Cell adaptations, Injury and Death

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Introduction of Pathology

Cell adaptations

Cell injury

Cell death

Intracellular accumulations

Pathologic calcification
Objectives

1. Describe overview of cellular responses to stress and noxious stimuli
2. Explain the overview of cell adaptations
3. Explain mechanisms of reversible and irreversible injury
4. Distinguish between reversible and irreversible cell injury
5. Describe the overview and pathogenesis of cell death
6. Distinguish between necrosis and apoptosis
7. Describe types of necrosis
8. Explain the types of apoptosis
9. Explain the overview of autophagy
10. Explain the overview of Intracellular accumulations
11. Explain the pathology of pathologic calcification
12. Explain the clinicopathologic correlations
Pathology

The study (logos) + Disease (pathos, suffering)

- There are two important terms that students will encounter throughout their study of pathology

1. Etiology is the origin of a disease
2. Pathogenesis refers to the steps in the development of disease
3. Molecular and Morphologic changes
4. Functional Derangements and Clinical Manifestations

Macroscopic/Gross appearance  Microscopic  Ultrastructure

Rudolf Virchow: (1821-1902)
<table>
<thead>
<tr>
<th>Nature of Injurious Stimulus</th>
<th>Cellular Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered physiologic stimuli; some nonlethal injurious stimuli</td>
<td>Cellular adaptations</td>
</tr>
<tr>
<td>Increased demand, increased stimulation (e.g., by growth factors, hormones)</td>
<td>Hyperplasia, hypertrophy</td>
</tr>
<tr>
<td>Decreased nutrients, decreased stimulation</td>
<td>Atrophy</td>
</tr>
<tr>
<td>Chronic irritation (physical or chemical)</td>
<td>Metaplasia</td>
</tr>
<tr>
<td>Reduced oxygen supply; chemical injury; microbial infection</td>
<td>Cell injury</td>
</tr>
<tr>
<td>Acute and transient</td>
<td>Acute reversible injury</td>
</tr>
<tr>
<td></td>
<td>Cellular swelling fatty change</td>
</tr>
<tr>
<td>Progressive and severe (including DNA damage)</td>
<td>Irreversible injury → cell death</td>
</tr>
<tr>
<td></td>
<td>Necrosis</td>
</tr>
<tr>
<td></td>
<td>Apoptosis</td>
</tr>
<tr>
<td>Metabolic alterations, genetic or acquired; chronic injury</td>
<td>Intracellular accumulations; calcification</td>
</tr>
<tr>
<td>Cumulative sublethal injury over long life span</td>
<td>Cellular aging</td>
</tr>
</tbody>
</table>
Cell Adaptations

Reversible changes in

- The number
- Size
- Phenotype
- Metabolic activity
- Functions of cells in response

** to changes in their environment**
Physiologic adaptations

• Hormones (endogenous)
• Chemical mediators
• Exercise
• Aging
• Ex. the hormone induced enlargement of the breast and uterus during pregnancy

Pathologic adaptations

• Stress according to disease or abnormality condition
Cell Adaptations

• Hypertrophy
• Hyperplasia
• Atrophy
• Metaplasia
Proliferative Capacities of Tissues

1. Labile (continuously dividing) tissues
   ▪ Regenerate after injury as long as the pool of stem cells is preserved
   ▪ Skin, oral cavity, GI, vagina, and cervix mucosa
   ▪ Hematopoietic cell

2. Stable/Quiescent tissues
   ▪ Minimal replicative activity in their normal state
   ▪ These cells are capable of proliferating in response to injury or loss/wound healing of tissue mass
   ▪ Liver, kidney, pancreas, endothelial cells, fibroblasts, osteoblast, salivary gland and smooth muscle cells

3. Permanent tissues
   ▪ Terminally differentiated and non-proliferative in postnatal life
   ▪ Repair is typically dominated by scar formation
   ▪ Neurons, cardiac muscle cells, skeletal muscle
Hypertrophy is an increase in the size of cells resulting in an increase in the size of the organ. It occurs in tissues incapable of cell division.
Physiologic hypertrophy

