Cell Injury....An Introduction
By
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Pathology is the science dealing with diseases as regards

- **Etiology...** Causes of the disease
- **Nature...** Inflammation, degeneration, circulatory, infections & neoplastic...
- **Pathogenesis...** Mechanism of disease formation
- **Pathological features (gross - Microscopic)**
- **Prognosis...** Expected disease outcome
- **Complications...** Added difficulties to the course of a disease
- **Fate...** Prognosis + complications
- **Pathological investigations (biopsy - autopsy...)**
Cellular Basis of Disease: Cell Injury

- Cellular dysfunction → Organ dysfunction → Clinical expression

- This concept dates to the 19th century and Rudolph Virchow, the father of modern pathology

- “...all forms of organ injury start with molecular or structural alterations in cells...”
Key Concepts

* Normal cells have a fairly narrow range of function or steady state: **Homeostasis**.

* Excess physiologic or pathologic stress may force the cell to a new steady state: **Adaptation**.
  **Adaptation** = Change in cell morphology and function in response to a stimulus. It is reversible.

* Too much stress exceeds the cell's adaptive capacity: **Injury**.
Adaptation

It is modification of cell morphology and function in relation to stress, it is reversible and preserves the viability of cells.

**It includes**

1- Hypertrophy
2 - Atrophy
3- Hyperplasia
4- Metaplasia
Hypertrophy is an increase in the size of individual cells, in response to a stimulus or injury.
Atrophy

It is decrease size and weight of an organ due to decreased size and number of its component cells.
Hyperplasia

- Is an increase in the **absolute number** of cells, in response to a stimulus or persistent cell injury. It may be physiological or pathological.
Metaplasia

-A reversible change in which one mature/adult cell type (epithelial or mesenchymal) is replaced by another mature cell type of the same category.
Cell injury

- It is change in cell’s morphology and function in response to stress.
- Cell injury occurs when the limits to an adaptive response (adaptation) have been exceeded or if the cells are not able to adapt.

Factors that affect cell injury:

A. Type, duration and severity of injury.
B. Type of injured tissue, its adaptability and genetic makeup e.g.
   - brain tissue is very sensitive to hypoxia (2-5 min)
   - skeletal muscles can adapt hypoxia for (2-6 hours)
Causes of Cell Injury

1- Oxygen deprivation (hypoxia, ischemia) most important cause

2- Oxygen free radicals.

3- Physical agents (heat, cold, radiation, trauma).

4- Chemical agents e.g. drugs, toxins

5- Infectious organisms.

6- Immunologic reactions.

7- Genetic derangements.

8- Nutritional imbalances e.g. starvation, obesity
Pathogenesis of cell injury (role of mitochondria)

Mitochondria is concerned with cell respiration and the production of ATP which is responsible about important vital functions of the cell:

1- Cellular osmolarity (Na/K)
2- membrane transport process
3- Protein synthesis.
Pathogenesis of cell injury  
(role of mitochondria)

**Mitochondrial oxidative phosphorylation is disrupted first → Decreased ATP →**

1- Decreased Na/K pump → gain of intracellular Na → cell swelling

2- Altered metabolism → depletion of glycogen (anaerobic respiration with glycogenolysis).

3- Lactic acid accumulation → decreased pH and increased intracellular osmotic pressure intracellular H2O...... cell swelling.
Reversible cell injury

Light microscopic changes
- Cell swelling
- Cloudy swelling and hydropic change)
Hydropic degeneration

- A severe form of cloudy swelling.
- Cytoplasm accumulates vacuoles of water.
Fatty change (Steatosis)

- It is abnormal accumulation of intracellular neutral fat that occurs in parenchymatous organs most commonly liver and heart.
Causes and Pathogenesis

- **Causes**..... As other causes of cell injury

- **Pathogenesis:**

  a. **Mitochondrial theory**

  Mild prolonged or severe short injury leads to injury of the mitochondria with release of its fat that accumulates in the cytoplasm.
1- Increased fatty acids entry to the liver (Obesity, starvation and cortisone therapy).

2- Increased fatty acid synthesis in the liver from acetate (alcoholism).

3- Decreased oxidation of fatty acids (hypoxia, anemia, respiratory failure).

4- Increased estrification of fatty acids to triglycerides (DM, alcoholism).

5- Decreased formation of apoprotein (protein malnutrition, alcoholism and CCL4 toxicity).
Causes of fatty change liver

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Fatty liver

Start of Oktoberfest

Jah! Beer!

Alcohol-damaged liver cells can take up fatty acids normally...

...but cannot incorporate them into lipoproteins for export.

End of Oktoberfest

by itself, it's reversible
Cell death

An irreversible type of cell injury. It has two types

1- **Necrosis**
   - Definition
   - Causes...
   - Pathogenesis
   - Pathological changes (gross and microscopic)
   - Types

2- **Apoptosis**
Necrosis

Death of a group of cells within living organism.

Two factors characterize irreversibility of the cell damage
1- Irreversible mitochondrial damage.
2- Increased intracellular calcium (Ca).
Pathogenesis of necrosis

1- Irreversible mitochondrial dysfunction → markedly decreased ATP.

