### Concepts

I. The nature of disease  
II. Reactions of cells to injury/stress  
III. Cell adaptation  
IV. Mechanisms of cell injury and death  
V. Morphology of cell injury and death

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### THE NATURE OF DISEASE

**Concept:**

*Disease* may be thought of as reaction of a cell or group of cells to an injury.  

The injury may:
  
  a) disrupt the *biochemical processes* of the cell  
  
  or  
  
  b) *directly damage components of the cell*  
  
  *ie membrane, nucleus or intracytoplasmic organelles*
Steps in the Evolution of Disease

General Categories (Etiologies) of Injury
1. Oxygen deprivation (hypoxia)
2. Chemical
3. Physical
4. Infectious
5. Immunologic
6. Genetic
7. Nutritional
8. Aging (Degenerative)

REACTIONS OF CELLS TO INJURY
Concept:
Living cells change in structure and function when stressed (injured)
In disease these changes are clinically apparent as physical signs and symptoms
Homeostasis

- Cells maintain a steady state in which the intracellular milieu is kept within fairly narrow range of physiologic parameters
- Physiologic response

Example: What is the early physiologic response of the heart to exercise?
Cell Adaptation

- Definition
  - Adaptation = process by which cells change in size, number and appearance in response to changes in cell environment
  - Changes may be physiologic or pathologic

Types of Cell Adaptation

a. Hyperplasia: Increase in the number of cells
   Clinical Examples:
   a. Physiologic: What happens to glandular epithelium of the breast during pregnancy?
   b. Pathologic: Abnormally high levels of estrogen can cause proliferation of endometrial gland epithelium, a condition known as endometrial hyperplasia

b. Hypertrophy: Increase in the size of a cell because of increased cellular substance
   Clinical Examples:
   a. Physiologic: What happens to an athlete who repeatedly lifts weights?
   b. Pathologic: Patient with systemic hypertension will increase cardiac muscle mass because heart must work harder to overcome vascular resistance
Types of Cell Adaptation

c. **Atrophy:** Decrease in the size of a cell because of loss of cellular substance

Clinical Examples:

a. **Physiologic:** What happens to the endometrium of a post-menopausal woman?

b. **Pathologic:** Muscles will atrophy when leg is placed in a plaster cast for a broken bone.
d. Metaplasia: Substitution of one type of an adult cell for another type of adult cell.

Clinical Example: Normal trachea and bronchi are lined by ciliated columnar epithelium. Chronic irritation and inflammation of the respiratory epithelium by cigarette smoking may cause replacement of columnar cells by stratified squamous cells.
PRINCIPLE MECHANISMS OF CELL INJURY

Hypoxic Injuries (ischemia, hypoxemia, decreased O2 carrying capacity)

Robbins Figure 2-15

Robbins Figure 2-16
Clinical Correlation

- Altered membrane permeability
- Allows intracellular enzymes to leak from cell into vascular compartment
  - Elevated levels can be measured clinically, confirm clinical diagnosis of disease
    - Myocardial cells
      - Elevated CK or troponin → acute MI
    - Hepatocytes
      - Elevated AST/ALT → hepatitis

Clinical Correlation

- Decreased ATP, decreased intracellular oxygen
  - Causes cell to switch from aerobic to anaerobic respiration
  - Lactic acid levels increased as a byproduct of anaerobic glycolysis
    - leading to state of metabolic acidosis
    - Lactic levels are measurable clinically.
      - Lactate Clearance is a way of confirming adequate resuscitation in shock

Free Radical Injury Model

Definition: A free radical is an atom or group of atoms which have a single unpaired electron in the outer orbit. Free radicals are chemically unstable and very reactive with components of the cell, ie membrane, intracytoplasmic organelles.

Chain reaction:
Free radicals + molecules → more free radical generation
Free Radical Injury

- **Ischemia-Reperfusion Injury**
  - Return of blood/oxygen to ischemic tissue
  - Oxygen derived free radicals produced from leukocytes, parenchymal and endothelial cells; mitochondrial dysfunction
  - (Paradoxical) Further injury to cells

Accumulation of Misfolded Proteins → Endoplasmic Reticulum Stress

- **Etiologies include:**
  - Gene mutations
  - Aging
  - Infections, Viral

- **Examples of Diseases:**
  - Alzheimer Disease (protein accumulation)
  - Cystic Fibrosis (protein loss of function)
**Mechanisms of Cell Injury**

- Hypoxia, ischemia
- Multiple injuries, alcohol
- Malnutrition, cell stress, infection
- Radiation, other insults
- Infection, immunologic disorders