- Hormone-induced enlargement an organ
  - Uterus (Estrogen)
  - Breast (Prolactin/Estrogen)
- Exercise/ weight training
Pathologic hypertrophy

- **Predisposing factor**
  - Hypertension
  - Congenital heart disease ex. aortic valve stenosis

- **Mechanisms of hypertrophy**
  1. Mechanism triggers
  2. Trophic triggers
Robbins and Cotran pathologic basis of disease. 9th edition, 2015

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Hyperplasia is characterized by an increase in cell number. It occurs in tissues whose cells are able to divide or contain abundant tissue stem cells and stable cell.
Mechanisms of hyperplasia

- Hyperplasia is the result of growth factor-driven proliferation of mature cells.

  \[ \text{Intracellular signaling pathway} \]

  \[ \text{Transcription factor} \]

  \[ \text{Cell proliferation} \]

  \[ \text{Increased output of new cells from tissue stem cells} \]
Physiologic hyperplasia

- Hormonal hyperplasia
  - Glandular epithelium of the female breast at puberty and during pregnancy

(Prolactin/Estrogen Department of Pathology, Faculty of Medicine, Khon Kaen University)
Physiologic hyperplasia

• **Compensatory hyperplasia**
  - Partial hepatectomy
  - Transplantation

• **Adaptive hyperplasia**
  - Marrow is remarkable in its capacity to undergo rapid hyperplasia
    - Lymphoid hyperplasia
    - Secondary polycytemia
Liver Regeneration

- Proliferation of remaining hepatocytes
- Repopulation from progenitor cells
Physiologic hyperplasia

https://clinicalgate.com/normal-bone-marrow-histology/

Pathologic hyperplasia

• Inappropriate actions of hormones or growth factors acting on target cells

  > Endometrial hyperplasia
    - Imbalance of estrogen & progesterone
    - Pituitary gland or ovarian abnormalities

  > Benign prostatic hyperplasia
    - Excessive androgens hormone
Endometrial hyperplasia
Benign prostatic hyperplasia

https://webpath.med.utah.edu/HISTHTML/NORMAL/NORM078.html

https://www.auanet.org/education/auauniversity
Pathologic hyperplasia

- **Viral infections**
  - Such as papillomaviruses
  - Viral wart” or “Verruca vulgaris”

https://www.dentistry.uiowa.edu/oprm-verruca-vulgaris

Atrophy

- Shrinkage in the size of the cell by the loss of cell substance
- The mechanisms consist of decreased protein synthesis and increased protein degradation in cells

http://vet.uga.edu
Mechanisms of atrophy

- Reduced metabolic activity
- Autophagy/Ubiquitin-proteasome pathway

- Decreased protein synthesis
- Increased protein degradation
Nabavi et al (2018)
Physiologic atrophy

➢ Loss of hormone stimulation in menopause
➢ Aging atrophy
➢ Embryogenesis

Pathologic atrophy

➢ Atrophy of disuse
➢ Diminished blood supply
➢ Denervation atrophy
➢ Inadequate nutrition
➢ Pressure atrophy
➢ Loss of endocrine stimulation
Brain Atrophy

A

B

Metaplasia is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type. Able to withstand the adverse environment. The most common epithelial metaplasia is columnar to squamous. Epithelial metaplasia. Connective tissue metaplasia.
Cause of metaplasia

- Chronic inflammation
- Chronic irritation
- Nutrition depletion
- Trauma
Squamous metaplasia of bronchus

Squamous metaplasia of endocervix

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Epithelial metaplasia (squamous metaplasia)

- Stratified squamous metaplasia of urinary bladder
- Stratified squamous metaplasia of gall bladder

Epithelial metaplasia (columnar/glandular metaplasia)

