Histopathology

Lecture 3

Cell Injury and Cell Death

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Cell Injury

Overview: Cell injury occurs when the cells cannot adapt to their new environment.

Causes of cell injury: Hypoxia (decreased oxygen), ischemia (decreased blood flow), physical and chemical agents, trauma, infectious agents, radiation and toxins, metabolic abnormalities (genetic or acquired), immune dysfunction (hypersensitivity reactions and autoimmune disease), aging, and nutritional imbalances.

Important points regarding cell injury

- Hypoxia and ischemia are two common sources of cellular injury. Of the two, ischemia is much more damaging because it involves hypoxia plus a lack of other nutrients and an accumulation of toxic cellular metabolites.
- When does injury occur? This varies from cell to cell. It depends upon the type, duration, and severity of injury, and the type, adaptability, and makeup of the affected cell.
- Cellular injury may or may not result in the death of the cell. Four cellular systems are especially vulnerable to cellular injury, and include:

    1. DNA
    2. Cell membranes
    3. Protein generation
    4. Adenosine triphosphate (ATP) production

Although some of the causes of cellular injury have specific mechanisms, the mechanism of cellular injury due to many substances is not understood.

Mechanisms of cellular injury :

1. Hypoxia: In general, decreased oxygen results in decreased production of ATP. ATP is normally required by the Na/K pump and Ca^{+2} pump. When ATP levels decrease, these pumps fail, and sodium (along with water, which follows sodium) enters the cell, causing swelling. Also, calcium enters the cell, which activates endonucleases, proteases, phospholipases, and DNAses, which damage the cell. Cells switch to anaerobic respiration to produce ATP, which results in accumulation of lactic acid. The accumulation of lactic acid decreases the cellular pH. Decreased pH causes disaggregation of ribosomes from endoplasmic reticulum.
2. Generation of oxygen-derived free radicals by a stressing agent: Damage by free radicals. Lipid peroxidation (damages cell membranes), DNA fragmentation, and protein cross-linking (e.g., sulfhydryl groups), which results in increased degradation and decreased activity.

Basic description of free radical: A free radical is a molecule with an unpaired electron in the outer orbit. Another term for oxygen-derived free radicals is reactive oxygen species.

3. Chemical injury: Some chemicals are directly toxic to the cells, and others require conversion to a toxic metabolite. For example, ethylene glycol (antifreeze) is not toxic, but its metabolite, oxalic acid, is. In contrast, cyanide directly inactivates cytochrome oxidase, which impairs the formation of ATP.
4. Increased mitochondrial cytosolic calcium: Increased mitochondrial cytosolic calcium leads to lipid peroxidation and formation of mitochondrial permeability transition. Also, increased mitochondrial cytosolic calcium causes release of cytochrome c, which in turn activates apoptosis.

Two types of cellular injury

Reversible cellular injury: As described above in the discussion of mechanisms of cellular injury, the decreased production of ATP causes sodium to enter the cell, bringing water and causing cellular and organelle swelling. The conversion from aerobic to anaerobic respiration decreases the pH of the cell. These changes are all reversible. If ATP is once again produced by the cell, the Na/K ratio and pH will be corrected.

Irreversible cellular injury: This type of injury occurs with damage to plasma or lysosomal membranes, loss of DNA, or loss of mitochondria. In these cases, the damage cannot be reversed.

Cell Death

Overview: There are two forms of cell death, apoptosis and necrosis.

Apoptosis is controlled (programmed) breakdown of cells occurring in response to damage to DNA or as part of normal growth and development. Necrosis is uncontrolled break down of cells in response to injurious stimuli

APOPTOSIS

Basic description: Programmed cell death.

Patterns of occurrence of apoptosis

- During growth and development,some cells serve a function in the growth phase but need to be removed after their purpose is fulfilled. In neonates, a rapid cell growth rate is necessary; in adults, however, unrestrained cell growth can lead to cancer.
- When DNA sustains irreparable damage (e.g., after low-dose radiation exposure), the cell must be destroyed so mutations that have developed will not be propagated. In this manner, apoptosis serves as a

Phases of apoptosis
- *Initiation is the phase in which caspases (cysteine aspartic acid proteases) become catalytically active.*
- *Execution is the phase in which the action of caspases causes death of cell.*

safety step by removing damaged cells from the body.

