Pathology - Topic 2 - Cell Injury and Adaptation

Causes and Mechanisms of Cell Injury

- Cell injury occurs when stress or a harmful agent exceeds a cell's ability to adapt and maintain normal function.

The Response to Stress

- A cell maintains a relatively stable internal state while meeting the demands placed on it.
    - A change in demand may produce adaptation, but a harmful stimulus that exceeds the cell's capacity produces injury.
- **Reversible injury** allows recovery when the harmful stimulus is removed before critical damage develops.
    - **Irreversible injury** crosses the point beyond which the cell cannot recover and leads to cell death.
- The outcome depends on the nature, intensity and duration of the insult and on the type and metabolic state of the affected cell.
    - A neuron with a high oxygen requirement is less tolerant of interrupted blood supply than many connective-tissue cells.

Major Causes of Injury

1. Oxygen Deprivation

- **Hypoxia** means an inadequate oxygen supply, while **ischaemia** means inadequate blood flow.
    - Ischaemia also reduces nutrient delivery and waste removal, so it usually causes injury more rapidly than isolated hypoxia.
- Oxygen delivery may fall because of vascular obstruction, respiratory failure, severe anaemia or impaired haemoglobin function.

2. Physical and Chemical Agents

- Trauma, temperature extremes, radiation and electrical injury can damage cells directly or disrupt their blood supply.
- Poisons, pollutants and drugs may injure membranes, enzymes, mitochondria or DNA.
    - Some chemicals are harmful in their original form, while others become harmful after metabolism into reactive products.

3. Infections and Immune Reactions

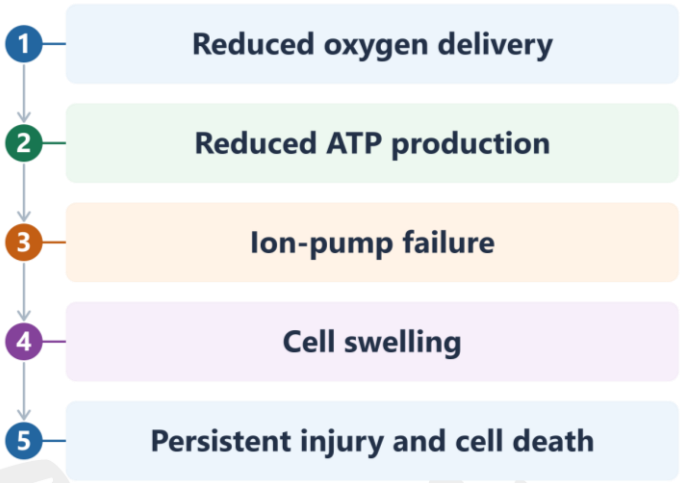
- Microorganisms cause injury through invasion, toxins, disturbed cell function or the host's inflammatory response.
- Immune reactions can damage tissues during allergy, autoimmunity, transplant rejection or a response to persistent infection.

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4. Genetic and Nutritional Disturbances

- A genetic alteration may produce an abnormal protein, reduce an essential enzyme or disturb chromosome balance.
- Nutritional deficiency and nutritional excess both cause injury.
    - Examples include protein deficiency, vitamin deficiency, obesity-related metabolic stress and excess iron accumulation.

Common Molecular Mechanisms



1. ATP Depletion

Energy Failure and Ion Balance

- Reduced mitochondrial oxidative phosphorylation lowers the supply of **adenosine triphosphate**, or ATP.
- Failure of the sodium–potassium pump allows sodium and water to enter the cell, producing swelling.

Metabolic and Protein-Synthesis Changes

- The cell increases anaerobic glycolysis, which consumes glycogen and increases lactic acid.
- The resulting fall in pH contributes to chromatin clumping and reduced enzyme activity.
- Ribosomes may detach from rough endoplasmic reticulum, reducing protein synthesis.
- Persistent ATP depletion eventually prevents restoration of ion balance and membrane integrity.
- Reduced synthesis of apoproteins can impair triglyceride export from hepatocytes and contribute to fatty change.

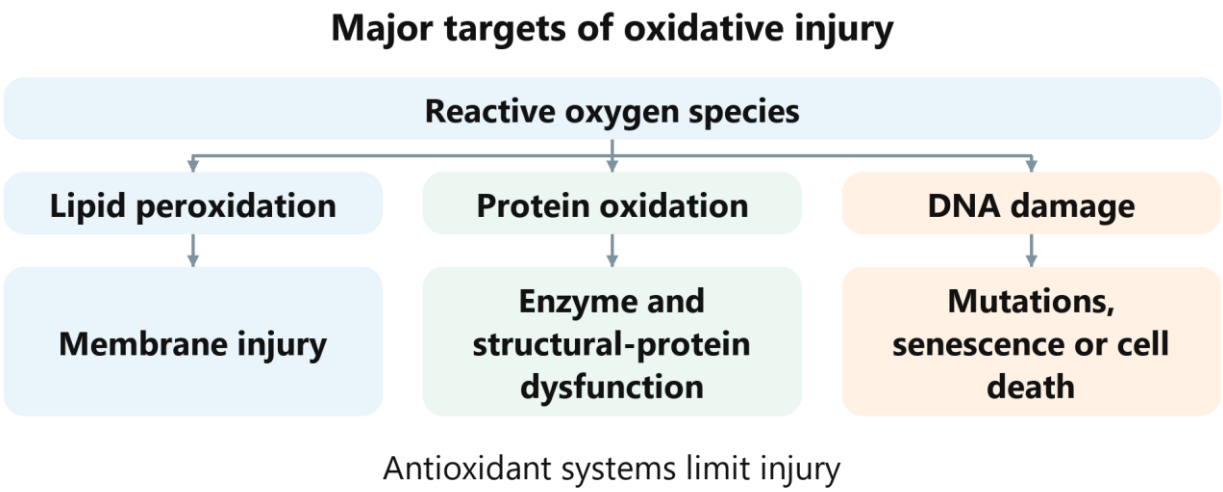
2. Mitochondrial and Calcium Disturbances

- Mitochondrial damage reduces ATP production and may allow pro-apoptotic proteins to enter the cytoplasm.