- Simple columnar metaplasia (with mucus secreting) of lower respiratory mucosa
- Glandular metaplasia of esophagus
Glandular metaplasia of esophagus (Barrett esophagus)

https://www.proteinatlas.org/learn/dictionary/rnormal/esophagus

Robbins and Cotran pathologic basis of disease. 9th edition, 2015
Connective tissue metaplasia

- Alteration of stem cell or undifferentiated mesenchymal cells

Bony (Osseous) metaplasia at skin
Mechanism of metaplasia

Growth factor, cytokines, extracellular matrix components

Stem cells / Undifferentiated mesenchymal cells

Phenotype alteration
Dysplasia

➢ Precancerous lesion
➢ Pleomorphism
➢ Disorientation

➢ Hyperchromatic nuclease
➢ No invasion
➢ Reversible process
NORMAL CELL (homeostasis)

ADAPTATION

Stress
Injurious stimulus

Inability to adapt

CELL INJURY

Severe, progressive

IRREVERSIBLE INJURY

NECROSIS
CELL DEATH
APOPTOSIS

REVERSIBLE INJURY

Mild, transient
The diagram illustrates the relationship between the duration of injury and the effect on cell function. It categorizes the effects into reversible and irreversible cell injury.

- **Reversible cell injury**
  - Cell function
  - Biochemical alterations
    - Cell death

- **Irreversible cell injury**
  - Ultrastructural changes
  - Light microscopic changes
  - Gross morphologic changes

The graph shows how different durations of injury lead to various effects on cell function, progressing from reversible to irreversible stages with increasing duration.
Cell Injury

- **Reversible cell injury** >> early stages or mild forms of injury the functional and morphologic changes are reversible if the damaging stimulus is removed

- **Irreversible cell injury** >> pathologic changes that are permanent and cause cell death, they cannot be reversed to normal state

- Reversible/ Irreversible injury depend on the type, severity and duration of injury

- **Cell death** >> the result of irreversible injury
Causes of Cell Injury:

1. Hypoxia (loss of aerobic oxidative respiration)
2. Ischemia (loss of blood supply)
3. Physical agents (temperature, trauma, radiation)
4. Chemical agents and drugs
5. Infectious agents (virus, bacteria, fungi, and protozoans)
6. Immunologic reactions (autoimmune reactions)
7. Genetic derangements
8. Nutritional imbalances
9. Aging
Important aspects of cell injury

1. Wide-spread effect of changes
2. Time factor
3. Cell susceptibility to injury
4. Types of injury, duration and its severity
<table>
<thead>
<tr>
<th>Susceptibility of Cells to Ischemic Necrosis</th>
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</thead>
<tbody>
<tr>
<td>High</td>
</tr>
<tr>
<td>Neurons (3-4 min)</td>
</tr>
<tr>
<td>Intermediate</td>
</tr>
<tr>
<td>Myocardium, hepatocytes, renal epithelium (30 min-2hr)</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Fibroblasts, epidermis, skeletal muscle (many hours)</td>
</tr>
</tbody>
</table>
1. ATP depletion
2. Loss of intracellular calcium homeostasis
3. Oxygen and oxygen-derived free radicals/reactive oxygen species
4. Defects in membrane permeability
5. Irreversible mitochondrial damage: cause apoptotic cell death
FIGURE 1–16 The principal mechanisms of cell injury, and their biochemical and functional effects, are shown. These are described in detail in the text.

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1. ATP depletion

*Figure 2-17* Functional and morphologic consequences of decreased intracellular adenosine triphosphate (ATP) during cell injury. The morphologic changes shown here are indicative of reversible cell injury. Further depletion of ATP results in cell death, typically by necrosis. ER, Endoplasmic reticulum.
2. Loss of intracellular calcium