Acidophil bodies *were defined as well demarcated, eosinophilic cytoplasmic globules, either anuclear or possessing nuclear fragments.*

Mechanism of apoptosis: There are multiple pathways by which apoptosis is initiated, including the extracellular and intracellular pathways. Both pathways share similar endpoints, culminating with the use of caspases and prevention of inflammatory reaction.

■ Initiation of extracellular pathway: In Fas-Fas ligand binding, the Fas ligand binds to a member of the tumor necrosis factor family known as the Fas receptor. The activated Fas receptor in turn activates FADD (Fas-associated death domain), which in turn activates caspases.

■ Initiation of intracellular pathway: The mitochondria release cytochrome c , which combines with Apaf-1 (apoptosis activating factor-1) to activate caspases.

-Caspases,which cleave DNA,are activated. DNA is cleaved in a coordinated manner so the fragments.

-Apoptosis does not generate an inflammatory reaction as necrosis does. Fragments of cells express phosphatidyl serine, which is recognized by macrophages; therefore, fragments can be engulfed without generating an inflammatory reaction.

Morphology of apoptosis: The key feature microscopically is chromatin condensation and fragmentation (Figure 1).

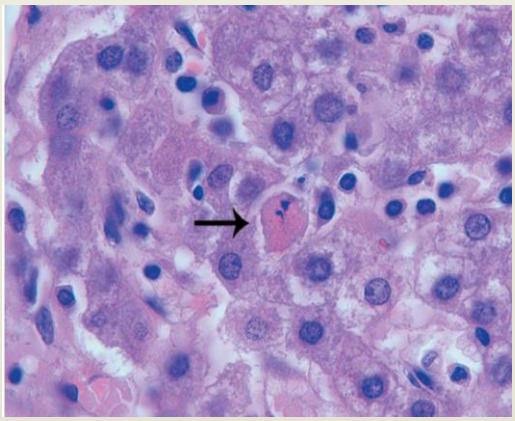

Figure 1 . Acidophil body in the liver. The acidophil body (arrow) represents apoptosis, or programmed cell death. The nucleus is condensed and fragmented.

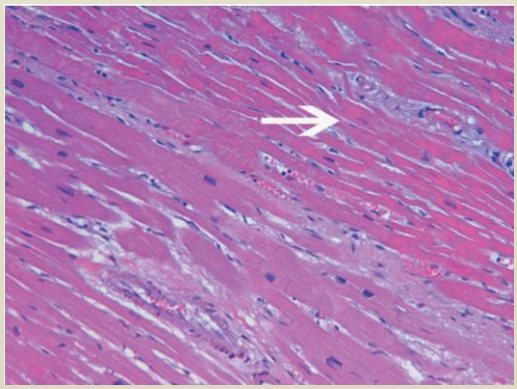

Figure 2. Coagulative necrosis of the myocardium. In the right upper half of the image (arrow), the cellular architecture is preserved; however, the cells are necrotic. The cytoplasm is eosinophilic from loss of protein, which imparts basophilia, and karyolysis of the nuclei has occurred (few cardiac myocyte nuclei are visible). Compare these features to the cells in the left lower half of the figure, which represent non-necrotic cardiac myocytes.

NECROSIS

Basic description: Necrosis is a term used to describe uncontrolled death of cells due to one of the various causes of cellular injury.

Gross morphology of necrosis: Necrosis is typically manifested by softening and discoloration of the organ. Other processes can have a similar appearance, so the gross appearance of necrosis is not specific.

Microscopic morphology of necrosis: The two main types of necrosis are coagulative necrosis and liquefactive necrosis.

✓ Coagulative necrosis

Basic description: Coagulative necrosis is the type of necrosis in which protein denaturation is more prominent than enzymatic breakdown.

Microscopic morphology of coagulative necrosis (Figure 2): There is increased eosinophilia of the cytoplasm and decreased basophilia of the nucleus; both are associated with preservation of the general cellular architecture (the organ type is identifiable).

