RESPONSES TO CELLULAR INJURY

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CELLULAR INJURY

• A sequence of events that occur if the limits of adaptive capability of cells are exceeded or no adaptive response is possible.
significant structural and functional abnormalities, the injury has typically not progressed to severe membrane damage and nuclear dissolution

**CELL INJURY**

**REVERSIBLE CELL INJURY**

**NECROSIS**

Major pathway of cell death. Occurs when damage to membranes is severe, enzymes leak out of lysosomes, enter the cytoplasm, and digest the cell

**IRREVERSIBLE CELL INJURY**

**APOPTOSIS**

Cell death. With continuing damage, the injury becomes irreversible, at which time the cell cannot recover and it dies

Occur more on normal body functions. When a cell is deprived of growth factors, or the cell’s DNA or proteins are damaged beyond repair, typically the cell kills itself.
CAUSES OF CELL INJURY

• Oxygen Deprivation (Hypoxia)
• Chemical Agents
• Infectious Agents
• Immunologic Reactions
• Genetic Factors
• Nutritional Imbalances
• Physical Agents
• Aging (Cellular Senescence)
OXYGEN DEPRIVATION (Hypoxia)

• Oxygen deficiency
• Interferes with aerobic oxidative respiration
• Most commonly caused by *ischemia* (loss of blood supply in a tissue due to impeded arterial flow or reduced venous drainage)
• Also caused by inadequate oxygenation of blood, ↓O₂-carrying capacity of blood, Carbon monoxide (CO) poisoning
CHEMICAL AGENTS

• An increasing number of chemical substances
• Innocuous substances such as glucose, salt, or even water, if absorbed or administered in excess, can so derange the osmotic environment that cell injury or death
INFECTIOUS AGENTS

- Range from submicroscopic viruses to meter-long tapeworms; in between are the rickettsiae, bacteria, fungi, and protozoans
IMMUNOLOGIC REACTIONS

- Autoimmune reactions against one’s own tissues and allergic reactions against environmental substances in genetically susceptible individuals
GENETIC FACTORS

• May cause cell injury as a consequence of deficiency of functional proteins, such as enzymes in inborn errors of metabolism, or accumulation of damaged DNA or misfolded proteins, both of which trigger cell death when they are beyond repair
NUTRITIONAL IMBALANCES

• Can be caused by an inability of the body to absorb certain nutrients or result from a poor diet.
• Depending on the nutrients in short or excess supply, imbalances create unpleasant side effects and conditions that could lead to serious disease.
Physiological Agents

- Trauma, extremes of temperature, radiation, electric shock, and sudden changes in atmospheric pressure all have wide-ranging effects on cells.
AGING (Cellular Senescence)

• Leads to alterations in replicative and repair abilities of individual cells and tissues
• Diminished ability to respond to damage and, eventually, the death of cells and of the organism
MECHANISMS OF REVERSIBLE AND IRREVERSIBLE INJURY

• ATP Depletion
• Mitochondrial Damage
• Influx of Calcium
• Accumulation of Reactive Oxygen Species
• Defects in Membrane Permeability
• Accumulation of damaged DNA and misfolded proteins
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ATP DEPLETION

EFFECTS ON CRITICAL CELLULAR SYSTEMS:

1) The activity of plasma membrane ATP-dependent sodium pumps is reduced. (Na-K Pumps) ↑sodium ↓potassium →cell swelling and dilation of ER
2) There is a compensatory increase in anaerobic glycolysis. ↑glucose demand ↓glycogen ↑lactic acid ↓intracellular pH ↓activity of many cellular enzymes
3) Failure of ATP-dependent Ca2+ pumps
4) Prolonged or worsening depletion of ATP causes structural disruption of the protein synthetic apparatus ↓protein synthesis →necrosis
MITOCHONDRIAL DAMAGE

- Mitochondria – producer of ATP
  - sensitive to many injurious stimuli

ATP depletion → failure of energy dependent cellular functions → ultimately, necrosis; under some conditions, leakage of mitochondrial proteins that cause apoptosis
INFLUX OF CALCIUM

• Cytosolic free calcium is normally maintained by ATP-dependent calcium transporters at concentrations
• Activation of enzymes that damage cellular components and may also trigger apoptosis
• *Increased cytosolic Ca2+ activates a number of enzymes*, with potentially deleterious cellular effects
  - *phospholipases* (membrane damage)
  - *proteases* (break down both membrane and cytoskeletal proteins)
  - *endonucleases* (responsible for DNA and chromatin fragmentation)
  - *adenosine triphosphatases* ((ATPases) (thereby hastening ATP depletion)
• May also induce apoptosis, by direct activation of caspases and by increasing mitochondrial permeability
ACCUMULATION OF OXYGEN-_DERIVED FREE RADICALS (OXIDATIVE STRESS)