2- Increased level of intra-cellular Ca……activation of many enzymes e.g.
   a. Proteases
   b. Phospholipases
   c. Endonucleases
Injurious agent

Mitochondrion

Ca^{2+}

Endoplasmic reticulum

Ca^{2+}

Increased cytosolic Ca^{2+}

ATPase

Phospholipase

Protease

Endonuclease

Decreased ATP

Decreased phospholipids

Disruption of membrane and cytoskeletal proteins

Nuclear chromatin damage
- Microscopic changes of necrosis

*Microscopically*
- Cell membrane disappears.
- Cytoplasm is swollen, mitochondria is swollen, rupture, forms myelin figures and may be calcified.

- **Nuclear changes:**
  - **Pyknosis**
    - Nuclear shrinkage and increased basophilia
  - **Karyorrhexis**
    - Fragmentation of the pyknotic nucleus
  - **Karyolysis**
    - Fading of basophilia of chromatin
Types of Necrosis

- Coagulative (most common)
- Liquefactive
- Caseous
- Fat necrosis (traumatic and enzymatic)
- Fibrinoid necrosis
Coagulative Necrosis

- Cell’s basic outline is preserved but details are lost.
- Protein denaturation predominates enzymatic digestion.
Liquefactive Necrosis

- Usually due to enzymatic dissolution of necrotic cells (usually due to release of proteolytic enzymes from neutrophils)

- Most often seen in CNS and in abscesses
Caseous Necrosis

- Gross: Resembles cheese
- Usually seen in infections (esp. mycobacterial (TB) and fungal infections)
Fat necrosis

Necrosis of fat cells
....release of triglycerides which are hydolysed by lipase into fatty acids and glycerol.
- Fatty acids attracts Ca (from the blood) to form Ca. soaps.
- May be traumatic or enzymatic.
Fibrinoid Necrosis

- Usually seen in the walls of blood vessels (e.g., in vasculitis)
- Glassy, eosinophilic fibrin-like material is deposited within the vascular walls

Renal glomerulus - influx of fibrin into the afferent arteriole, due, in this case, to malignant hypertension.
Apoptosis

- A type of cell death referred to as single or (programmed) cell death.

- It is an important mechanism for the removal of cells as occurs in cells with irreparable DNA damage (from viruses, free radicals, chemical....etc), protecting against neoplastic transformation.
Apoptosis

Physiologic Processes
1. Embryogenesis
2. Menstruation
3. Menopause
4. Intestinal homeostasis
5. Immune tolerance

Pathologic Processes
1. Acute inflammation
2. Organ atrophy
3. Neoplasia
4. Graft rejection
5. Viral hepatitis
Apoptosis

1. Loss of microvilli and junctions
2. Nuclear changes
3. Fragmentation
4. Phagocytosis
Apoptosis

Mechanism

1. Cell shrinkage, loss of microvilli and cell junctions.
2. Regular fragmentation of DNA each 180 bp intervals.
3. Membrane blebbing.
4. Formation of apoptotic bodies.
5. Rapid phagocytosis of apoptotic bodies.
6. Absence of inflammation.
What are the differences between necrosis and apoptosis

<table>
<thead>
<tr>
<th></th>
<th>Necrosis</th>
<th>Apoptosis</th>
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<tbody>
<tr>
<td>Definition</td>
<td>Death of group of cells within the living tissue</td>
<td>Single (programmed) cell death</td>
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<tr>
<td>Causes</td>
<td>Always Pathological</td>
<td>May be pathological or physiological</td>
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<tr>
<td>Nucleus</td>
<td>Pyknosis, karyorrhexis and karyolysis</td>
<td>Regular fragmentation of the DNA</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Swells</td>
<td>Shrinks</td>
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<td>Cell membrane</td>
<td>Dissolves</td>
<td>Blebs forming apoptotic bodies</td>
</tr>
<tr>
<td>Surrounding inflammation</td>
<td>Present</td>
<td>Absent</td>
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Pathologic Calcification

It is deposition of calcium salts in sites other than bone and teeth.

1. **Dystrophic calcification**
   - Occurs in nonviable tissue with normal blood calcium level

2. **Metastatic calcification**
   - Occurs in viable tissue
   - Caused by hypercalcemia

3. **Stone formation**
Dystrophic Calcification

Abnormal calcification in which there is Normal blood calcium level + diseased or necrotic tissue.
1. Necrotic tissue
   - fat, coagulative, liquefactive, caseous necrosis
2. Atherosclerosis
   - Central necrotic core
3. Cells....Psammoma bodies
4. Damaged or aging heart valves
- Atherosclerosis

- Calcified cardiac cusp

- Psammoma bodies
Pathologic Calcification

Calcification in the wall of a blood vessel
Metastatic Calcification
Increased blood calcium+ normal tissue

1. Increased PTH secretion
   - parathyroid tumor
   - ectopic PTH secretion
2. Bone destruction
   - osteolytic tumors
   - Paget’s disease
   - immobilization
3. Vitamin D disorders
   - vitamin D toxicity
   - sarcoidosis
4. Excess calcium intake, as in milk alkali syndrome
   (nephrocalcinosis and renal stones caused by milk and antiacid self-therapy)
Metastatic Calcification

1. Lungs
   - respiratory failure
2. Kidneys
   - nephrocalcinosis, kidney failure
3. Stomach

4. Arteries.... Sometimes affection of small blood vessels of the skin cause ischemic ulcers with necrosis (calciphylaxis)
Metastatic Calcification
Lung

Von Kossa Stain
3- Stone formation
Thank u