- ATP
- ROS
- DNA damage
- Toxic molecules
- Apoptosis
- Necrosis

**MORPHOLOGY OF REVERSIBLE CELL INJURY**

1. Cellular swelling
2. Steatosis (fatty change) in organs involved with lipid metabolism
3. Myelin figures (collections of phospholipids)
4. Endoplasmic reticulum swelling
5. Membrane blebs

- Normal reversible cell injury
- Reversible cell injury showing surface blebs
- Necrotic (irreversible) injury of epithelial cells, with pyknosis, loss of nuclei, and leakage of contents

- Morphology of reversible cell injury
- Renal Tubules
- Nucleus + Cytoplasm
- Lumen

- Early (reversible) ischemic injury showing surface blebs
- Increased eosinophilia of cytoplasm, and swelling of occasional cells

- Necrotic (irreversible) injury
- Necrosis or apoptosis

- Normal renal tubule
- Early (reversible) ischemic injury
- Necrotic (irreversible) injury
- Lumen
B. Irreversible Cell Injury: Cell DEATH

Necrosis

- Sum total of morphologic changes which occur in tissue following cell death
- Includes structural changes of nucleus and cytoplasm of dead cell
- Characterized by the presence of leukocytes (especially neutrophils) infiltrating dead tissue from adjacent living tissue
- Morphologic changes occur as result of enzymatic breakdown of cell and denaturation of proteins

Robbins Figure 2-3
Morphologic Patterns of Necrosis

- Necrosis is not a specific disease
- Necrosis is a pathologic process found in many diseases.

- Common descriptive terms used for histologic patterns of necrosis.
- Coagulative necrosis
- Liquefactive necrosis
- Caseous necrosis
- Enzymatic fat necrosis
- Gangrene

1. Coagulative Necrosis

- Pattern of necrosis associated with severe ISCHEMIA
- In solid organs (heart, kidney)
- Histologically: Ghost-like remnants of intact cells which lack nuclei. The cell outline is preserved. The cytoplasm stains intense pink (eosinophilia)
- Macroscopically: Tissue firm (in early stages)
- Examples: Myocardial infarct, renal infarct
2. Liquefactive Necrosis

- Pattern of necrosis often associated with bacterial infections
- Microscopic: Bacteria release enzymes causing rapid loss of cellular structure and collection of liquid, amorphous debris
- Macroscopic: creamy yellow material
  - ABSCESS = collection of neutrophils, dead cells, liquid

- Pattern of necrosis with BRAIN hypoxia/infarct
3. Caseous Necrosis

- Pattern of necrosis associated with an inflammatory reaction called "granuloma"
- Histologically: amorphous debris (dead cells) in the center of granulomatous cell reaction
- Macroscopically: necrotic tissue is soft, white, friable
4. Enzymatic Fat Necrosis

- Term used to describe cell death in pancreas and adjacent fat
  - Example: Acute pancreatitis

Enzymatic Fat Necrosis

- Pancreatitis
- Lipase
- Calcium
- Fatty acids
- Chalky white areas (saponification)

4. Gangrene

- Clinical term
- Represents coagulation (ischemic) necrosis
  - usually of an extremity, bowel, gallbladder
Dry Gangrene

Wet Gangrene
If bacteria contaminate dying tissue, superimposing liquefactive necrosis, the process is referred to as wet gangrene.

B. Irreversible Cell Injury: Cell DEATH

Apoptosis
• Regulated pattern of cell death characterized by nuclear condensation and fragmentation coupled with fragmentation of cytoplasm into “apoptotic bodies”.
  – Physiologic
  – Pathologic
• Apoptosis is not associated with an inflammatory reaction
• Recognition & removal of dead cells by phagocytes
Where is Apoptosis Seen?

- Normal embryogenesis
  - Example: menstrual cycle
- Hormone dependent physiologic involution
  - Example: intestinal crypts
- DNA damage
  - Example: Radiation exposure
  - Infections
    - Example: Viral hepatitis
  - Accumulation of misfolded proteins
    - Example: CNS degenerative diseases

Necrosis of myocytes
Lecture Summary

Can I Answer These Questions?

- Ischemic injury to the central nervous system from right internal carotid arterial occlusion suffered by a 72 year old man will result in what pattern of necrosis?

- Which are the major mechanisms which result in membrane damage typical for a reperfusion injury following myocardial ischemia in a 68 year old woman?

- Scattered acidophilic bodies are found in the liver of a 57 year old man who has recently developed nausea, vomiting, and scleral icterus. His serologic test for viral hepatitis A is positive. What is the most likely pattern of tissue alteration?

- An endocervical biopsy in a 23 year old woman demonstrates the presence of squamous epithelium (not columnar epithelium). What process has occurred? Why?