Cell Injury

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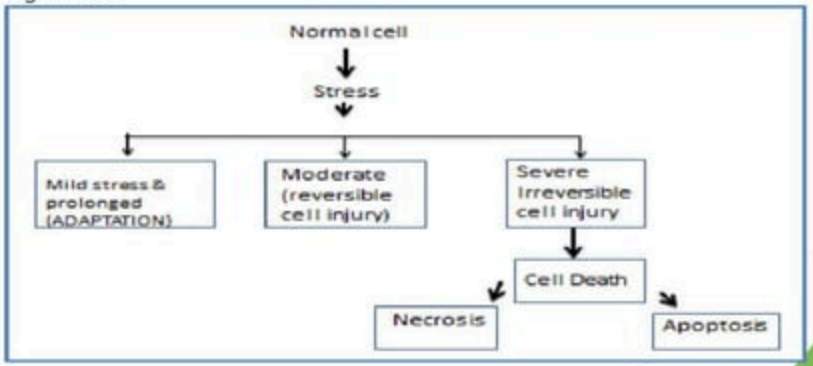
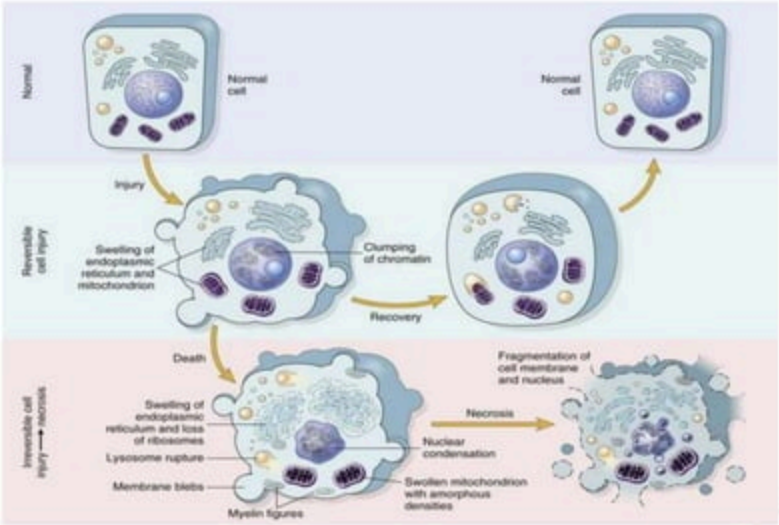
CELL INJURY AND STAGES

- Cell injury is defined as a variety of stresses a cell encounters as a result of changes in its internal and external environment.
- The cellular response to stress may vary and depends upon the following: - The type of cell and tissue involved. - Extent and type of cell injury .
- Cell injury results when cells are stressed so severely and no longer able to adapt.
- Different injurious stimuli affect many metabolic pathways and cellular organelles.

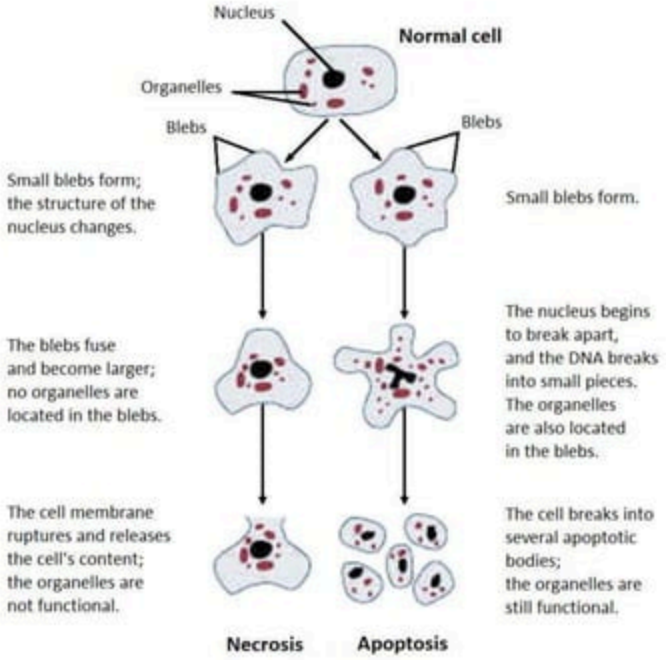


Cell Injury events



Types of Cell Injury

- **Reversible cell injury**: In early stages or mild forms of injury the functional and morphologic changes are reversible if the damaging stimulus is removed. At this stage, although there may be significant structural and functional abnormalities, the injury has typically not progress to severe membrane damage and nuclear dissolution.
- **Irreversible cell injury (Cell death):**Because of cell death with continuing damage, the injury becomes irreversible, at which time the cell cannot recover and it dies. There are two types of cell death, necrosis and apoptosis which differ in their morphology, mechanisms, and roles in disease and physiology.
- **When damage to membranes is severe, enzymes leak out of lysosomes, enter the cytoplasm, and digest the cell, resulting in necrosis.**
- Necrosis is the major pathway of cell death in many commonly encountered injuries, such as those resulting from ischemia (Reduced blood flow), exposure to toxins, various infections and trauma(distressing or disturbing event)
- **When a cell is deprived of growth factors or the cell's DNA or proteins are damaged beyond repair, the cell kills itself by another type of death, called apoptosis**, which is characterized by nuclear dissolution without complete loss of membrane integrity.


