Farmaceutical pathology

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Causes of cell injury

Oxygen Deprivation

Hypoxia, or oxygen deficiency, interferes with aerobic oxidative respiration and is an extremely important and common cause of cell injury and death.

Hypoxia should be distinguished from *ischemia,* which is a loss of blood supply in a tissue.

While ischemia is the most common cause of hypoxia, oxygen deficiency can also result from inadequate oxygenation of the blood, as in pneumonia, or from reduction in the oxygen-carrying capacity of the blood, as in blood loss anemia or carbon monoxide (CO) poisoning.

Chemical Agents

Agents commonly known as poisons cause severe damage at the cellular level by altering membrane permeability, osmotic homeostasis, or the integrity of an enzyme or cofactor, and exposure to such poisons can culminate in the death of the whole organism.

Other potentially toxic agents are encountered daily in the environment; these include air pollutants, insecticides, CO, asbestos, and ethanol.

Causes of cell injury

Infectious Agents

- Agents of infection range from submicroscopic viruses to meter-long tapeworms.

Immunologic Reactions

- Although the immune system defends the body against pathogenic microbes, immune reactions can also result in cell and tissue injury.

Genetic Factors

- Genetic aberrations can result in pathologic changes as the congenital malformations associated with Down syndrome.
- Genetic defects 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.
- Genetic variations (polymorphisms) contribute to the development of many complex diseases.

Causes of cell injury

Nutritional Imbalances

- Protein–calorie insufficiency; specific vitamin deficiencies.
- Disorders of nutrition rather than lack of nutrients:obesity markedly increases the risk for type 2 diabetes mellitus and cancer.

Physical Agents

- Trauma, extremes of temperature, radiation, electric shock.

Aging

- Cellular senescence leads to alterations in replicative and repair abilities of individual cells and tissues.

Morphology of cell injury

The cellular derangements of **reversible** injury can be corrected, and if the injurious stimulus abates, the cell can return to normalcy.

Persistent or excessive injury, however, causes cells to pass the "point of no return" into **irreversible** injury and cell death.

Two phenomena consistently characterize irreversibility:

1. the inability to correct mitochondrial dysfunction (lack of oxidative phosphorylation and ATP generation)
2. profound disturbances in membrane function.

Different injurious stimuli may induce death by **necrosis or apoptosis.**

Reversible cell injury

The two main morphologic correlates of reversible cell injury are

1. cellular swelling and
2. fatty change.

Cellular swelling is the result of failure of energy-dependent ion pumps in the plasma membrane, leading to an inability to maintain ionic and fluid homeostasis.

Fatty change occurs in hypoxic injury and in various forms of toxic or metabolic injury and is manifested by the appearance of small or large lipid vacuoles in the cytoplasm.

Morphology of cellular swelling

When cellular swelling affects many cells in an organ, it causes some pallor (as a result of compression of capillaries), increased turgor, and increase in weight of the organ.

Microscopic examination may reveal small, clear vacuoles within the cytoplasm; these represent distended and pinched-off segments of the endoplasmic reticulum.

Morphology of fatty change

Fatty change is manifested by the appearance of lipid vacuoles in the cytoplasm. It is principally encountered in cells participating in fat metabolism (hepatocytes, myocardial cells) and is also reversible.

Intracellular changes

The intracellular changes associated with reversible injury include

(1) plasma membrane alterations such as blebbing, blunting, or distortion of microvilli, and loosening of intercellular attachments;

(2) mitochondrial changes such as swelling and the appearance of phospholipid-rich amorphous densities;

(3) dilation of the ER with detachment of ribosomes and dissociation of polysomes; and

(4) nuclear alterations, with clumping of chromatin. The cytoplasm may contain phospholipid masses, called myelin figures, which are derived from damaged cellular membranes.

Irreversible injury - Necrosis

Necrosis is the type of cell death that is associated with loss of membrane integrity and leakage of cellular contents culminating in dissolution of cells.

The leaked cellular contents often elicit a local host reaction, called inflammation, that attempts to eliminate the dead cells and start the subsequent repair process.

Nuclear

The general changes occurring in necrotic cell:

Cytoplasmic changes: Increased eosinophilia.

