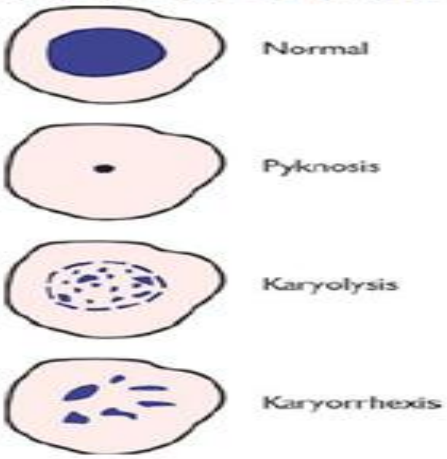
***On microscopic examination*, small clear vacuoles may be seen within the cytoplasm; these represent distended and pinched-off segments of the endoplasmic reticulum(ER). This pattern of nonlethal injury is sometimes called hydropic change or vacuolar degeneration.**

The cytoplasm of injured cells appears red (eosinophilic) when stained with hematoxylin and eosin (H&E) due to the loss of RNA, which
binds the blue hematoxylin dye. The eosinophilia becomes more pronounced with progression toward necrosis.
2. *Fatty change:* occurs in organs that are actively involved in lipid metabolism (e.g., liver). It results when a toxic injury disrupts metabolic pathways and leads to rapid accumulation of triglyceride-filled lipid vacuoles.

2. Morphology of irreversible injury

1. Necrotic cells show increased *eosinophilia* in H&E stains, attributable in part to the loss of cytoplasmic RNA and in part to the accumulation of denatured cytoplasmic proteins (which bind the red dye eosin).
2. The necrotic cell may have a glassy homogeneous appearance as a result of the loss of glycogen particles and the cytoplasm becomes vacuolated and appears moth-eaten by enzyme.
3. Dead cells may be replaced by large whorled phospholipid precipitates called *myelin figures*, which
are either phagocytosed by other cells or further degraded into fatty acids; calcification of such fatty acid residues results in the deposition of calcium-rich precipitates.
4. Nuclear changes appear in one of three patterns, all due to the breakdown of DNA.
a. Karyolysis: The basophilia of the chromatin may fade due to loss of DNA because of enzymatic degradation by endonucleases.
b. Pyknosis: characterized by nuclear shrinkage and increased basophilia. Here the chromatin condenses into a dense, shrunken basophilic mass.
c. Karyorrhexis: the pyknotic nucleus undergoes fragmentation. With the passage of time (1 or 2 days),
the nucleus in the necrotic cell totally disappears.

Figure 1.7 Nuclear changes in cell death



Key facts

Features of reversible and irreversible cell damage

Reversible	Irreversible
Cell swelling	Release of lysosomal enzymes
Mitochondrial swelling	Protein digestion
Endoplasmic reticulum swelling	Loss of basophilia
Detachment of ribosomes	Membrane disruption
'Myelin' figures	Leakage of cell enzymes and proteins
Loss of microvilli	Nuclear changes: pyknosis, karyorrhexis, karyolysis
Surface blebs	
Clumping of nuclear chromatin	
Lipid deposition (fatty change)	

Figure 1.3 Reversible and irreversible changes

Cell death: **The removal of damaged, unneeded, and aged cells through *cell death* is a normal and essential process in embryogenesis, the development of organs, and the maintenance of homeostasis into adulthood.**

Types of cell death:

1. **Unprogrammed means, *necrosis:* Severe mitochondrial damage with depletion of ATP and rupture**
   Lysosomal and plasma membranes are typically associated with necrosis. Necrosis occurs in many commonly encountered injuries, such as those following ischemia, exposure to toxins, various infections, and trauma.
2. **Programmed means, *apoptosis:* a term derived from an ancient Greek word for the *falling of leaves in the autumn*. In apoptosis, specific stimuli initiate the execution of well-defined pathways leading to orderly resorption of individual cells with minimal leakage of cellular components into the extracellular space.**

Table 2.1 Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis, karyorrhexis, karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Usually pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

Causes of Cell Injury:

1. ***Oxygen Deprivation*:** **Hypoxia is a deficiency of oxygen, which causes cell injury by reducing aerobic oxidative respiration.**
   Causes of hypoxia include reduced blood flow (ischemia); inadequate oxygenation of the blood due to
   Cardiorespiratory failure; and decreased oxygen-carrying capacity of the blood, as in anemia or carbon monoxide poisoning and severe blood loss.
   E.g. if an artery is narrowed, the tissue supplied by that vessel may initially shrink in size (atrophy), whereas more severe or sudden hypoxia induces cell injury and cell death.
   2. *Physical Agents*: Physical agents capable of causing cell injury include mechanical trauma, extremes of temperature (burns and deep cold), and sudden changes in atmospheric pressure, radiation, and electric shock.
   3. *Chemical Agents and Drugs*: Simple chemicals such as glucose or salt, oxygen at high concentrations are toxic, trace amounts of *poisons,* such as arsenic, cyanide, or mercury, environmental pollutants, and recreational drugs such as alcohol; and the ever-increasing variety of therapeutic drugs, many of which have toxic side effects.
   4. *Infectious Agents:* These agents range from submicroscopic viruses to tapeworms several feet in length. In between are rickettsia, bacteria, fungi, and higher forms of parasites.
   5. *Immunologic Reactions:* The immune system serves an essential function in defense against infectious pathogens, but immune reactions may also cause cell injury. Injurious reactions to endogenous self-antigens are responsible for autoimmune diseases. Also Immune reactions too many external agents, such as viruses and environmental substances.

6. *Genetic Abnormalities:* genetic aberrations as extreme as an extra chromosome, as in Down syndrome, and amino acid substitution, as in sickle cell anemia.
7. *Nutritional Imbalances:* Protein-calorie deficiencies, Deficiencies of specific vitamins, Obesity lead to several important diseases, such as diabetes and cancer, diets high in certain lipids lead to elevated serum cholesterol and predispose to atherosclerosis, a leading risk factor for cardiovascular disease.

Patterns of Tissue Necrosis:

Coagulative necrosis: is a form of necrosis in which the architecture of dead tissue is preserved for a span of at least some days. the necrotic cells are broken down by the action of lysosomal enzymes derived from infiltrating leukocytes, which also remove the debris of the dead cells by phagocytosis. Ischemia caused by an obstruction in a vessel may lead to coagulative necrosis of the supplied tissue in all organs except the brain. A localized area of coagulative necrosis is called an infarct.

Liquefactive necrosis: in contrast to coagulative necrosis, is characterized by the digestion of the dead cells, resulting in a transformation of the tissue into a viscous liquid. It is seen in focal bacterial or, occasionally, fungal infections because microbes stimulate the accumulation of leukocytes and the liberation of enzymes from these cells. The necrotic material is frequently creamy yellow because of the presence of leukocytes and is called pus. For unknown reasons, hypoxic death of cells within the central nervous system often manifests as liquefaction necrosis.

Gangrenous necrosis: is not a specific pattern of cell death, but the term is commonly used in clinical practice. It is usually applied to a limb, generally the lower leg, that has lost its blood supply and has undergone necrosis (typically coagulative necrosis) involving multiple tissue planes. When bacterial infection is superimposed, there is more liquefactive necrosis because of the actions of degradative enzymes in the bacteria and the attracted leukocytes (giving rise to so-called wet gangrene).

Gaseous necrosis: is encountered most often in foci of tuberculous infection. The term *caseous* (cheeselike) is derived from the friable white appearance of the area of necrosis. On microscopic examination, the necrotic area appears as a structureless collection of fragmented or lysed cells and amorphous granular debris enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a *granuloma*.

Fat necrosis: refers to focal areas of fat destruction, typically resulting from release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. This occurs in acute pancreatitis. Fatty acids are generated that combine with calcium to produce grossly visible chalky-white areas (fat saponification). On histologic examination, the necrotic areas contain the shadowy outlines of necrotic fat cells, basophilic calcium deposits, and an inflammatory reaction.

Fibrinoid necrosis: is a special form of vascular damage usually seen in immune reactions involving blood vessels. It typically occurs when complexes of antigens and antibodies are deposited in the walls of arteries. Deposits of these immune complexes, together with plasma proteins that has leaked out of vessels, result in a bright pink and amorphous appearance in H&E stains called "fibrinoid" (fibrin-like) by pathologists.