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- An increased cytosolic calcium concentration activates enzymes that damage phospholipids, proteins and DNA.
    - Calcium also activates ATP-consuming enzymes and worsens mitochondrial dysfunction.

3. Reactive Oxygen Species



Major targets of oxidative injury

- **Reactive oxygen species** are reactive oxygen-containing molecules that can damage lipids, proteins and nucleic acids.
    - They arise during normal metabolism and increase during radiation exposure, inflammation and several toxic injuries.
- Lipid peroxidation weakens membranes, while protein oxidation disrupts enzymes and structural proteins.
    - DNA damage may cause cell death, senescence or mutations in surviving cells.
- Superoxide dismutase, catalase, glutathione systems and other antioxidants help limit oxidative injury.

Formation and Removal of Reactive Molecules

- Electron leakage from the mitochondrial respiratory chain can generate superoxide.
- Oxidases and superoxide dismutase generate hydrogen peroxide, which can form highly reactive hydroxyl radicals through iron-dependent reactions.
- Catalase and glutathione peroxidase remove hydrogen peroxide, while iron-binding proteins limit radical formation.

4. Membrane and Protein Damage

A. Membrane Damage

- Damage to the plasma membrane causes loss of cellular contents and failure of osmotic control.
- Lysosomal membrane damage releases hydrolytic enzymes that digest cell components.

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B. Protein Misfolding and Endoplasmic-Reticulum Stress

- An excess of misfolded proteins causes **endoplasmic-reticulum stress**.
- The cell initially reduces protein production and increases protein folding and removal, but severe unresolved stress may trigger apoptosis.

Ischaemia–Reperfusion Injury

- Restoring blood flow is essential for threatened tissue, but reperfusion may add injury to already damaged cells.
  - Reactive oxygen species, calcium disturbance, inflammation and complement activation contribute to this effect.
- Reperfusion injury explains why tissue damage may continue after an occluded vessel has been reopened.

Examples of Direct and Metabolically Activated Injury

- A corrosive chemical can injure membranes directly at the site of contact.
- Carbon tetrachloride is metabolised to reactive radicals that damage endoplasmic-reticulum membranes and promote fatty change.
- Excess paracetamol can generate more reactive metabolite than glutathione can neutralise, producing hepatocellular injury.
- The same dose of a toxin may have different effects depending on metabolism, nutritional status and prior enzyme induction.

Reversible and Irreversible Cell Injury

- Reversible cell injury can resolve when the harmful stimulus is removed, whereas irreversible injury progresses to cell death.

Morphology of Reversible Injury

1. Cellular Swelling

Gross Appearance

- **Cellular swelling** is a common early sign of disturbed ion and fluid balance.
- The organ may become enlarged, pale and heavier, although mild injury may produce no obvious gross change.

Microscopic and Ultrastructural Appearance

- Microscopy may show enlarged cells with pale cytoplasm and small clear vacuoles.
- These vacuoles often reflect distended endoplasmic reticulum and are called hydropic or vacuolar change.
- Ultrastructural changes include membrane blebs, loss of microvilli, mitochondrial swelling and dilation of endoplasmic reticulum.

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2. Fatty Change

- **Fatty change**, or steatosis, is abnormal accumulation of triglyceride within parenchymal cells.
    - It is especially common in the liver, which has a central role in lipid metabolism.
- Fatty change may follow alcohol exposure, metabolic dysfunction, hypoxia, toxins or nutritional disturbances.
    - Its presence does not by itself identify the cause or prove that cell death has occurred.

Membrane, Mitochondrial and Enzyme Changes

- Persistent failure of mitochondrial function and severe loss of membrane integrity are major features of irreversible injury.
    - Nuclear changes then provide important microscopic evidence of cell death.
- Dense amorphous mitochondrial deposits, major membrane disruption and lysosomal enzyme leakage support irreversible injury ultrastructurally.
- Cytoplasmic eosinophilia reflects loss of RNA basophilia and denaturation of proteins.

Nuclear Changes in Irreversible Injury

1. Pyknosis

- **Pyknosis** is shrinkage of the nucleus with dense, dark chromatin.

2. Karyorrhexis

- **Karyorrhexis** is fragmentation of the condensed nucleus.

3. Karyolysis

- **Karyolysis** is fading and dissolution of nuclear staining because DNA is degraded.

Leakage as a Clinical Clue

- Injured cells may release intracellular proteins into the blood.
    - Cardiac troponins support assessment of myocardial injury, while aminotransferases can indicate hepatocyte injury.
- A raised marker must be interpreted with its timing and clinical context because cell injury has many possible causes.
- Morphological changes lag behind biochemical injury, so early lethal injury may not yet be visible by routine light microscopy.

Cell Death: Necrosis and Apoptosis

- Cell death occurs through different mechanisms, with necrosis and apoptosis showing important differences in membrane integrity, morphology and inflammation.

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