Cell Injury

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Cells are stressed so severely that they are no longer able to adapt

Exposed to inherently damaging agents.
Causes

- Hypoxia
- Physical agents
- Chemical agents and drugs
- Infectious agents
- Immunological reactions
- Genetic defects
- Nutritional imbalances
Hypoxia

Due to

- Ischaemia (loss of blood supply)
- Inadequate oxygenation of blood (cardio respiratory failure)
- Depletion of oxygen carrying capacity of blood (anaemia)
- Poisoning of oxidative enzymes (CO poisoning)
Physical agents

- **Trauma** - abrasion, laceration, contusion, haemorrhage, fracture, crush injury
- **Hyperthermia** - heat stroke, heat cramps, heat exhaustion
- **Hypothermia** - generalized or localized
- **Changes in atmospheric pressure** - Caisson disease
- **Electric shock** - burns / ventricular arrhythmia
- **Thermal injury** - various degrees of burns
Chemical agents and drugs

Virtually any chemical agent can cause cell injury.

- Injury due to poisons (toxic substances-Ar, Cy, Hg).
- Air pollutants, insecticides, CO, asbestos, alcohol.

Can cause: Metabolic effects, corrosive effects, mutagenic effects
One or two general mechanisms:

1. Some chemicals act directly by combining with a critical molecular component or cellular organelle.

2. Many other toxic chemicals are not intrinsically biologically active, must be first converted to reactive toxic metabolites, which then act on target cells.
Radiation injury

- Electro magnetic waves (X-rays and gamma rays)
- High-energy neutrons and charged particles (alpha and beta particles and protons)
- Cause damage to DNA / cell membranes/ cytoplasmic alterations/ vascular damage.
- Target effect
- Indirect effect (after a latent period)
Infectious agents

- Bacteria, viruses, fungi, parasites, rickettsiae
- Insects, snakes, spiders, jelly fish etc.,

Injury is due to-

- Intracellular multiplication
- Competition for essential nutrients
- Production of toxic substances
- Hypersensitivity reactions
Nutritional imbalances

- Inadequate intake of food, anorexia
- Malabsorption
- Protein – calorie malnutrition
- Excessive intake of lipids (dietary excess)

Other Causes

- Genetic (Downs, Sickle cell),
- Immunologic (anaphylactic reaction to foreign protein).
Pathogenesis of cell injury

- No common pathway.
- Important mechanisms involve:
  - Hypoxia / ischaemia / metabolic / toxins / infective and target cell membranes / mitochondria / cytoskeleton / cellular DNA
- Can be sublethal or lethal. Sublethal- reversible
- Lethal- nonreversible. Cell death is primarily recognized by changes in the nucleus. **
Intracellular damage

Four intracellular systems are particularly vulnerable:
1. Maintenance of the integrity of cell membranes
2. Aerobic respiration
3. Protein synthesis
4. Preservation of the integrity of the genetic apparatus of the cell.
Common biochemical themes

**Important in the mediation of cell injury:**
- ATP depletion.
- Irreversible mitochondrial damage
- Intracellular calcium and loss of calcium homeostasis
- Defects in membrane permeability
- Oxygen and oxygen-derived free radicals
Calcium Influx

Injurious Agent

Cytosolic Ca++

Phospholipase

Phospholipids

Membranes Cytoskeleton

Protease

ATPase

Endonuclease

ATP
Forms and patterns of cell injury

- Patterns of reversible acute cell injury
- Patterns of cell death after irreversible injury (necrosis)
- Pattern of ‘cell death by suicide’ called apoptosis
Reversible cell injury

2 patterns: cellular swelling and fatty change.

- Cellular swelling: also called hydropic change or vacuolar degeneration.
- Appears whenever cells are incapable of maintaining ionic and fluid homeostasis.
- First manifestation of almost all forms of cell injury.
- When all cells in an organ are affected, there is pallor, increased weight and increased turgor.
Morphology

- Small clear vacuoles seen in the cytoplasm
- Plasma membrane alterations: blebbing, blunting or distortion of microvilli:
- Mitochondrial and endoplasmic reticulum dilation
- Nuclear alterations.
Reversible Cell Injury

1. Cell injury with loss of cell function and structural changes occurs.
2. The cell can revert to normal if the stress or injury is removed.
Fatty change

- Occurring in hypoxic injury and various forms of toxic or metabolic injury
- Lipid vacuoles in the cytoplasm.
- Principally seen in cells participating in fat metabolism (hepatocytes and myocardial cells).
Reversible Cell Injury
Light Microscopic Changes

1. Cell Swelling
2. Chromatin clumping
3. Lipidosis
Irreversible cell injury

- Accumulation of amorphous, calcium-rich densities in the mitochondrial matrix.
- Cell membrane damage is the central factor
- Progressive loss of membrane phospholipids, cytoskeletal abnormalities, toxic oxygen radicals, lipid breakdown products.
Dead cells

- Cytoplasm:
  - Increased eosinophilia
  - Glassy homogenous appearance

- Nuclear changes:
  - Karyolysis
  - Pyknosis
  - Karyorrhexis

- Nuclear changes:
  - Nuclear fading
  - Nuclear shrinkage
  - Nuclear fragmentation
Progression of cell injury

1. **Normal cell**
   - Injury
     - Swelling of endoplasmic reticulum and mitochondria
     - Clumping of chromatin
   - Recovery

2. **Reversible cell injury**
   - Death
     - Swelling of endoplasmic reticulum and loss of ribosomes
     - Lysosome rupture
     - Membrane blebs
     - Myelin figures