Homeostasis

Mitochondrial damage
3. Oxygen and oxygen-derived free radicals

A. FREE RADICAL GENERATION

- Inflammation
- Radiation
- Oxygen toxicity
- Chemicals
- Reperfusion injury

O$_2$

- P-450 oxidase
- NADPH oxidase

ER

Mitochondrion

- Respiratory chain enzymes
- Cytosolic enzymes

Peroxisome

- Oxidase

Reactive oxygen species:
- O$_2^-$, H$_2$O$_2$, OH$^-$

Reactive oxygen species:
- O$_2^-$, H$_2$O$_2$, OH$^-$

Membrane lipid peroxidation

All membranes
- Vitamins E and A
- β-carotene

B. CELL INJURY BY FREE RADICALS

DNA fragmentation

Protein cross-linking and fragmentation

C. NEUTRALIZATION OF FREE RADICALS – NO CELL INJURY

Mitochondria
- SOD
- Glutathione peroxidase
- Ferritin
- Ceruloplasmin

Cytosol
- SOD
- Glutathione peroxidase
- Vitamin C
- Glutathione peroxidase

Peroxisomes
- Catalase

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FREE RADICALS AND DISEASE

• Some examples are:-
  • oxygen toxicity, ischaemia/reperfusion injury, radiation injury (hydrolyses \( \text{H}_2\text{O} \) to \( \text{OH} \) & \( \text{H} \)), metabolism of drugs, toxins, pollutants (eg Paracetamol to reactive metabolite; \( \text{CCl}_4 \) to \( \text{CCl}_3 \), cigarette smoke)
  
  • leukocyte killing of bacteria or in non-bacterial inflammations, release of iron in haemorrhages enhances oxidative stress (important in CNS)
  
  • lipid peroxidation of low-density lipoproteins in atherosclerosis, cancer production (damage to DNA), aging

• Therapies for combating oxidative stress are available for prevention or treatment with antioxidants and/or free-radical scavengers.
- Lipid peroxidation leading to membrane damage
- Protein damage
- DNA damage
Ischemic and Hypoxic Injury
1. Ischemia tends to injure tissues faster than does hypoxia
2. If O$_2$ is restored, all of the disturbances are reversible
3. If ischemia persists, irreversible injury and necrosis ensue

Ischemia-Reperfusion Injury
1. Damage may be initiated during re-oxygenation by increased generation of oxygen free radicals
2. Reactive oxygen species can further promote the MPT may lead to cell death
3. Ischemic injury is associated with inflammation; production of cytokines; increased expression of adhesion molecules
4. Activation of Complement pathway

Nature Reviews Cardiology (2014)
4. Defects in membrane permeability

- Plasma membrane
- Mitochondrial membrane
- Lysosomal membrane
5. Mitochondrial Damage

• 3 major consequences:
  
  • Mitochondrial permeability transition (MPT) pore opens \( \rightarrow \) loss of mitochondrial membrane potential \( \rightarrow \) decreased oxidative phosphorylation / decreased ATP
  
  • Production of reactive oxygen species
  
  • Leakage of pro-apoptotic proteins
Reversible Vs. Irreversible Injury

**Reversible Cell Injury**
- Injury
- Swelling of endoplasmic reticulum and mitochondria
- Recovery

**Irreversible Cell Necrosis**
- Death
- Fragmentation of cell membrane and nucleus
- Necrosis
  - Swelling of endoplasmic reticulum and loss of ribosomes
  - Lysosome rupture
  - Membrane blebs
  - Myelin figures
  - Swollen mitochondria with amorphous densities

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<table>
<thead>
<tr>
<th>Organelles</th>
<th>Reversible injury</th>
<th>Irreversible injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma membrane:</td>
<td>loss of microvilli, blebbing</td>
<td>disruption</td>
</tr>
<tr>
<td>Mitochondria:</td>
<td>modest swelling</td>
<td>massive swelling, leakage</td>
</tr>
<tr>
<td>Endoplasmic reticulum</td>
<td>dilation with detachment of polysomes</td>
<td>extensive disruption and fragmentation, myelin figures</td>
</tr>
<tr>
<td>Nuclease</td>
<td>Clumping Chromatin</td>
<td>Nuclear condensation, fragmentation, lysis</td>
</tr>
<tr>
<td>Lysosome</td>
<td>Lysosome swelling</td>
<td>Lysosome rupture</td>
</tr>
</tbody>
</table>
A. Normal kidney
B. Reversible changes
C. Dying Cell
Reversible injury
Hydropic Change

- Early signs of cellular degeneration in response to injury.

