The Cellular Basis of Disease
Cell Injury 1

Adaptation and Reversible Injury
Patterns of Tissue Necrosis (Irreversible Injury)

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APPROVED
The Cellular Basis of Disease

Cell Injury 1: Adaptation and Reversible Injury
Patterns of Irreversible Injury (Necrosis)

Cell Injury 2: Mechanisms of Cell Injury

Cell Injury 3: Apoptosis and Necrosis
Cellular Aging

Cell Injury 4A: Sub lethal Cell Injury
John Shelburne MD PhD

Cell Injury 4B: Intracellular accumulations
Objectives

- Understand the cellular response to injury and stress.
- Understand the differences between hyperplasia, hypertrophy, atrophy and metaplasia at the cellular and organ level.
- List and understand the causes of cell injury and death including oxygen deprivation; physical and chemical agents including drugs; infections and immunologic reactions; genetic derangements and nutritional imbalances.
- Discriminate cell adaptation, reversible cell injury and irreversible cell injury (cell death) based on etiology, pathogenesis and histological and ultrastructural appearance.
- Define and understand the morphologic patterns of lethal cell injury and the clinical settings in which they occur.
Cellular Adaptation to Injury or Stress

Injury or Stress
- Increased demand
- Decreased stimulation or nutrients
- Chronic irritation

Adaptation
- Hyperplasia or hypertrophy
- Atrophy
- Metaplasia

This process is important for neoplastic transformation (abnormal growth)

increase in cell number
increase in size
replacement of one cell type with another
abnormal growth
Adapted - Normal - Injured Cells

If the cell can adapt, it will hypertrophy.

Normal myocardium

Reversibly-injured myocyte

Cell death

Cell injury

Adaptation: response to increased load

Adapted myocyte (hypertrophy)

Normal myocyte

such as blocked blood flow

Dead tissue

Not dead tissue

Cardiac

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Adaptations

- Hypertrophy
- Hyperplasia
- Atrophy
- Metaplasia
Hypertrophy

Increase in the size of cells results in increased size of the organ

May be Physiologic or Pathologic
Examples of Physiologic Hypertrophy

Increased workload - skeletal muscle
cardiac muscle

Hormone induced – pregnant uterus
Physiologic hypertrophy
Gravid uterus and Normal uterus

"gravid" uterus, is larger

normal uterus

Normal Uterus

Gravid uterus
- Number of muscle cells is the same, they are all just larger in size

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Biochemical Mechanisms of Myocardial Hypertrophy

How physiological hypertrophy happens

Mechanical stretch (increased work load)

Agonists (e.g., α-adrenergic hormones, angiotensin)

Growth factors (e.g., IGF-1)

Signal transduction pathways

Transcription factors (Myc, Fos, Jun, others)

Induction of embryonic/fetal genes (e.g., cardiac α-actin, ANF)

↑ Synthesis of contractile proteins

↑ Production of growth factors

↑ Mechanical performance; ↓ Work load

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Adaptations

• Hypertrophy
• **Hyperplasia**
• Atrophy
• Metaplasia
Hyperplasia

Increase in the number of cells results in increase in size of the organ.

May be Physiologic or Pathologic.
Physiologic Hyperplasia

• **Hormonal hyperplasia**
  Female breast; puberty and pregnancy

• **Compensatory hyperplasia**
  Prometheus
  Unilateral nephrectomy
  Erythroid hyperplasia of bone marrow in chronic hypoxia (mountain climbers).

*If you lose a kidney for whatever reason, your other one will undergo hyperplasia.*
Pathologic Hyperplasia

- Excessive hormone stimulation
  - Endometrial hyperplasia (common during menopause)
  - Prostatic hyperplasia
- Viral infections
  - Papilloma virus (warts)
Adaptations

- Hypertrophy
- Hyperplasia
- Atrophy
- Metaplasia
Atrophy

• Reduced size of an organ due to a decrease in cell size and number.
• Physiologic atrophy – notochord, post partum uterus
• Pathologic atrophy – local or generalized
Causes and Examples of Atrophy

- Decreased workload (disuse atrophy)
- Loss of innervation (denervation atrophy)
- Diminished blood supply (ischemia)
- Inadequate nutrition (marasmus, cachexia)
- Loss of endocrine stimulation (menopause)
- Aging (senile atrophy)
- Pressure (enlarging benign tumor)
Mechanisms of Atrophy

• Decreased protein synthesis
• Increased protein degradation
• Ubiquitin-proteasome pathway-degrades cytosolic and nuclear proteins
• Autophagic vacuoles
• Lipofuscin granules
• Brown atrophy

When the above three happen to a whole organ we call it Brown atrophy.

Lipofuscin is the name given to finely granular yellow-brown pigment granules[1] composed of lipid-containing residues of lysosomal digestion. It is considered one of the aging or "wear and tear" pigments, found in the liver, kidney, heart muscle, adrenals, nerve cells, and ganglion cells. It is specifically arranged around the nucleus, and is a type of Lipochrome.
You do get normal physiological atrophy as you age but compare to alzheimer patient with increased atrophy

Normal

Atrophy
Adaptations

- Hypertrophy
- Hyperplasia
- Atrophy
- Metaplasia
Metaplasia

Reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type. Usually occurs in response to stress or chronic irritation.
Causes and Examples of Metaplasia

- Tobacco smoke - Squamous metaplasia in the respiratory tract, most common.
- Gastric acid reflux - Gastric metaplasia of distal esophagus; Barrett esophagus.
- Repeated skeletal muscle injury with hemorrhage - muscle replaced by bone; myositis ossificans.

