CELL INJURY

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Types/ Examples of Cell Injury

1. Hypoxic and Ischemic cell Injury
   • When there is partial or total deprivation of oxygen for tissues.
   • Ischemia injures cells more than hypoxia.
Hypoxia

- any state where oxygen is reduced. I.e. anemia, carbon monoxide poisoning.
- Oxygen reaching to the tissues is reduced
- Essential amino acids, glucose and metabolites reach the tissues.
- Mechanisms of non oxygen dependent (Anaerobic) respiratory mechanisms synthesize a lesser amount of ATP and help maintain basic cell function

Ischemia

- total stoppage of both oxygen and nutrients
- Due to
  - a mechanical obstruction (obstruction to an artery) - most common
  - sudden loss of a lot of blood or
  - sudden reduction in blood pressure
- Anaerobic respiration too unavailable due to unavailability of the substrate Glucose
Example & mechanism of Ischemic injury

- Complete occlusion of an end artery of an organ. i.e. blockage of a coronary artery by atheroma causing myocardial damage.
- Up to a certain point in the occlusion, if blood flow is re-established, the injury is reversed.
- If not progressive damage with further loss of ATP till a point of no return is reached and further damage is irreversible.
- One minute after coronary blockade myocardium ceases to contract. This does not mean that cell death has occurred. The death of cardiac muscle cells takes up to 30 – 40 minutes.
2. Ischemia- reperfusion injury

- Tissues are damaged due to ischemia and if blood flow is restored suddenly in the cells that are reversibly injured, they recover completely.
- If they are irreversibly damaged no difference is made with reperfusion (Restoration of blood flow).
- Reperfusion injury- more cells can die after reperfusion of an ischemic tissue by necrosis or apoptosis.
  - due to formation of oxygen free radicals. These are metabolites which form with the metabolites of cell injury and the oxygen.
1.6 Morphology of cell injury

- Cell injury- first biochemical changes and changes at molecular level
- Morphological changes takes a longer time to appear
- Evidence of ischemic cell injury and death: in minutes or hours when using histochemistry and ultrastructural examination
- Take hours or days for gross or light microscopic morphological changes to manifest themselves.
- Morphological changes of reversible cell injury occur earlier than those of irreversible injury.
• Example: Myocardial infarction due to blockade of a coronary artery.
  – Release of and leakage of cellular enzymes: within 2 hours of the injury
  – Irreversible damage to the myocardium: Within 30 to 60 minutes
  – Light microscopic changes of cell death: in 4 to 12 hours.
1.6.1 Morphology of reversible cell injury

1. Cell swelling
   - The first morphologic change

![Diagram showing the process of reversible cellular injury]

<table>
<thead>
<tr>
<th>ATP ↓</th>
<th>Activity of Na/K Pump ↓</th>
<th>Na in the cell ↑</th>
<th>Water in cell (osmosis) ↑</th>
<th>Cellular Swelling</th>
</tr>
</thead>
</table>

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• Difficult to see in individual cells, easier to realize in the whole organ.
• Make the organ large, increase its turgor and its weight, appear pale.
2. Fatty Change

- Occurs as a result of hypoxic damage, chemical and metabolic injury.
- Abnormal accumulations of triglycerides within parenchymal cells.
- Manifested by the appearance of lipid vacuoles in the cytoplasm.
- Occurs in cells involved in fat metabolism. I.e. myocardial cells and liver cells.
- Morphologically small or large lipid vacuoles are seen in the cytoplasm.
Cell death

• Impossible to determine the sequence of damage because
  – there are numerous causes of cell injury
  – there are numerous mechanisms causing cell damage

• There is no definite point for the point of no return and therefore there is no final common pathway by which cells die.
• However, there are two things consistently indicate irreversibility.

1. mitochondrial damage even after the original injury is resolved.

2. Severe membrane damage with profoundly compromised function.
   - The most important sites of membrane - mitochondrial membrane, the plasma membrane, and membranes of lysosomes.
   - Damage to lysosomal membrane releases enzymes into the cell and digests it. Enzymes are also released into the extracellular space and digest the cells and tissues around it.

• Two principal types of cell death, necrosis and apoptosis differ in their morphology, mechanisms, and roles in physiology and disease.
Definition

- Two principal types of cell death, necrosis and apoptosis differ in their morphology, mechanisms, and roles in physiology and disease.
- Necrosis- a series of changes that accompany cell death, largely resulting from the degradative action of enzymes on lethally injured cells.
- 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.
Necrosis

- Occurs when damage to membranes is severe, lysosomal enzymes enter the cytoplasm and digest and degrade the cells. The cell and cellular contents leak out.
- Pathologic process.