- The accumulation of water in the tubular cells is usually due to hypoxia of the tissue with a resultant decrease in aerobic respiration in the mitochondria and a decreased production ATP.
The lipid accumulates when lipoprotein transport is disrupted and/or when fatty acids accumulate.

Alcohol, the most common cause, is a hepatotoxin that interferes with mitochondrial and microsomal function in hepatocytes, leading to an accumulation of lipid.
Mallory Bodies

- Cytoplasmic organelle damage leads to a variety of injury patterns, most of which are best seen by electron microscopy.

- Mallory bodies (the red globular material) composed of cytoskeletal filaments in liver cells chronically damaged from alcoholism.
Neurofibrillary Tangles

• Here are neurofibrillary tangles in neurons of a patient with Alzheimer's disease.

• The cytoskeletal filaments are grouped together in the elongated pink tangles.
Lewy bodies

- The intracytoplasmic, eosinophilic inclusions with a clear halo around.

- **Lewy bodies** are abnormal aggregates of protein that develop inside nerve cells.
Cell Death

• Death of cells occurs in two ways:
  
  • **Necrosis**—(irreversible injury) changes produced by enzymatic digestion of dead cellular elements
  
  • **Apoptosis**—vital process that helps eliminate unwanted cells—an internally programmed series of events effected by dedicated gene products
1. **Apoptosis**

- Greek language, which originally refers to falling of leaves from trees in the autumn
- “Programmed cell death”

**Physiologic:**
1. The programmed destruction of cells during embrogenesis
2. Hormone-dependent involution in the adult
3. Cell deletion in proliferating cell populations
4. Elimination of potentially harmful self-reactive lymphocytes

**Pathologic:**
1. Injurious stimuli – radiation, cytotoxic chemotherapy
2. Viral diseases
3. Pathologic atrophy in parenchymal organs after duct obstruction
4. Cell death in tumors
Apoptosis (Physiology)

- In the human body ~ 100,000 cells are produced every second by mitosis and a similar number die by apoptosis.

- Development and morphogenesis
  - During limb formation separate digits evolve
  - Ablation of cells no longer needed (tadpole)

- Homeostasis
  - Immune system
  - >95% T and B cells die during maturation (negative selection)

- Deletion of damaged/dangerous cells
Mechanisms of Cell Death

- O₂ supply, Toxins, Radiation
- Survival signals, DNA, protein damage

Mitochondrial damage or dysfunction
- ATP generation, Production of ROS
- Leakage of mitochondrial proteins

Multiple cellular abnormalities
- Necrosis
- Apoptosis

Pro-apoptotic proteins, Anti-apoptotic proteins

Robins and Cotrans Pathologic Basis of Disease
Morphological Forms of Programmed Cell Death

Type I = Apoptosis
Type II = Autophagic Cell Death
Type III = Non-lysosomnal

Figure 2-23 Mechanisms of apoptosis. The two pathways of apoptosis differ in their induction and regulation, and both culminate in the activation of caspases. In the mitochondrial pathway, proteins of the BCL2 family, which regulate mitochondrial permeability, become imbalanced and leakage of various substances from mitochondria leads to caspase activation. In death receptor pathway, signals from plasma membrane receptors lead to the assembly of adaptor proteins into a “death-including signaling complex,” which activates caspases, and the end result is the same.
Two pathways