**Free Radicals** - chemical species with a single unpaired electron in an outer orbital, extremely unstable, react with inorganic and organic chemicals → avidly attack nucleic acids as well as a variety of cellular proteins and lipids

- Covalent modification of cellular proteins, lipids, nucleic acids
DEFECTS IN MEMBRANE PERMEABILITY

• *Increased permeability of cellular membranes*
• Leads to membrane damage, may affect plasma membrane, lysosomal membranes, mitochondrial membranes; typically culminates in necrosis
DAMAGE TO DNA AND PROTEINS

• Cells have mechanisms that repair damage to DNA, but if this damage is too severe to be corrected the cell initiates its suicide program and dies by apoptosis
MORPHOLOGY OF CELL DAMAGE

• Observed in *reversible cell injury*

Types:
Cellular Swelling
Fatty Change
CELLULAR SWELLING

• First manifestation of almost all forms of injury to cells
• Reversible
• Microscopic examination may reveal small, clear vacuoles within the cytoplasm representing distended and pinched off segments of the ER (hydropic change or vacuolar degeneration)
• Result of failure of energy-dependent ion pumps in the plasma membrane, leading to an inability to maintain ionic and fluid homeostasis.
FATTY CHANGES

• Manifested by the appearance of lipid vacuoles in the cytoplasm
• Reversible
• Occurs in hypoxic injury and various forms of toxic or metabolic injury, and is manifested by the appearance of small or large lipid vacuoles in the cytoplasm
• Occurs mainly in cells involved in and dependent on fat metabolism, such as hepatocytes and myocardial cells
MORPHOLOGY OF CELL DAMAGE

Figure 1–8
Morphologic changes in reversible and irreversible cell injury (necrosis). A, Normal kidney tubules with viable epithelial cells. B, Early (reversible) ischemic injury showing surface blebs, increased eosinophilia of cytoplasm, and swelling of occasional cells. C, Necrotic (irreversible) injury of epithelial cells, with loss of nuclei and fragmentation of cells and leakage of contents. The ultrastructural features of these stages of cell injury are shown in Fig. 1–9. (Courtesy of Drs. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Center San Antonio.)
CELLULAR ADAPTATIONS

ADAPTATION

Reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to the changes in their environment

PHYSIOLOGIC ADAPTATION

usually represent responses of cells to normal stimulation by hormones or endogenous chemical mediators (e.g., hormone-induced enlargement of the breast and uterus during pregnancy)

PATHOLOGIC ADAPTATION

responses to stress that allow cells to modulate their structure and function and thus escape injury
CELLULAR ADAPTATIONS

• Hypertrophy
• Hyperplasia
• Atrophy
• Metaplasia
HYPERTROPHY

- Increased cell and organ size
- Often in response to increased workload
- Induced by growth factors produced in response to mechanical stress or other stimuli
- Occurs in tissues incapable of cell division
- Can either be a physiologic or pathologic adaptation
HYPERTROPHY: Physiologic

*The massive physiologic enlargement of the uterus during pregnancy occurs as a consequence of estrogen stimulated smooth muscle hypertrophy and smooth muscle hyperplasia.
HYPERTROPHY: Pathologic*

*Hypertrophy: caused by hypertension or aortic valve disease
HYPERPLASIA

• Increased cell numbers in response to hormones and other growth factors
• Occurs in tissues whose cells are able to divide or contain abundant tissue stem cells
• Can be physiologic or pathologic
HYPERPLASIA

• Increased cell numbers in response to hormones and other growth factors
• Occurs in tissues whose cells are able to divide or contain abundant tissue stem cells
• Can be physiologic or pathologic
• The hyperplastic process remains controlled; if the signals that initiate it abates, the hyperplasia disappears
PHYSIOLOGIC HYPERPLASIA

• **Hormonal Hyperplasia**
  • Occurs mainly in organs that depend on estrogen
  • e.g. Exemplified by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy
PHYSIOLOGIC HYPERPLASIA

• **Compensatory Hyperplasia**
  • Residual tissue grows after removal or loss of part of an organ
  • e.g Compensatory Liver Hyperplasia*

*The liver undergoes cellular division after acute injury, resulting in new cells that restore liver function back to baseline. Approximately 75% of the liver can be acutely damaged or resected with seemingly full regeneration through hepatocyte division*
PATHOLOGIC HYPERPLASIA

• An abnormal increase in cell division caused by excessive hormonal or growth factor stimulation
• e.g Endometrial Hyperplasia*

*Caused by the disturbed balance between estrogen and progesterone. After a normal menstrual period, there is a burst of uterine epithelial proliferation that is normally tightly regulated by stimulation through pituitary hormones and ovarian estrogen and by inhibition through progesterone.

