Cell Injury
MHD 2019-20

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

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
   i.e. membrane, nucleus or intracytoplasmic organelles
Steps in the Evolution of Disease

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

Enlarged liver due to hepatomegaly
Homeostasis

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

Example: What is the an 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:
- Physiologic: What happens to glandular epithelium of the breast during pregnancy?
- Pathologic: Abnormally high levels of estrogen can cause proliferation of endometrial gland epithelium, a condition known as endometrial hyperplasia.

Types of Cell Adaptation

b. Hypertrophy: Increase in the size of a cell because of increased cellular substance

Clinical Examples:
- Physiologic: What happens to an athlete who repeatedly lifts weights?
- 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.
General Categories of Cell Reactions

PRINCIPLE MECHANISMS OF CELL INJURY

Robbins Figure 2-15
**Hypoxic Injury Model**
*(ischemia, hypoxemia, decreased O2 carrying capacity)*

**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 $\rightarrow$ more free radical generation
Free Radical Injury

- Ischemia-Reperfusion Injury
  - Return of blood/oxygen to ischemic tissue
  - Provides molecular O$_2$ to combine with free radicals to form additional ROS
  - Also involves other factors including:
    - Inflammatory mediators, platelet-activating factor (PAF), NOS and NO$^\cdot$, dysregulation of Ca$^{2+}$ homeostasis
  - (Paradoxical) further injury to cells

Accumulation of Misfolded Proteins → Endoplasmic Reticulum Stress

Examples include:
- Gene mutations
- Aging
- Infections, etc.

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

General Categories of Cell Reactions

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 vs. Reversible cell injury

Irreversible cell injury

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

Increased eosinophilia of cytoplasm, and swelling of occasional cells.

Necrotic (irreversible) injury of epithelial cells, with pyknosis, loss of nuclei, fragmentation of cells, leakage of contents.

Renal Tubules

Nucleus + Cytoplasm

Lumen

Normal

Reversible cell injury

Irreversible cell injury

B. Irreversible Cell Injury: Cell DEATH

NORMAL CELL (prematurely)

Adaptation

Hypoxic stimulus

Reversible injury

Necrosis/Cell death

Apoptosis

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
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.
  1. Coagulative necrosis
  2. Liquefactive necrosis
  3. Caseous necrosis
  4. Enzymatic fat necrosis
  5. 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)
- Examples: Myocardial infarct, renal infarct
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

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

...more in the upcoming MHD "Chronic Inflammation" lecture
4. Enzymatic Fat Necrosis

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

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
  - Hormone dependent physiologic involution
    - Example: menstrual cycle
- Proliferating cell populations
  - Example: intestinal crypts
- DNA damage
  - Example: Radiation exposure
  - Infections
    - Example: Viral hepatitis
- Accumulation of misfolded proteins
  - Example: CNS degenerative diseases
Features of "irreversible" injury:
- Non-repairable mitochondrial dysfunction
- Profound membrane dysfunction

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?
- A patient is diagnosed with "wet gangrene" of their lower extremity. The patient wants you to explain what this diagnosis means. How will you respond?
- 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?

Sample Multiple Choice Questions

#1
A 63-year-old man angina suffers an acute myocardial infarction. Thrombolytic therapy with tissue plasminogen activator (tPA) is administered to restore coronary blood flow. In spite of this therapy, the degree of myocardial fiber injury may increase because of which of the following cellular abnormalities?

A. Cytoskeletal intermediate filament loss
B. Decreased intracellular pH from anaerobic glycolysis
C. Increased free radical formation
D. Mitochondrial swelling
E. Nuclear chromatin clumping
F. Reduced protein synthesis
A 28-year-old woman gives birth to her first child. She begins breast feeding the infant and continues breast feeding for almost a year with no difficulties and no complications. Which of the following cellular processes that began in the breast during pregnancy allowed her to nurse the infant for this period of time?

A. Stromal hypertrophy  
B. Steatocyte atrophy  
C. Ductal epithelial metaplasia  
D. Lobular hyperplasia

A 40-year-old woman has the sudden onset of severe abdominal pain. On physical examination she has diffuse tenderness in all abdominal quadrants, with marked guarding and muscular rigidity. She has laboratory findings that include elevation of serum lipase at 415 U/L. An abdominal CT scan is done and reveals findings consistent with pancreatic inflammation and peritoneal fluid collections. Which of the following cellular changes is most likely to accompany these findings?

A. Coagulative necrosis  
B. Dry gangrene  
C. Fat necrosis  
D. Apoptosis  
E. Liquefactive necrosis

Answers:

#1 – C  
#2 – D  
#3 - C