- Death receptor (left)
- Mitochondrial (right)
- Both Converge
  - Caspase 3 activation
- Then branch causing eventual cell death
Figure 2-24: The intrinsic (mitochondrial) pathway of apoptosis. **A,** Cell viability is maintained by the induction of anti-apoptotic proteins such as BCL2 by survival signals. These proteins maintain the integrity of mitochondrial membranes and prevent leakage of mitochondrial proteins. **B,** Loss of survival signals, DNA damage, and other insults activate sensors that antagonize the anti-apoptotic proteins and activate the pro-apoptotic proteins BAX and BAK, which form channels in the mitochondrial membrane. The subsequent leakage of cytochrome c (and other proteins, not shown) leads to caspase activation and apoptosis.
Figure 2-25 The extrinsic (death receptor initiated) pathway of apoptosis, illustrated by the events following Fas engagement. FAAD, Fas-associated death domain; FasL, Fas ligand.
Role of mitochondria in apoptosis

Disrupts the normal function of the anti-apoptotic bcl-2 proteins

the formation of pores in the mitochondria

the release of cytochrome C and other pro-apoptotic molecules + Apaf-1

Apoptosome

Activation of the caspase cascade
Caspases and Apoptosis

• The hallmarks of apoptosis is the cleavage of chromosomal DNA into nucleosomal units

• The caspases play an important role in this process by activating DNases, inhibiting DNA repair enzymes, breaking down structural proteins in the nucleus
Autophagy

- A regulated process for the removal of damaged proteins and organelles.
- Stimulated by environmental factors such as starvation.
- The removal of damaged cellular components, especially damaged mitochondria, might decrease the level of reactive oxygen species (ROS).

\[\text{Autophagy} \uparrow \]

\[\text{Oncogenes (Bcl2, Akt-1)} \rightarrow \text{Autophagy} \]

\[\text{Tumour suppressors (p53, Pten)} \rightarrow \text{Autophagy} \]

\[\uparrow \text{Removal of damaged proteins/organelles} \]

\[\downarrow \text{Senescence} \rightarrow \downarrow \text{ROS} \rightarrow \downarrow \text{Genomic instability} \]

\[\downarrow \text{Lifespan} \rightarrow \uparrow \text{Cancer} \]

\[\downarrow \text{reduce genomic instability or forestall cellular senescence} \]

\[\downarrow \text{reduce the incidence of cancer and prolong lifespan} \]
Autophagy

- Autophagy involves sequestration of cellular organelles into cytoplasmic autophagic vacuoles (autophagosomes) that fuse with lysosomes.
- Autophagy is an adaptive response that is enhanced during nutrient deprivation, allowing the cell to cannibalize itself.
- Autophagosome formation is regulated by more than a dozen proteins.
- Dysregulation of autophagy occurs in many diseases.
- Autophagy plays a role in host defense against certain microbes.
Figure 2-28  Autophagy. Cellular stresses, such as nutrient deprivation, activate an autophagy pathway that proceeds through several phases (initiation, nucleation, and elongation of isolation membrane) and eventually creates double-membrane-bound vacuoles (autophagosome) in which cytoplasmic materials including organelles are sequestered and then degraded following fusion of the vesicles with lysosomes. In the final stage, the digested materials are released for recycling of metabolites. See text for details. (Modified from Choi, AMK, Ryter S, Levine B: Autophagy in human health and disease. N Engl J Med 368:651, 2013.)
Autophagy involves:

• Formation of a double membrane within the cell which envelops the materials to be degraded into a vesicle called an **autophagosome**.

• The autophagosome then fuses with a lysosome forming an **autolysosome** whose hydrolytic enzymes degrade the materials.
• The confocal microscopy image shows stable HeLa cells expressing EGFP-LC3.
• An autophagy-inducing small molecule increases the formation of autophagosomes (green punctate structures) in these cells.