Nuclear changes: These may take up one of three patterns.

- Pyknosis: Shrinkage of nucleus which appears shrunken and deeply basophilic (similar to ink drop).
- Karyolysis: Progressive fading of basophilic staining of the nuclei and leads to a ghost nuclei.
- Karyorrhexis: Nucleus breaks up into many smaller fragments.

Coagulative Necrosis - morphology

Common type, outline of dead tissues is preserved (at least for few days).

Infarct is a localized area of coagulative necrosis.

Causes: Ischemia caused by obstruction in a vessel.

Mechanism: Ischemia denatures and coagulates structural proteins and enzymes.

Gross:

— Organs affected: All organs except the brain. More frequent in heart, kidney, spleen and limb.

— Appearance: Involved region appear dry, pale, yellow and firm. It is wedge shaped in organs.

Anemic - White/Pale Infarcts

They occur

1. With **arterial occlusions (end arteries)**
2. In **solid** (firm) organs
3. With end-arterial circulation **without a dual blood supply** (e.g. heart, spleen, and kidney)

Red/Hemorrhagic Infarcts

They occur

1. With **venous occlusion due to torquation:** ovary, testis.
2. In **loose textured** tissues: lung: They allow red cells to diffuse through and collect in the necrotic zone.
3. In tissues with **dual blood supply**, e.g. lung and small intestines: It allows blood flow from an unobstructed parallel blood supply into a necrotic zone.
4. In tissues **previously congested** due to decreased venous drainage: liver.
5. When blood flow is re-established to a site of previous arterial occlusion and necrosis: reprefusion.

Liquefactive Necrosis

Dead tissue rapidly undergoes softening and transforms into a liquid viscous mass.

Causes:

1. Ischemic injury to central nervous system (CNS)
2. Suppurative infections: Infections by bacteria which stimulate the accumulation of leukocytes.

Mechanism: Liquefaction is due to digestive action of the **hydrolytic enzymes** released from dead cells (autolysis) and leukocytes (heterolysis).

Gross: Organs affected are:

Brain: Necrotic area is soft and center show liquefaction

Abscess anywhere: Localized collection of pus. Pus consists of liquefied necrotic cell debris, dead leukocytes and macrophages.

Caseous Necrosis

Distinctive type of necrosis which shows combined features of both coagulative and liquefactive necrosis.

- Cause: Characteristic of tuberculosis and is due to the hypersensitivity reaction.

Gross:

- Organs affected: Tuberculosis may involve any organ, most common in lung and lymph node.
- Appearance: Necrotic area appears yellowish white, soft, granular and resembles dry, clumpy cheese, hence the name caseous (cheese-like) necrosis.

Microscopy:

- Focal lesion of tuberculosis is a granuloma which may be caseating (soft granuloma).

Fat Necrosis (fat digestion)

It refers to focal areas of fat destruction, which affects adipose tissue.

Enzymatic fat necrosis: Occurs **in adipose tissue** around acutely inflamed pancreas (in acute pancreatitis).

Mechanism: In pancreatitis, the enzymes (one of them is lipase) leak from acinar cells and

causes tissue damage. Lipase destroys fat cells and liberates free fatty acids which combine

with calcium and form calcium soaps (fat saponification).

- Gross: Appears as chalky-white areas.
- Microscopy: The necrotic fat cells appear pale with shadowy outlines surrounded by an inflammatory reaction.

Gangrene

It is massive necrosis with superadded putrefaction. Two types, namely dry and wet gangrene.

Dry Gangrene

Causes: Arterial occlusion (e.g. atherosclerosis).

Sites: the distal part of lower limb (leg, foot, and toe).

Gross: Affected part is dry, shrunken (shriveled) and dark brown or black resembling the foot of a mummy. The black color is due to the iron sulfide. A line of demarcation is seen between gangrenous and adjacent normal area.

Microscopy: The necrosis (coagulative type) shows smudging of soft tissue and overlying skin.

Wet Gangrene

Sites: Occurs in moist tissues or organs (e.g. bowel, lung, mouth, etc).

Gross: The affected part is soft, swollen, putrid and dark. No clear line of demarcation.

Microscopy: Liquefactive type of necrosis.