MECHANISMS OF CELL INJURY:

Several principles are relevant to most forms of cell injury:

1. **The cellular response to injurious stimuli depends on the nature of the injury, its duration, and its severity.**
2. **The consequences of cell injury depend on the type, state, and adaptability of the injured cell.**
3. **Any injurious stimulus may simultaneously trigger multiple interconnected mechanisms that damage cells.**

General Mechanisms of Cell Injury and Intracellular Targets of Injurious Stimuli:

Cell injury results from abnormalities in one or more essential cellular components:

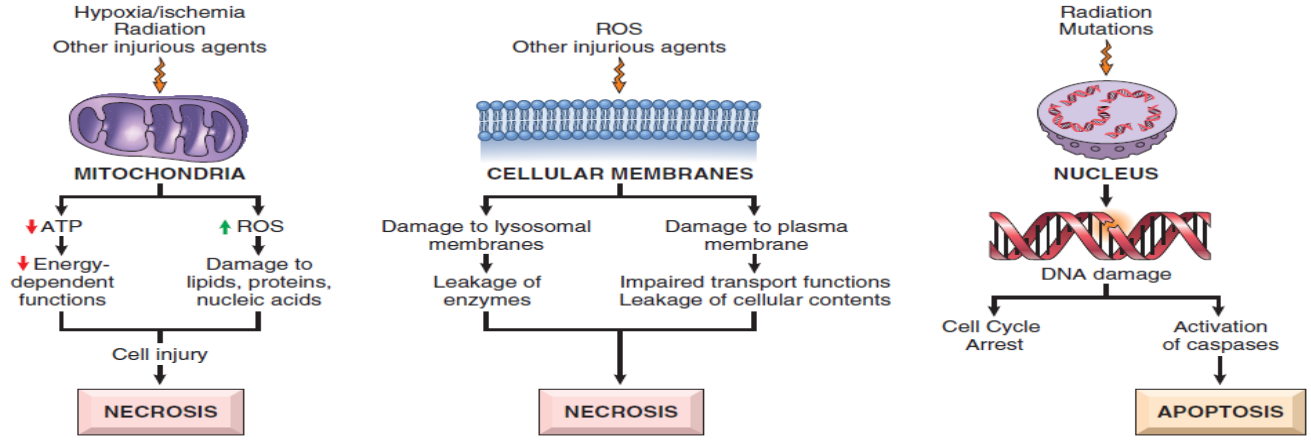


Figure 2.18 The principal forms and sites of damage in cell injury. *ATP*, Adenosine triphosphate; *ROS*, reactive oxygen species.

1.ATP depletion: failure of energy-dependent functions → reversible injury → necrosis.

2• Mitochondrial damage: ATP depletion → failure of energy dependent cellular functions → ultimately, necrosis; under some conditions, leakage of mitochondrial proteins that cause apoptosis.

3• Increased permeability of cellular membranes: may affect plasma membrane, lysosomal membranes, and mitochondrial membranes; typically culminates in necrosis.

4• Accumulation of damaged DNA and misfolded proteins: triggers apoptosis.
5• Accumulation of ROS: covalent modification of cellular proteins, lipids, nucleic acids
6• Influx of calcium: activation of enzymes that damage cellular components and may also trigger apoptosis.
7• Unfolded protein response and ER stress: Accumulation of misfolded proteins in the ER activates adaptive mechanisms that help the cell to survive, but if their repair capacity is exceeded they trigger apoptosis.

Apoptosis:

Regulated mechanism of cell death that serves to eliminate unwanted and irreparably damaged cells, with the least possible host reaction.
Characterized by enzymatic degradation of proteins and DNA, initiated by caspases, and by recognition and removal of dead cells by phagocytes.
Initiated by two major pathways:
1. The mitochondrial (intrinsic) pathway is triggered by loss of survival signals, DNA damage, and accumulation of misfolded proteins (ER stress), which leads to leakage of pro-apoptotic proteins from the mitochondrial membrane into the cytoplasm and subsequent caspase activation; can be inhibited by anti-apoptotic members of the BCL2 family, which are induced by survival signals including growth
Factors.

