Ischaemia & Infarction

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Evolution of Cell Injury

Figure 1-7 Stages in the evolution of cell injury and death.

- INJURIOUS STIMULUS
- REVERSIBLE CELL INJURY
- Point of irreversibility
- NECROSIS
- APOPTOSIS

Reversible stage?
Cellular Reaction To Injury

Adaption to Environmental Stress

- **Hypertrophy** – increase in organ or tissue size due to increase in cell size.
- **Hyperplasia** – increase in organ size or tissue due to increase in cell number.
- **Aplasia** – failure in cell production resulting in agenesis (in-utero) or permanent loss of precursor cells (e.g. bone marrow failure).
- **Hypoplasia** – decrease in cell production (less extreme than aplasia).
- **Atrophy** – decrease in organ or tissue size from decrease in mass of preexisting cells.
- **Metaplasia** – replacement of one differentiated tissue/cells by another.
E.g. of Cell Adaptation
E.g. of Metaplasia

Columnar metaplasia of esophagus

Stratified squamous cells

Columnar cells with glands
Hypoxic Cell Injury

- Hypoxic cell injury results from several mechanisms
  - Ischaemia
  - Anemia
  - Carbon monoxide poisoning
  - Decreased perfusion of tissues by oxygen-carrying blood (e.g. cardiac failure, hypotensive shock)
  - Poor oxygenation of blood (e.g. pulmonary diseases)
Stages in hypoxic cell injury

**Early Stage**

- Decreased ATP availability leads to:
  1. Na-K-ATPase failure
  2. Disaggregation of ribosomes
  3. Stimulation of phosphofructokinase

**Late Stage**

- Membrane damage: plasma, lysosomal & other organelle membranes, loss of membrane phospholipids.

**End Stage**

- Irreversible damage to cell membranes.
- Loss of intracellular enzymes & proteins into circulation.

**Decreased oxidative phosphorylation & ATP synthesis**

- 1. Increased intracellular Na & H2O, decreased intracellular K.
- Visible as cellular swelling & swelling of organelles
- 2. Leads to failure of protein synthesis
- 3. Increased glycolysis, accumulation of lactate, decreased intracellular pH

**Reversible signs:**
- Myelene figures – whorl like structures (damaged membranes)
- Cell blebs – cell surface deformity (dysfunctional cellular cytoskeleton)

**Irreversible signs:**
- Ca influx, calcification of mitochondria & cell death
- 3-5 mins for neurons, 1-2 hrs for myocardial & liver cells. Skeletal muscles longer.
Molecular Sites of Cell Injury

- **Injurious Stimulus**
  - ATP decrease
  - Membrane damage
    - Mitochondria: Loss of energy-dependent cellular functions
    - Lysosome: Cell death, Enzymatic digestion of cellular components
    - Plasma membrane: Loss of cellular contents
  - Intracellular Ca$^{2+}$
  - Reactive oxygen species: O$_2^-$, H$_2$O$_2$, OH$^-$
  - Protein breakdown, DNA damage
Consequences of decreased intracellular ATP
Consequences of increased intracellular Ca
Reversible & Irreversible Cell Injury

NORMAL

Normal cell

Injury

Swelling of endoplasmic reticulum and mitochondria

Clumping of chromatin

Recovery

REVERSIBLE CELL INJURY

Death

Swelling of endoplasmic reticulum and loss of ribosomes

Lysosome rupture

Membrane blebs

Myelin figures

Irreversible cell injury → necrosis

Fragmentation of cell membrane and nucleus

Necrosis

Nuclear condensation

Swollen mitochondria with amorphous densities
Where is the point of no return?
**Infarction**

- **Definition:** Tissue necrosis due to ischaemia.
- **In the myocardium – coagulative necrosis**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Necrosis</th>
<th>Apoptosis</th>
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</thead>
<tbody>
<tr>
<td>Cell size</td>
<td>Enlarged (swelling)</td>
<td>Reduced (shrinkage)</td>
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<tr>
<td>Nucleus</td>
<td>Pyknosis → karyorrhexis → karyolysis</td>
<td>Fragmentation into nucleosome size fragments</td>
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<tr>
<td>Plasma membrane</td>
<td>Disrupted</td>
<td>Intact; altered structure, especially orientation of lipids</td>
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<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>Invariably pathologic (culmination of irreversible cell injury)</td>
<td>Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage</td>
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# Types of Necrosis

<table>
<thead>
<tr>
<th>Types</th>
<th>Mechanism</th>
<th>Pathological Changes</th>
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| Coagulative necrosis | Results from Ischaemia  
Seen in organs with end arteries (e.g. heart, kidneys) | General architecture preserved. Nuclear changes, increased cytoplasmic binding of acidophylic dyes |
| Liquefactive necrosis | Enzymatic liquefaction of necrotic tissue. Often in CNS. Hypoxia/ischaemia common cause. Seen in areas of bacterial infection | Necrotic tissue soft & liquefied |
| Caseous necrosis | Shares features of coagulation & liquefactive necrosis. TB good example. | Architecture not preserved. Soft cheesy. Histology – amorphous with increased affinity of acidophilic dyes |
| Grangrenous necrosis | Ischaemic to lower limb or bowel | Dry or wet gangrene depending on tissue involved |
| Fibrinoid necrosis | Deposition of fibrin-like proteinaceous material in walls of arteries. Often seen in immune mediated vasculitis. | Smudgy pinky appearance in vascular walls. Actual necrosis may or may not be present |
| Fat necrosis | Autodigestion of pancreatic parenchyma from pancreatic enzymes. Trauma to fat cells | Necrotic fat cells. Acute inflammation, haemorrhage, Ca soap formation, clusterin of lipid-laden macrophages (in pancreas) |
Coagulative Necrosis