2. **Necrosis**

- The most common pattern of cell death
- Two principal processes influence the changes of necrosis:
  1. Enzymatic digestion of the cell
  2. Denaturation of proteins
- These enzymes are derived either from dying cells themselves = *autolysis*
- Lysosomal enzymes of leukocytes, referred to as = *heterolysis*
- **Causes of necrosis:**
  - Mechanical
  - Chemical
  - Physical
  - Infectious agents
  - Hypoxia/anoxia
  - Ischemia
Mechanisms of Cell Death

1. \(O_2\) supply, Toxins, Radiation

2. Survival signals, DNA, protein damage

3. Mitochondrial damage or dysfunction

   - \(\downarrow\) ATP generation
   - \(\uparrow\) Production of ROS
   - Multiple cellular abnormalities
      - \(\downarrow\) Necrosis
      - \(\uparrow\) Apoptosis

Robins and Cotrans Pathologic Basis of Disease
Features of Cell Death

- Reversible injury
  - Recovery
  - Normal cell

- Progressive injury
  - Membrane blebs
  - Myelin figure
  - Swelling of endoplasmic reticulum and mitochondria
  - Myelin figures
  - Breakdown of plasma membrane, organelles, and nucleus; leakage of contents
- Necrosis
  - Amorphous densities in mitochondria
  - Inflammation

- Apoptosis
  - Condensation of chromatin
  - Membrane blebs
  - Cellular fragmentation
  - Apoptotic body
  - Phagocyte
  - Phagocytosis of apoptotic cells and fragments
<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 (round nucleosome)</td>
</tr>
<tr>
<td>Plasma membrane</td>
<td>Disrupted</td>
<td>Intact</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>Pathologic</td>
<td>Physiologic and Pathologic</td>
</tr>
</tbody>
</table>
Patterns of Necrosis

- **Coagulative necrosis**: ex. Myocardial infarction
- **Liquefactive necrosis**: ex. Cerebrum in fraction
- **Caseous necrosis**: ex. Tuberculosis lesion
- **Fat necrosis**: ex. Pancreatitis
- **Gangrenous necrosis**: ex. Necrosis of distal limbs
- **Fibrinoid necrosis**: ex. Polyarteritis nodosa
Types of infarct

- **Red (hemorrhagic) infarct**
  - Venous occlusion/ congestion ex. torsion
  - Loose tissue where hemorrhage can occur and blood can collect ex. Lung
  - Tissues with dual blood supply ex. Lung, small intestine
  - When flow is re-established ex. Angioplasty

- **White infarct**
  - Arterial occlusion
  - Solid tissue where hemorrhage limited
  - Tissues with single blood supply ex. Kidney, spleen, heart, retina, brain, liver
Coagulative necrosis

➢ Most common pattern of necrosis
➢ Results from sudden severe ischemia (is encountered mostly in solid organs: ex. kidney, heart, spleen, adrenal gland
➢ Preservation of the basic outline of coagulated cells for several day
➢ Intracellular acidosis which denaturates structural proteins and enzymes
➢ Macroscopic appearance: consistency, yellowish colour, dry appearance
➢ Microscopic appearance: Preservation of cell outlines, Loss of nuclei
Liquefactive necrosis

- The dead cells undergo disintegration and affected tissue is liquefied
- Rapid action of hydrolytic enzymes
- Characteristic of ischemic necrosis of brain, pancreas also common in bacterial lesions
- Gross morphology - necrotic area becomes very soft and fluidly
- Microscopic – Loss of architecture, cystic space
Caseous necrosis

- Combination of coagulative and liquefactive necrosis
- Cheese-like lesion
- Common in tuberculosis
- **Gross morphology:** caseous necrosis appears grossly as soft, friable, whitish-gray debris
- **Microscopic:** caseous necrosis appears as amorphous eosinophilic material, cell debris, granulomatosus inflammatory reaction (epithelioid histiocytes, giant cells of Langhans type, lymphocytes
Fat necrosis

➢ Two type:
  - **Traumatic fat necrosis**: Following severe injury tissue with high fat content ex. Breast
  - **Enzymatic fat necrosis**:

    Necrosis in adipose tissue due to *action of activated lipases* ex. *acute pancreatic necrosis* by pancreatic enzymes (proteolytic and lipolytic)