Apoptosis

- Occurs when the cell’s DNA or proteins are damaged in a way that it is unable to repair, the cell kills itself.
- Physiologic process - a form of cell death characterized by nuclear dissolution, fragmentation of the cell without complete loss of membrane integrity, and rapid removal of the cellular debris.
- Serves many normal functions and is not necessarily associated with cell injury.
Morphology of irreversible cell injury

- Irreversible cell injury - necrosis.
- Necrosis is the death of a group of cells occurring in living tissue.
- Enzymes causing degradation may also come from the white blood cells that migrate to the scene of cell injury.
- The contents leaking out of these white cells may cause inflammation of the surrounding tissues.
- These changes occur in hours and so in a case of sudden death from a myocardial infarction where there would be no detectable changes except a blocked coronary artery.
FIGURE 1-9  Morphologic changes in reversible cell injury and 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, Necrosis (irreversible injury) of epithelial cells, with loss of nuclei, fragmentation of cells, and leakage of contents. The ultrastructural features of these stages of cell injury are shown in Figure 1-10. (Courtesy of Drs. Neal Pinckard and M.A. Venkatachalam, University of Texas Health Sciences Center, San Antonio, TX.)
Morphological changes of necrotic cells

1. Changes in Cytoplasm

- Extreme eosinophilia in hematoxylin and eosin (H & E) stains – can be caused by 2 reasons.
  - Increased uptake of eosin pigment by damaged cells due to increased binding to denatured proteins
  - RNA in the cytoplasm imparts basophilia. This is lost when RNA is denatured

- Glassy homogenous cytoplasm – due to loss of glycogen particles
• Vacuolation of the cytoplasm due to digestion of organelles

• Myelin figure eventually replace the dead cells. These are large whorled (i.e spiral) phospholipid masses.

• Formation of fatty acids by degradation products of myelin figures and calcification of such fatty acids leading to generation of calcium soaps
2. **Changes in Nuclei** - Three patterns are seen
   - **Pyknosis** - Nuclear shrinkage and increased basophilia. Chromatin condenses into a solid, shrunken basophilic mass.
   - **Karyorrhexis** - Pyknotic nucleus undergoes fragmentation. The nucleus of the necrotic cell totally disappears in a day or two.
   - **Karyolysis** - A change that presumably reflects loss of DNA because of enzymatic degradation by endonucleases. Basophilia of the chromatin may fade in this condition.
Live cells:
- Nuclei are normal in morphology

Dead cells:
- Pyknosis
- Karyorrhexis
- Karyolysis

Nuclei are condensed & dense
Nuclei break up into fragments
Nuclei are dissolved
Necrotic changes occur in individual necrotic cells. When these changes are seen as a whole several patterns are recognized. These are;

1. **Coagulative Necrosis** –
   - The primary change – **denaturing of proteins**.
   - The basic **outlines** of the cells are **preserved** at least for some days.
   - Affected tissue is firm in texture. The necrotic cells are later phagocytosed by scavenger cells.
   - Hypoxic cell death in all tissues except the brain.
   - Occurs as a result of infarcts.
Coagulative necrosis in kidney tissue
2. **Liquefactive necrosis** –

- Prominent event is enzyme digestion
- Liquefaction completely digests the dead cells and form a viscous liquid mass.
- In the cases of bacterial and fungal infections inflammatory cells accumulation is increased while increased release of enzymes of inflammatory cells give rise to liquefaction.
- Hypoxic injury to the brain also results in this pattern.
- In bacterial infections this mass is creamy and yellow and is called pus.
Liquefactive necrosis - lung abscess