Common

Fertile ground for lung cancer

Uncommon
Bronchus with Columnar to Squamous Metaplasia

ciliated columnar cells being replaced by stratified squamous
Esophagus with Squamous to Columnar metaplasia

this type of cell is being replaced by this type of cell
Mechanisms of Metaplasia

- Re-programing of stem cells that exist in normal tissue.
- Induced by cytokines, growth factors and other environmental signals.
- Retinoic acid may play a role.
- Exact mechanism is unknown.
Under the influence of cytokines and growth factors, stem cell differentiation can be altered to result in an epithelial cell type other than what normally lines a tissue surface. What is the name of this process?

A. Atrophy  
B. Hyperplasia  
C. Hypertrophy  
D. Metaplasia  
E. Neoplasia
You have been working out and lifting weights. The increase in the size of your skeletal muscles induced by weight lifting is an example of

A. Atrophy
B. Hyperplasia
C. Hypertrophy
D. Metaplasia
E. Neoplasia
Cell Injury and Death

• Reversible – reduced ATP, cellular swelling
• Irreversible – two types of cell death
  Necrosis – always pathologic
  Apoptosis – may be physiologic or pathologic (Cell Injury 3)
Causes of Cell Injury

• Oxygen deprivation (hypoxia or ischemia)
• Physical Agents (trauma)
• Chemical agents and Drugs
• Infectious Agents
• Immunologic Reactions
• Genetic Derangements
• Nutritional Imbalances
This line is frequently blurred at a microscopic level.

Measuring levels of troponin released by damaged myocardium to determine if a patient had a heart attack is a common example.
All these things happen when there is any sort of injury. However, it can go back to normal if the injury is not that great or if the injurious stimulus is removed.

Nucleus becomes more dense, ER becomes swollen and starts to disintegrate, ribosomes detach.

Point of no return.

Because this process is programmed, it is very organized.

Regular fragments form vs cell rupture.

The cell ruptures and releases its contents which attract inflammatory cells.
Kidney cells

nucleus starts to shrink, but doesn't disappear and you get the pink blebs = eosinophilic

here the nucleus disappears entirely

Normal

Reversible

Necrosis
Morphologic Alterations in Reversible Cell Injury

- Cellular swelling
- Fatty change

really characteristic in the liver
Morphologic Alterations in Irreversible Injury (Necrosis)

Cytoplasmic eosinophilia

Karyolysis - nucleus becomes pale and eventually disappears

Pyknosis - nucleus shrinks, chromatin condenses, becomes deeply basophilic

Karyorrhexis – nucleus undergoes fragmentation
Patterns of Tissue Necrosis

Coagulative Necrosis
Liquefactive Necrosis
Fat Necrosis
Caseous Necrosis
Fibrinoid Necrosis
Coagulative Necrosis

Pattern of cell death characterized by progressive loss of cell structure, with coagulation of cellular constituents and persistence of cellular outlines for a period of time, often until inflammatory cells arrive and degrade the remnants.
coagulative necrosis in the myocarium

myocytes - you don't see any nuclei because they're all dead
Coagulative Necrosis

Similar in many respects to autolysis.

Autolysis is self digestion and does not require the participation of inflammatory cells.

Autolysis occurs in tissue incubated for a period of time in the absence of blood flow or oxygen (very common in autopsy material).
Coagulative Necrosis

Characterized by changes in cytoplasmic staining in routine histology sections and changes in nuclear morphology and/or staining characteristics.

Cytoplasm becomes more eosinophilic.

Several patterns of nuclear change.
These are all signs of irreversible injury

- Rupture of lysosomes and autolysis
- Myelin figures
- Lysis of ER
- Defects in cell membrane
- Large densities
- Mitochondrial swelling

C. Irreversible injury

Process is dependent on what the injury is
Liquefactive Necrosis

Pattern of cell death characterized by dissolution of necrotic cells.

Typically seen in an abscess where there are large numbers of neutrophils present, which release hydrolytic enzymes that break down the dead cells so rapidly that pus forms.

Pus is the liquefied remnants of dead cells, including dead neutrophils.
Coagulative Necrosis

Liquefactive Necrosis

May be surrounded by inflammatory cells and is commonly seen in infections.
Caseous Necrosis

The pattern of cell injury that occurs with granulomatous inflammation in response to certain microorganisms (tuberculosis). The host response to the organisms is a chronic inflammatory response and in the center of the caseating granuloma there is an area of cellular debris with the appearance and consistency of cottage cheese.
This is a coronal section through the lung.
Fat Necrosis

When lipases are released into adipose tissue, triglycerides are cleaved into fatty acids, which bind and precipitate calcium ions, forming insoluble salts.

These salts look chalky white on gross examination and are basophilic in histological sections stained with H&E.
omentum from a person who died of pancreatitis; pancreatic enzymes including lipases were released into the peritoneum
Fibrinoid Necrosis

The pattern of cell injury that occurs in the wall of arteries in cases of vasculitis. There is necrosis of smooth muscle cells of the tunica media and endothelial damage which allows plasma proteins, (primarily fibrin) to be deposited in the area of medial necrosis.
Fibrinoid necrosis

- eosinophilic ribbon of necrotic tissue
- ARTERY

endothelial cells are enlarged because "they're responding to whatever caused this in the first place"
Your patient has experienced an acute myocardial infarct and expired due to ventricular rupture seven days later. You ask for an autopsy and examine a section of the heart under the microscope. What type of necrosis do you see?

A. Caseous necrosis  
B. Liquefactive necrosis  
C. Fibrinoid necrosis  
D. Fat Necrosis  
E. Coagulative necrosis
Summary

Cellular Adaptation to Injury or Stress

- Hypertrophy
- Hyperplasia
- Atrophy
- Metaplasia

Patterns of Tissue Necrosis

- Coagulative Necrosis
- Liquefactive Necrosis
- Caseous Necrosis
- Fat Necrosis
- Fibrinoid Necrosis