2. Death receptor (extrinsic) pathway eliminates self-reactive lymphocytes and is a mechanism of cell killing by cytotoxic T lymphocytes; is initiated by the engagement of death receptors (members of the TNF receptor family). The responsible ligands can be soluble or expressed on the surface of adjacent cells.

Causes of Apoptosis:

Apoptosis occurs in two types:

1. ***Apoptosis in Physiologic Situations*: Death by apoptosis is a normal phenomenon that serves to eliminate cells that are no longer needed, or as a mechanism to maintain a constant number of various cell populations in tissues.**
   Apoptosis is important in the following physiologic situations:
   a. **The removal of supernumerary cells (in excess of the required number) during development.**
   b. **Involution of hormone-dependent tissues on hormone withdrawal. (e.g. menstrual cycle, menopause and regression of the lactating breast after weaning).**
   c. **Cell turnover in proliferating cell populations.e.g. immature lymphocytes in the bone marrow and thymus.**
   d. **Elimination of potentially harmful self-reactive lymphocytes to prevent immune reactions against one's own tissues.**
   e. **Death of host cells that have served their useful purpose, such as neutrophils in an *acute inflammatory response,* and lymphocytes at the end of an *immune response*.**
2. ***Apoptosis in Pathologic Conditions*: Apoptosis eliminates cells that are injured beyond repair.**

Death by apoptosis is responsible for loss of cells in a variety of pathologic states.

a. ***DNA damage*. Radiation and cytotoxic anticancer drugs can damage DNA, either directly or via production of free radicals.**
b. **Accumulation of misfolded proteins. Cell death is triggered by improperly folded intracellular proteins and the subsequent endoplasmic reticulum (ER) stress response.**
c. **Apoptosis can be induced during certain infections, particularly viral infections e.g. HIV, HBV infections, killing of tumor cells, cellular rejection of transplants, and tissue damage in graft-versus-host disease (commonly associated with bone marrow transplants and stem cells transplants).**
d. **Apoptosis may also contribute to *pathologic atrophy in parenchymal organs after duct obstruction,* such as occurs in the pancreas, parotid gland, and kidney.**

Morphologic and Biochemical Changes in Apoptosis:

1. **Cell shrinkage.**
2. **Chromatin condensation**
3. **Formation of cytoplasmic blebs and apoptotic bodies.**
4. **Phagocytosis of apoptotic cells or cell bodies, usually by macrophages.**

In H&E-stained tissue, the apoptotic cell appears as a round or oval mass of intensely eosinophilic cytoplasm with fragments of dense nuclear chromatin.

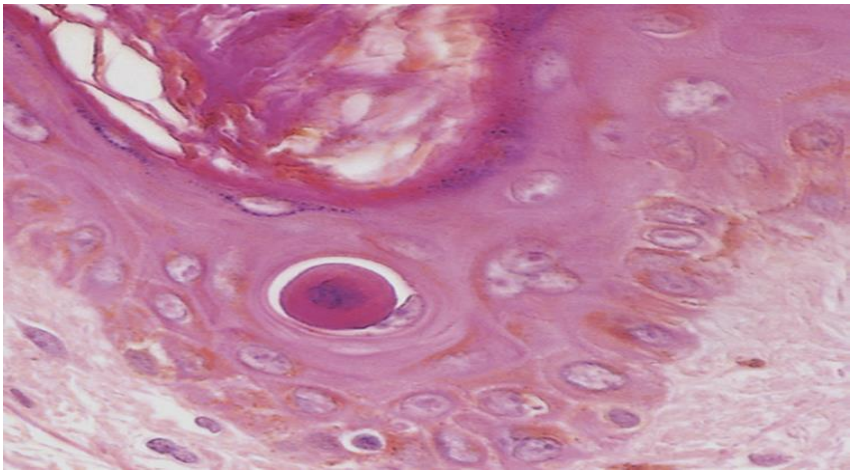


Figure.Apoptosis of an epidermal cell in an immune reaction. The cell is reduced in size and contains brightly Eosinophilic cytoplasm and a condensed nucleus.