Normal myocardial fibers

Coagulative necrosis of myocardial fibers

Upper 2/3 shows: strongly eosinophilic anucleate myocardial fibres. Leucocytes in interstium (early rxn to necrotic material).
Loss of nuclei, clumping of cytoplasm. Basic outline of glomerular & tubular architecture preserved.
Cerebral Infarct

- 4 major causes hypoxic injury to brain.
- **Thrombosis** – involves cerebral arteries from atherosclerosis.
- **Embolism** – middle cerebral artery is more prone. Embolus from cardiac mural thrombi, vegetations (infective endocarditis), tumor cells, air bubbles or fat droplets (from fractures).
- **Hypotension** – involves “watershed” areas & deep layers of the cortex. *What are “watershed” areas?*
- **Hypertension** – lacunae (small pits) infarcts common (multiple cystic infarcts, prominent in basal ganglia). Due to arteriolar occlusion in hypertensive patients.
Myocardial Infarct

General Considerations

- Results from partial or complete interruption of arterial blood flow to the myocardium.
- Most occurs because of atherosclerotic plaque within one or more coronary arteries.
- Ischaemia may be clinically silent, manifest as angina pectoris or MI.
Types of MI

Transmural: infarct localised to anatomical area supplied by affected artery.

Subendocardial: necrosis of subendocardium
the myocardial fibre outlines can be recognised and most fibres lack nuclei

viable and degenerate neutrophils
Recent and healed myocardial infarction with hypertrophy

irregular areas of virtually acellular, dense connective tissue (scar tissue)
The mounted specimen of the brain shows marked swelling of the left cerebral hemisphere. Thrombus can be seen occluding the left internal carotid artery. This appearance is consistent with that of an extremely recent (10 hours) cerebral infarct.

Ref: UTAS interactive Pathology CD
Gross pathology - magnified view of thrombus and uncal herniation

Thrombus

Herniation
The photograph shows a coronal slice of brain. An old cerebral infarct is present in the territory of the left middle cerebral artery represented by a cystic space surrounded by gliosis.
thin pink ribbon overlying part of the infarced tissue

amorphous, granular, pink material in which the ghost outlines of some necrotic neurones can be identified
amorphous, granular, pink material in which the ghost outlines of some necrotic neurones can be identified

compound granular corpuscle
Kidney showing 2 areas of recent renal infarction. At the upper pole is a well-circumscribed geographic area of hyperaemia admixed with creamy yellow tissue. The cut surface shows a necrotic tissue with a focally hyperaemic border. *An impacted embolus is visible in* a branch of the renal artery supplying this area. In the lower pole is a small triangular shaped area of medullary congestion probably related to ischaemic damage.
Renal infarct

- viable and degenerate neutrophil polymorphs
- ghost outlines of tubules and glomeruli
Renal infarct

ghost outlines of tubules and glomeruli are recognised
Gross Pathology

Most of the pulmonary artery branches contain emboli. The apical segment of the lower lobe and most of the middle lobe show evidence of pulmonary infarction. These infarcts are haemorrhagic (dark brown to black in colour) and the surrounding pulmonary parenchyma is consolidated. Compare this parenchyma with that of the upper lobe which is normal.
most of the pulmonary artery branches contain emboli

the apical segment of the lower lobe and most of the middle lobe show evidence of pulmonary infarction.

Pulmonary embolism and infarction

1. history 2. macro 3. slide 4. micro 5. comment
Pulmonary embolism and infarction

*thromboembolus*. It has the same internal structure as seen in recent thrombus.
Pulmonary embolism and infarction

the pulmonary parenchyma is intensely congested with intra-alveolar oedema and haemorrhage
Pulmonary embolism and infarction

The zone of infarction shows well developed coagulative necrosis.
Laboratory Diagnosis

- Serum: Enzyme assays – e.g. AST, LDH, CK
- Serum: protein markers – e.g. Troponin I & T, myoglobin
- Tissue – biopsy (post mortem).
- CT scan – CVA
- CT angiogram – pulmonary embolism
- Ventilation-Perfusion scan – pulmonary angiogram
- USS – kidneys.
Study Guides

• List the cellular adaptive mechanisms to environmental stress & give an example for each type.

• Agents of cellular injury are generally classified as: hypoxic injury, free radical injury & chemical injury. Describe the mechanism in each type using an example in each.

• Describe the light microscopic features of necrosis.

• Compare & contrast reversible & irreversible cellular injury, including microscopic features.

• Define the following: pyknosis, karyorrhexis & karyolysis in the setting of coagulative necrosis.
END

References
Robins Pathologic Basis of Disease 6th & 7th Ed
Images from: UTAS interactive Pathology CD

Download PDF copy of notes at:
www.pathologyatsmhs.wordpress.com