***Organs affected by coagulative necrosis**: Coagulative necrosis may occur in any organ. In organs with a high fat content, such as the brain, coagulative necrosis is followed rapidly by liquefactive necrosis.*

✓ Liquefactive necrosis

Basic description: Liquefactive necrosis occurs in situations in which enzymatic breakdown is more prominent than protein denaturation or in organs that lack

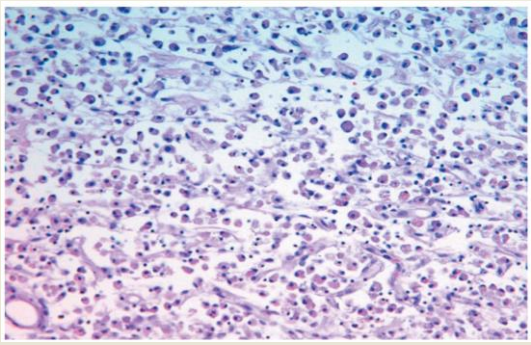

Figure 3. Liquefactive necrosis of the brain. The field contains sheets of foamy macrophages. In contrast to coagulative necrosis, the native tissue architecture has been lost.

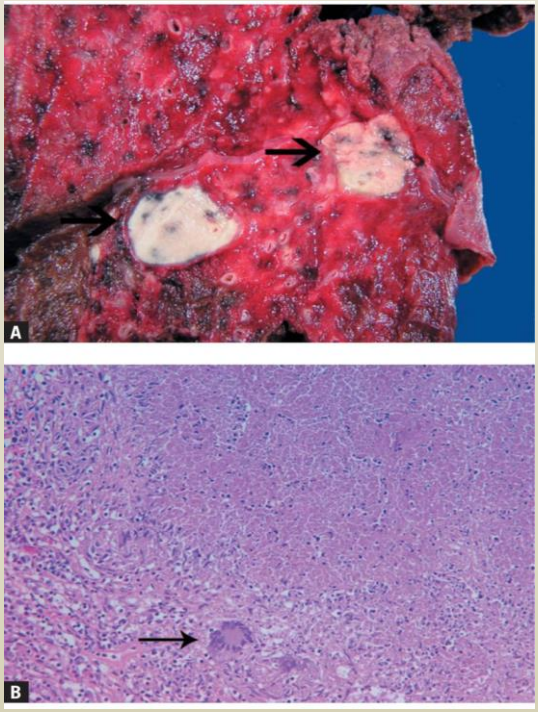

Figure 4. Caseous necrosis of the lung due to pulmonary tuberculosis. A, Gross section. The soft, cheese-like nature of the process is apparent (arrows). B, Microscopic section. The section shows central necrosis, and the left side shows large, activated ("epithelioid") histiocytes and a multinucleated giant cell (arrow).

a substantial protein-rich matrix (e.g., lipid-rich organs such as the brain).

Microscopic morphology of liquefactive necrosis (Figure 3): There is loss of organ cellular architecture. In liquefactive necrosis of the brain, there are sheets of lipid-laden macrophages that replace the dead tissue.

Organs affected by liquefactive necrosis: Liquefactive necrosis is most commonly associated with organs that have a high fat and low protein content (e.g., the brain), or those with a high enzymatic content (e.g., the pancreas).

Other necrosis

✓ **Fat necrosis**

Fat necrosis is a term applied to a change in adipose tissue due to trauma or the release of enzymes from adjacent organs (e.g., the pancreas).

✓ **Caseous necrosis** (Figure 4 A and B)

Caseous necrosis is a "cheesy-looking" necrosis associated with tuberculosis infections and other granulomatous disease processes. Granulomas are a form of chronic inflammation due to some infections (e.g., mycobacterial), foreign bodies, and other chronic stimuli

Important points regarding necrosis

■ The terms coagulative and liquefactive necrosis are not mutually exclusive. For example, the death of heart muscle begins as coagulative necrosis, but once neutrophils enter the tissue as part of an inflammatory reaction and release enzymes, cellular architecture is lost (more consistent with liquefactive necrosis).

■ Cell death involves the release of intracellular enzymes into blood. These enzymes in the blood can be measured and used clinically to detect disease.

■ Cell death affects morphology (the shape of the cell) and function. Morphologic changes (both gross and microscopic) can develop over a period of time, while loss of function may occur almost immediately. Because of this immediate loss of function, the clinical manifestations of cellular injury may be present before the morphologic changes occur.

References:-

- **Pathologic basis of diseases, 8th edition, 2012**
- **Junqueiras basic histology, 15th edition, 2018**
- **Pathology illustrated, 17th edition, 2011.**