3. **Irreversible cell necrosis**
   - Fragmentation of cell membrane and nucleus
     - Nuclear condensation
     - Swollen mitochondria with amorphous densities

**Diagram:**
- Top: Normal cell with injury, recovery.
- Middle: Reversible cell injury with stages of injury and recovery.
- Bottom: Irreversible cell necrosis with death and necrosis stages.
Irreversible Cell Injury

1. Cell passes “point of no return”
2. It cannot recover if pathologic stimulus removed
Apoptosis

- Means “a falling away form”
- **Programmed cell death.**
- Can be both physiological or pathological.
- Usually involves single cells or clusters of cells - appear as round or oval masses with intensely eosinophilic cytoplasm.
Events in Apoptosis

1. Receptor-ligand interactions
   - FAS-FAS ligand
   - TNF-TNF receptor

2. Withdrawal of growth factors or hormones

3. DNA fragmentation
   - Endonuclease activation
   - Catabolism of cytoskeleton

4. Apoptotic body
   - Cytoplasmic bud
   - Ligands for phagocytic cell receptors

Injury
- Radiation
- Toxins
- Free radicals

Regulators
- Inhibit: Bcl-2, Bcl-XL, Bad, Others
- Promote: Bax, Others
Events in Apoptosis

Apoptotic Bodies with ligands for phagocytic receptors

Macrophage or Adjacent Epithelial Cell
Necrosis

- Refers to a sequence of morphologic changes that follow cell death in living tissue. This occurs in the setting of irreversible exogenous injury.

**Types of necrosis are:**
- Coagulative necrosis
- Liquefactive necrosis
- Caseous necrosis
- Fat necrosis
- Gangrene
Necrosis

- Result of two concurrent processes:
  1. Denaturation of proteins.
  2. Enzymatic digestion of the cell (autolytic or heterolytic).

- Requires hours to develop.

- Classic histological picture not apparent until 4 to 12 hours after irreversible injury has occurred.
Irreversible Cell Injury: Necrosis

Light Microscopic Changes

1. Nuclear
   Pyknosis
   Karyorrhexis
   Chromatolysis

2. Increased eosinophilia of cytoplasm
Irreversible Cell Injury: Necrosis
Ultrastructural Changes

1. High amplitude mitochondrial swelling
2. Membrane defects
3. Lysosomal membrane rupture
4. Nuclear condensation, fragmentation, dissolution
Irreversible Cell Injury: Necrosis

Gross Changes
Coagulative necrosis

- When denaturation of proteins is the primary factor
- Preservation of the basic structural outline of the coagulated cell or tissue for a span of few days
- Affected tissues exhibit a firm texture.
- Seen in hypoxic cell death in all tissues except brain
- Myocardial Infarction is a prime example: coagulated, anucleate cells may persist for weeks
Coagulative necrosis
Nuclear ghosts
Liquefactive necrosis

- Characteristic of focal bacterial or occasionally fungal infections
- In brain hypoxic death cells invokes this type of necrosis
- Complete digestion of dead cells
- Transformation of tissue into a liquid viscous mass
- If initiated by acute inflammation, the material is frequently creamy yellow because of the presence of dead white cells and is called pus
Liquefactive necrosis
Liquefactive necrosis
Caseous necrosis

- Distinctive form of coagulatative necrosis.
- Seen most often in tuberculous infection.
- Caseous- white and cheesy in the area of necrosis ( gross).
- Histology: necrotic focus appears as granular debris composed of fragmented, coagulated cells and enclosed within a distinctive inflammatory border.
- Tissue architecture is completely obliterated.
Caseous necrosis
Caseative necrosis
Other types of necrosis

**Fat necrosis**
- Descriptive of a focal area of fat destruction.
- Occurs in acute pancreatitis.
- Pancreatic enzymes escape from acinar cells and ducts and liquefy fat cell membranes.
- Chalky white areas.
**Gangrenous necrosis**

- Usually applied to a limb that has lost its blood supply and has undergone coagulative necrosis.

- There is superimposed bacterial infection and there is liquefactive action of the bacteria and leukocytes (wet gangrene)
Gangrene
<table>
<thead>
<tr>
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<th>Necrosis vs Apoptosis</th>
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<tbody>
<tr>
<td><strong>Pathologic (hypoxia, toxins).</strong></td>
<td>Consequence of irreversible cell injury. <strong>&quot;cell homicide&quot;</strong></td>
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<tr>
<td>Many cells affected</td>
<td>- Cell swelling, Organelle disruption, Loss of membrane integrity. - Coagulation or liquefaction</td>
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<tr>
<td>Few cells affected</td>
<td>- Cell shrinkage, apoptotic bodies which are eaten by macrophages.</td>
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<td>Karyorrhexis and karyolysis: random, diffuse fragmentation and dissolution of the nucleus.</td>
<td>Orderly nuclear condensation and fragmentation.</td>
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<td>Inflammation with injury to surrounding normal tissues.</td>
<td>No Inflammation or tissue injury.</td>
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</tbody>
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Thank you

Pathologic Basis of disease – Robbins & Cotran, 8th Ed
General & systemic pathology – Underwood, 2nd Ed
Principles of Internal Medicine – Harrisons, 15th Ed
Textbook of Medical Physiology – Guyton, 9th Ed
Aids to Pathology – Dixon/ Quirke, 4th Ed
Surgical Pathology – Ackerman, 9th Ed;
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http://clinicalpathology.wordpress.com/