Apoptosis

Programmed cell death, suicide programme.

Pathway of cell death, induced by a tightly regulated suicide program.

Activate enzymes that degrade the cells' own nuclear DNA an cytoplasmic proteins.

Apoptotic cells break up into fragments (apoptotic body)

Clean, no inflammation is present.

Apoptosis in Physiological Situation

- Removal of excess cells during embryogenesis and developmental processes: e.g. disappearance of web tissues between fingers and toes.
- Elimination of cells after withdrawal of hormonal stimuli: e.g. endometrial cell breakdown during the menstrual cycle.
- Elimination of cells after withdrawal of tropic stimuli: e.g. neutrophils in an acute inflammatory response, lymphocytes after immune response.
- Elimination of potentially harmful cells: the clones of self-reactive lymphocytes that recognize normal self antigens are deleted by apoptosis.

Apoptosis in Pathologic Conditions

- Elimination of cells with damaged DNA.
- Elimination of cells with excessively accumulated misfolded proteins.
- Elimination of viral infected cells.
- Elimination of neoplastic cells/rejection of transplant.
- Elimination of parenchymal cells in atrophy.

Microscopic finding

The apoptotic cells appear as round or oval mass having intensely eosinophilic cytoplasm. The nuclei appear as fragments of dense nuclear chromatin and shows pyknosis.

Apoptosis does not elicit an inflammatory reaction in the host.

Mechanism of apoptosis

The genes and proteins, that control the process and the sequence of apoptosis are conserved in organisms.

Initiation of apoptosis occurs by two ways: extrinsic and intrinsic pathways.

Intrinsic pathway is the major mechanism.

Cellular Responses to Stress and Noxious Stimuli

- The normal cell is confined to a fairly narrow range of function and structure.
- It is nevertheless able to handle physiologic demands, maintaining a steady state called **homeostasis.**
- **Adaptations** are reversible functional and structural responses to changes in physiologic states and some pathologic stimuli, during which new but altered steady states are achieved, allowing the cell to survive and continue to function.

Pathological adaptation

- Left ventricular hypertrophy can develop in response to some factor — such as high blood pressure or aortic stenosis — that causes the left ventricle muscle to work harder.
- In response to this pressure overload inside the left ventricle, heart muscle cells **ADAPT** by getting thicker along the inner walls of the heart. This thickened wall can cause the left ventricle chamber to weaken, stiffen and lose elasticity, which may prevent healthy blood flow.
- Left ventricular hypertrophy is a strong independent predictor of cardiovascular deaths.

Definition of degeneration

Definition of degeneration: degeneration is deterioration in the medical sense. Generally, it is the change from a higher to a lower form. More specifically, it is the change of tissue to a lower or less functionally active form.

Degeneration: sublethal injury.

Two features of reversible cell injury can be recognized under the light microscope: cellular swelling and fatty change. **Parenchymal degeneration: cellular swelling. Fatty degeneration: fatty change.**

Cellular swelling appears whenever cells are incapable of maintaining ionic and fluid homeostasis and is the result of failure of energy-dependent ion pumps in the plasma membrane.
Fatty change occurs in hypoxic injury and various forms of toxic or metabolic injury. It is manifested by the appearance of lipid vacuoles in the cytoplasm. It is seen mainly in cells involved in and dependent on fat metabolism, such as hepatocytes and myocardial cells.

MORPHOLOGY

Cellular swelling is the first manifestation of almost all forms of injury to cells. It is a difficult morphologic change to appreciate with the light microscope; it may be more apparent at the level of the whole organ.
When it affects many cells, it causes some pallor, increased turgor, and increase in weight of the organ. On microscopic examination, small clear vacuoles may be seen within the cytoplasm; these represent distended and pinched-off segments of the ER. This pattern of nonlethal injury is sometimes called **hydropic change** or **vacuolar degeneration**. Swelling of cells is reversible.