http://kobiljak.msu.edu/cai/HM561_Pathology/Injury/Lab1-Image16.html
IN LIQUEFACTIVE NECROSIS CELLS DISINTEGRATE AND DISAPPEAR. NO REMNANT OF NORMAL CELLS REMAINS, THOUGH SOME DEBRIS MAY BE SEQUESTERED IN AN ABSCESS IN SOME ORGANS, AS SHOWN ABOVE. AN ABSCESS IS A POCKET OF LIQUEFACTIVE NECROSIS SURROUNDED AND ISOLATED BY CONNECTIVE TISSUE, AND IS COMMON IN MUSCLE. IF THE NECROTIC AREA CAN'T BE REMOVED IT'S "CONTAINED" IN THIS WAY. AT LEFT, YOU SEE A LIQUIFACTIVE AREA IN AN ACTUAL SPECIMEN: THE DEBRIS HAS ELICITED AN INFLAMMATION AT THE PERIPHERY OF THE LESION WHERE INFLAMMATORY CELLS ARE REMOVING THE NECROTIC MATERIAL; THE LOWER PART OF THE FIELD HAS COMPLETED THIS PROCESS AND NO TRACE OF ANY CELLS REMAINS.
• **Caseous necrosis** - is a distinctive form of coagulative necrosis seen in tuberculosis. Microscopically it appears as amorphous granular debris composed of fragmented, coagulated cells within a distinctive inflammatory border.

• This is called a granulomatous reaction.

• Caseous’ indicates the cheese-like appearance of the tissue surrounded by the immune cells.
• **Fat necrosis** - describes focal areas of fat destruction. Ex: chronic pancreatitis.

• Pancreas- produce digestive enzymes which help us to break down the food that we have eaten: they are passed to the small intestine through the common bile duct.

• If this duct is blocked (usually by a gallstone), the enzymes then turn against the pancreas and result in acute pancreatitis: essentially, the pancreas starts digesting itself!
• Identification
  – naked eye: fat saponification (chalky white areas (Fatty acids combine with calcium salts) that develop as a result of fat breaking down into fatty acids)
  – Microscope: fat (clear) cells with calcium deposits that appear bluish and the presence of inflammation
• In this condition pancreatic enzymes leak out of acinar cells and liquefy the membranes of fat cells in the peritoneum.
• Enzymatic digestion of the pancreas take place.
• Fatty acids released and combine with calcium salts to produce chalky white areas on gross inspection.
• Microscopically there are shadowy outlines of necrotic fat cells, with inflammation and calcium deposition.
Fat necrosis
taken from the peripancreatic adipose of acute pancreatitis

Mitochondria are swollen due to loss of volume control; membranes from disrupted mitochondria form “myelin figures” such as the one shown here. These are stacks of laminated figures in the form of spheres in the injured cytoplasm. (Despite the name, they are not "myelin" and are not comparable to the myelin sheath of axons.)
Apoptosis

- Apoptosis is programmed cell death.
- Although it can happen in certain pathologic conditions, apoptosis is the process by which elimination of cells take place in physiological events.
- Important in the regulation of normal cell populations.
- An example is cell deletions in proliferating epithelial populations, parenchyma organs, endometrial cells, hormone dependent cells, immune cells.
- Apoptotic cell death also takes place in tumours, viral diseases and treatment with anti-cancer
Morphology of apoptosis

• Cells are single or in small clusters
• Cell shrinkage-Cells are smaller in size than the surrounding viable cells due to cell shrinkage.
• The cytoplasm is dense and eosinophilic due to tightly packed organelles.
• Chromatin condensation- This is the most characteristic feature of apoptosis. Chromatin is condensed near nuclear margins. Nucleus is dense and fragmented.
• Unlike necrosis apoptosis does not elicit an inflammatory response.
• Apoptosis is generally lasts a lifetime and be beneficial for the body.
Apoptosis
(Programmed Cell Death)

Normal cell → Cell shrinkage
              Chromatin Condensation

Membrane Blebbing → Apoptotic Body Formation

Lysis of Apoptotic Bodies → Nuclear Collapse
Continued Blebbing
<table>
<thead>
<tr>
<th>Feature</th>
<th>Necrosis</th>
<th>Apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell size</td>
<td>Enlarged (swelling)</td>
<td>Reduced (shrinkage)</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Pyknosis → karyorrhexis → karyolysis</td>
<td>Fragmentation into nucleosome-size fragments</td>
</tr>
<tr>
<td>Plasma membrane</td>
<td>Disrupted</td>
<td>Intact; altered structure, especially orientation of lipids</td>
</tr>
<tr>
<td>Cellular contents</td>
<td>Enzymatic digestion; may leak out of cell</td>
<td>Intact; may be released in apoptotic bodies</td>
</tr>
<tr>
<td>Adjacent inflammation</td>
<td>Frequent</td>
<td>No</td>
</tr>
<tr>
<td>Physiologic or pathologic role</td>
<td>Invariably pathologic (culmination of irreversible cell injury)</td>
<td>Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage</td>
</tr>
</tbody>
</table>
REFERENCES


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Thank You!!!!