*Hyper-proliferation of the endometrium, usually in response to unopposed estrogen stimulation in the setting of polycystic ovary syndrome or exogenous administration of hormones. A typical endometrial hyperplasia may represent an early neoplastic process which can lead to endometrial adenocarcinoma.
ATROPHY

• Shrinkage in the size of the cell by the loss of cell substance
• Decreased cell and organ size
• As a result of decreased nutrient supply or disuse
• Associated with decreased synthesis of cellular building blocks and increased breakdown of cellular organelles
• Characterized by the combination of decreased activity of protein synthesis and increase in protein degradation in cells
ATROPHY

• **Causes**
  • Decreased workload (e.g., immobilization of a limb to permit healing of a fracture)
  • Loss of innervation
  • Diminished blood supply
  • Inadequate nutrition
  • Loss of endocrine stimulation
  • Aging (senile atrophy)
Figure 1–4 Atrophy as seen in the brain. A, Normal brain of a young adult. B, Atrophy of the brain in an 82-year-old man with atherosclerotic disease. Atrophy of the brain is due to aging and reduced blood supply. Note that loss of brain substance narrows the gyri and widens the sulci. The meninges have been stripped from the bottom half of each specimen to reveal the surface of the brain.
METAPLASIA

• Reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.
• Change in phenotype of differentiated cells, often in response to chronic irritation, that makes cells better able to withstand the stress
• Usually induced by altered differentiation pathway of tissue stem cells
• May result in reduced functions or increased propensity for malignant transformation
METAPLASIA: Epithelial Metaplasia

• Exemplified by the squamous change that occurs in the respiratory epithelium of habitual cigarette smokers
• The normal ciliated columnar epithelial cells of the trachea and bronchi are focally or widely replaced by stratified squamous epithelial cells. The rugged stratified squamous epithelium may be able to survive the noxious chemicals in cigarette smoke that the more fragile specialized epithelium would not tolerate. Although the metaplastic squamous epithelium has survival advantages, important protective mechanisms are lost, such as mucus secretion and ciliary clearance of particulate matter. Moreover, the influences that induce metaplastic change, if persistent, may predispose to malignant transformation of the epithelium.
METAPLASIA: Epithelial Metaplasia

Figure 1–5 Metaplasia of normal columnar (left) to squamous epithelium (right) in a bronchus, shown schematically (A) and histologically (B).
CELL DEATH

NECROSIS

damage to membranes is severe, enzymes leak out of lysosomes, enter the cytoplasm, and digest the cell

APOPTOSIS

cell is deprived of growth factors or the cell’s DNA or proteins are damaged beyond repair
NECROSIS

• Type of cell death that is associated with loss of membrane integrity and leakage of cellular contents culminating in dissolution of cells
• A result from the degradative action of enzymes on lethally injured cells

Characterized by:
• increased eosinophilia
• nuclear shrinkage
• Fragmentation and dissolution
• breakdown of plasma membrane and organellar membranes
• abundant myelin figures
• leakage and enzymatic digestion of cellular contents
Necrosis

- Coagulative Necrosis
- Liquefactive Necrosis
- Gangrenous Necrosis
- Caseous Necrosis
- Fat Necrosis
- Fibrinoid Necrosis
COAGULATIVE NECROSIS

• a form of necrosis in which the underlying tissue architecture is preserved for at least several days
• affected tissues take on a firm texture
• characteristic of infarcts (areas of ischemic necrosis) in all of the solid organs
• Characterized by the presence of eosinophilic, anucleate cells
COAGULATIVE NECROSIS

Figure 1–9 Coagulative necrosis. A, A wedge-shaped kidney infarct (yellow) with preservation of the outlines. B, Microscopic view of the edge of the infarct, with normal kidney (N) and necrotic cells in the infarct (I). The necrotic cells show preserved outlines with loss of nuclei, and an inflammatory infiltrate is present (difficult to discern at this magnification).
LIQUEFACTIVE NECROSIS

• seen in focal bacterial or, occasionally, fungal infections, because microbes stimulate the accumulation of inflammatory cells and the enzymes of leukocytes digest (“liquefy”) the tissue
• dead cells are completely digested, transforming the tissue into a liquid viscous mass

BACTERIA-CAUSED
• the material is frequently creamy yellow and is called pus
LIQUEFACTIVE NECROSIS

Figure 1-10 Liquefactive necrosis. An infarct in the brain showing dissolution of the tissue.
GANGRENOUS NECROSIS