Intracellular accumulations

- There are four main pathways of abnormal intracellular accumulations:
- Inadequate removal of a normal substance, as in fatty change
- Accumulation of an abnormal endogenous substance as a result of genetic or acquired defects, as in hemosiderosis, amyloidosis
- Failure to degrade a metabolite due to inherited enzyme deficiencies, as in Gaucher's disease
- Deposition and accumulation of an abnormal exogenous substance when the cell has neither the enzymatic machinery to degrade it, as in anthracosis

Fatty change, fatty degeneration, steatosis

- Definition: the terms steatosis and fatty change describe abnormal accumulations of triglycerides within parenchymal cells. Fatty change is often seen in the liver because it is the major organ involved in fat metabolism but it also occurs in heart, muscle, and kidney.
- Etiology: the causes of steatosis include toxins, protein malnutrition, diabetes mellitus, obesity, and anoxia.

In developed nations, the most common causes of significant fatty change in the liver (fatty liver) are alcohol abuse and nonalcoholic fatty liver disease, which is often associated with diabetes and obesity.

Pathogenesis

- Exposure to alcohol causes steatosis, dysfunction of mitochondrial and cellular membranes, hypoxia, and oxidative stress.
- Hepatocellular steatosis results from
- (1) shunting of normal substrates away from catabolism and toward lipid biosynthesis, as a result of generation of excess reduced nicotinamide adenine dinucleotide (NADH + H+) by the two major enzymes of alcohol metabolism, alcohol dehydrogenase and acetaldehyde dehydrogenase;
- (2) impaired assembly and secretion of lipoproteins; and
- (3) increased peripheral catabolism of fat.

Morphology - macroscopy

Macroscopically, the fatty liver of chronic alcoholism is a **large** (as heavy as 4 to 6 kg), **soft** organ that is yellow and greasy. Although there is little or no fibrosis at the outset, with continued alcohol intake fibrous tissue develops around the terminal hepatic veins and extends into the adjacent sinusoids.

Liver enlargement: hepatomegaly

Severe liver fibrosis: hepatic cirrhosis

Morphology - microscopy

Hepatic Steatosis (Fatty Liver). After even moderate intake of alcohol, **microvesicular** lipid droplets accumulate in hepatocytes.
With chronic intake of alcohol, lipid accumulates creating large, clear **macrovesicular** globules that compress and displace the hepatocyte nucleus to the periphery of the cell.
The fatty change is completely reversible if there is abstention from further intake of alcohol.

More organ examples

Fatty change in the heart: It most often reflects poor oxygenation (i.e., chronic severe anemia). It is distributed away from the vessels, and produces a "tiger-stripe„ heart.

Accumulation of fat in phagocytic cells is a common theme in pathology. The fat is usually made up largely of cholesterol esthers. Xanthomas, cholesterolosis.

Atherosclerosis: In atherosclerotic plaques, smooth muscle cells and macrophages within the intimal layer of the aorta and large arteries are filled with lipid vacuoles, most of which are made up of cholesterol and cholesterol esters.

GLYCOGEN ACCUMULATION

- Glycogen ordinarily is present in the livers of people in the fed state, and is abundant if the patient has an IV line infusing glucose.
- In HYPERGLYCEMIA, it is common to see glycogen "in" hepatic nuclei, pancreatic beta cells, and in the proximal tubular epithelial cells. These accumulations are probably harmless.
- The various GLYCOGEN STORAGE DISEASES result from inborn errors of metabolism.

Atrophy

Shrinkage in the size of the cell by loss of cell substance. without the cell actually dying. When many cells each become smaller, the organ itself become smaller. Atrophy can be reversible.

Examples

- Wasting of skeletal muscle on disuse (casted extremity, couch potato, diaphragm of a patient on a ventilator
- In hydrocele fluid accumulates around the testis. Long standing pressure would cause parenchymal atrophy.

Examples

- Loss of normal trophic stimulation, for example endocrine stimulation. This is very important; most organs that depend for their function on endocrine stimulation (adrenals, testes, a man's skeletal muscles) will diminish in size if the stimulating hormone is no longer available.
- Lower sex hormonal levels explain atrophy of tissues dependent on them -- here the cells truly get smaller.
- Bone loss and thinning of the dermis as we age aren't well understood -- again, cells are lost rather than shrink.

Brain atrophy

- Elderly
- Alcoholics
- Vascular atrophy
- Alzheimer’s

Result: dementia.