    Fatty acids then complex with calcium to create calcium soaps

➢ **Gross morphology**: opaque and chalky white or yellowish

➢ **Microscopic**: ghost cells anucleate cells composed of amorphous granular debris, calcification
Fat necrosis

http://www.forensicpathologyonline.com
Gangrenous necrosis

- Necrosis (secondary to ischemia) usually with superimposed infection
- There are three major types of gangrene:
  - **Dry gangrene**
    - Necrotic tissue appears black and dry, occurs in extremities
  - **Wet gangrene**
    - Severe bacterial infection, extremities and internal organs, tissue swollen, reddish-black
  - **Gas gangrene**
    - Wound infection caused by *Clostridium perfringens*, tissue destruction, gas production by fermentative action of bacteria
    - **crepitus**: A sound that can be detected by palpation of necrotic tissues

Pic from V.G.R diabetes

http://www.uark.edu/
Fibrinoid necrosis

- Usually in immune reactions complexes are deposited in the wall of arteries
- Connective tissue necrosis
- Ag-Ab complex deposit in arterial wall
- Loss of normal structure of collagen fibres
- Circumferential bright pink area of necrosis with protein deposit and inflammation

Polyarteritis nodosa
Intracellular Accumulations

Some circumstances cells may accumulate abnormal amounts of various substances harmless or associated with varying degrees of injury.

Mechanisms of intracellular accumulation:

1. Abnormal metabolism, as in fatty change in the liver.
2. Mutations causing alterations in protein folding and transport, so that defective molecules accumulate intracellularly.
3. Deficiency of critical enzymes responsible for breaking down certain compounds, causing substrates to accumulate in lysosomes, as in lysosomal storage diseases.
4. **Inability to degrade phagocytosed particles**, as in carbon pigment accumulation.
Types of Accumulations

1. Lipids
- Steatosis and fatty change (LIVER, HEART, MUSCLE, KIDNEY)
- Cholesterol and cholesterol esters (atherosclerosis, xanthomas, inflammation and necrosis, cholesterolosis

The large, clear lipid droplets that fill the cytoplasm of many hepatocytes
Types of Accumulations

2. Proteins
- Reabsorption droplets in kidneys
- Synthesis of excessive amounts
- Defects in protein folding may lead to “unfolded protein response”

3. Glycogen
- Abnormalities in the metabolism of either glucose or glycogen
- Glycogen storage diseases
- Diabetes mellitus

4. Pigments
4.1 Exogenous pigments (carbon, coal dust) anthracosis
4.2 Endogenous pigments

- **Lipofuscin**
  - "wear-and-tear pigment", complexes of lipid and protein, marker of past free radical injury, intralysosomal location
  - insoluble brownish-yellow granular (heart, liver, brain) as a function of age or atrophy
Types of Accumulations

- **Melanin**
  - An endogenous, brown-black pigment, synthesized by melanocytes located in the epidermis
  - Melanosis

- **Hemosiderin**
  - Hemoglobin-derived granular pigment that is golden yellow to brown
  - Local or systemic excess of iron ex. *hereditary hemochromatosis*
  - Hemosiderosis
Pathologic Calcification

• A common process in a wide variety of disease states
• Abnormal deposition of calcium salts, smaller amounts of iron, magnesium, and other minerals

1. Dystrophic Calcification
   - Deposition of calcium and other minerals in dead tissue
   - Normal serum Ca++ levels
     - Initiation phase: precipitate of calcium phosphate begin to accumulation intracellularly in mitochondria
     - extracellular in membrane- bound vesicle
     - Propagation phase: mineral deposited form the mineral cristals
Bacterial Endocarditis

Dystrophic Calcification

Mönckeberg's sclerosis
2. Metastatic Calcification

- Calcium deposits in normal tissue in hypercalcemic states
- Common organs: kidney, lung, stomach, blood vessel, cornea,

Hypercalcemia - increased secretion of PTH
- destruction of bone tissue
- vitamin D-related disorders
- renal failure
- cancer

Alveolar walls from a hypercalcemia patient with breast cancer
Any Questions?