• a distinctive pattern of cell death, the term is still commonly used in clinical practice

• refers to the condition of a limb, generally the lower leg, that has lost its blood supply and has undergone coagulative necrosis involving multiple tissue layers
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• refers to the condition of a limb, generally the lower leg, that has lost its blood supply and has undergone coagulative necrosis involving multiple tissue layers

BACTERIA-CAUSED

coagulative necrosis is modified by the liquefactive action of the bacteria and the attracted leukocytes (resulting in so-called wet gangrene).
CASEOUS NECROSIS

• Caseous means “cheese-like,” referring to the friable yellow-white appearance of the area of necrosis
• Encountered most often in foci of tuberculous infection
• The area of caseous necrosis is often enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a granuloma
CASEOUS NECROSIS

Figure 1-11 Caseous necrosis. Tuberculosis of the lung, with a large area of caseous necrosis containing yellow-white (cheesy) debris.
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

• Released fatty acids combine with Calcium to produce grossly visible chalky white areas (fat saponification)
Figure 1–12 Fat necrosis in acute pancreatitis. The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery.
FIBRINOID NECROSIS

• a special form of necrosis, visible by light microscopy, usually in immune reactions in which complexes of antigens and antibodies are deposited in the walls of arteries

• These deposited immune complexes together with fibrin that has leaked out of vessels, produce a bright pink and amorphous appearance on H&E preparations called fibrinoid
FIBRINOID NECROSIS

Figure 1–13  Fibrinoid necrosis in an artery in a patient with polyarteritis nodosa. The wall of the artery shows a circumferential bright pink area of necrosis with protein deposition and inflammation.
APOPTOSIS

- A pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die activate enzymes capable of degrading the cells’ own nuclear DNA and nuclear and cytoplasmic proteins.
APOPTOSIS

• A pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die activate enzymes capable of degrading the cells’ own nuclear DNA and nuclear and cytoplasmic proteins

• 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 recognition and removal of dead cells by phagocytes
CAUSES OF APOPTOSIS

• PHYSIOLOGIC APOPTOSIS
  • The programmed destruction of cells during embryogenesis
  • Involution of hormone-dependent tissues upon hormone deprivation
  • Cell loss in proliferating cell populations
  • Death of cells that have served their useful purpose
  • Elimination of potentially harmful self-reactive lymphocytes
  • Cell death induced by cytotoxic T lymphocytes

• PATHOLOGIC APOPTOSIS
  • DNA damage
  • Accumulation of misfolded proteins
  • Cell injury in certain infections
  • Pathologic atrophy in parenchymal organs after duct obstruction
PHYSIOLOGIC APOPTOSIS

- The programmed destruction of cells during embryogenesis
  - Includes implantation, organogenesis, developmental involution and metamorphosis
PHYSIOLOGIC APOPTOSIS

• Involution of hormone-dependent tissues upon hormone deprivation
  • endometrial cell breakdown during the menstrual cycle
  • regression of the lactating breast after weaning
PHYSIOLOGIC APOPTOSIS

• Cell loss in proliferating cell populations
  • Cell loss in proliferating cell populations, such as intestinal crypt epithelia, so as to maintain a constant number
PHYSIOLOGIC APOPTOSIS

• Death of cells that have served their useful purpose
  • neutrophils in an acute inflammatory response
  • lymphocytes at the end of an immune response
PHYSIOLOGIC APOPTOSIS

• Elimination of potentially harmful self-reactive lymphocytes
  • either before or after they have completed their maturation, in order to prevent reactions against one’s own tissues
PHYSIOLOGIC APOPTOSIS

• Cell death induced by cytotoxic T lymphocytes
  • defense mechanism against viruses and tumors that serves to kill and eliminate virus-infected and neoplastic cells
PATHOLOGIC APOPTOSIS

• DNA damage
  • Radiation, cytotoxic anticancer drugs, extremes of temperature, and even hypoxia can damage DNA either directly or via production of free radicals
PATHOLOGIC APOPTOSIS

• Accumulation of misfolded proteins
  • Improperly folded proteins may arise because of mutations in the genes encoding these proteins or because of extrinsic factors, such as damage caused by free radicals
  • Excessive accumulation of these proteins in the ER leads to a condition called *ER stress*, which culminates in apoptotic death of cells
• Cell injury in certain infections
  • particularly viral infections, in which loss of infected cells is largely due to apoptotic death that may be induced by the virus (as in adenovirus and human immunodeficiency virus infections) or by the host immune response (as in viral hepatitis)
Pathologic atrophy in parenchymal organs after duct obstruction
  - occurs in the pancreas, parotid gland, and kidney
END

NAGETS NYO? 😊