Nucleus
Normal cell
Organelles
Blebs
Blebs
Small blebs form; the structure of the nucleus changes.
Small blebs form.
The blebs fuse and become larger; no organelles are located in the blebs.
The nucleus begins to break apart, and the DNA breaks into small pieces. The organelles are also located in the blebs.
The cell membrane ruptures and releases the cell's content; the organelles are not functional.
The cell breaks into several apoptotic bodies; the organelles are still functional.
Necrosis
Apoptosis

Etiology or causes of cell injury

- Cell injury is a sequence of events that occur if the limits of adaptive capability are exceeded or no adaptive response is possible. This can be due to physical, chemical, infectious, biological, immunological factors and nutritional cellular abnormalities.
- Acquired causes of cell injury are further categorized as:
- (a) Oxygen deprivation (Hypoxia)(absence of enough oxygen in the tissues to sustain bodily functions)
- (b) Physical agents
- (c) Chemical agents and drugs
- (d) Microbial agents
- (e) Immunologic agents
- (f) Nutritional derangement
- (g) Psychological factors

Events of cell injury

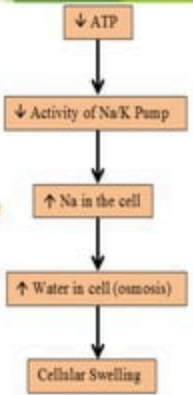
- Cell injury results from functional and biochemical abnormalities in one or more of several essential cellular components. The most important targets of injurious stimuli are
- Mitochondria, the sites of ATP generation;
- Cell membranes, on which the ionic and osmotic homeostasis of the cell and its organelles depends;
- Protein synthesis
- The cytoskeleton
- The genetic apparatus of the cell.

Mechanism of reversible cell injury:

1. ATP DELPETION:

- ATP depletion and decreased ATP synthesis are frequently associated with both hypoxic and (toxic) injury.
- ATP depletion leads to Na pump decrease in plasma membrane.
- Na retains intracellularly and potassium depletes out of the cell.
- Due to that cell gains water because of osmotic difference causes cell swelling.

Reversible Cellular Injury



2. Intracellular lactic acidosis and nuclear clumping:

- Due to low oxygen supply aerobic ATP formation is affected
- Failure of mitochondria
- Anaerobic glycolytic pathway starts to produce ATP
- Rapidly glycogen decreases and lactic acid accumulates
- More lactic acid accumulation changes intracellular pH and leads to clumping of chromatin.
- This releases lysosomes and leads to cell digestion

3. **Effect on plasma membrane (Failure of sodium and potassium ATPase):**

- Na^+ and K^+ ATPase is required for the active transport of the Na (inside to outside) and K levels (outside to inside)of the cell.
- Lower ATP affects the activity of the pump.
- Accumulation of Na^+ inside leads to water retention inside the cell causes cell swelling.

Failure of ca^{++} Pump:

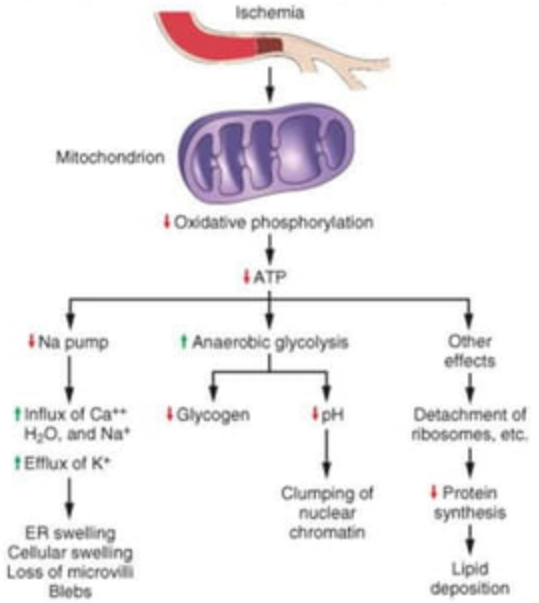
- Lack of sodium pump leads to accumulation of ca^{++} inside the cell as well in the mitochondria.
- Excess calcium in the mitochondria lead to reversible cell injury after the injury stimuli.

4. Degradation of protein synthesis:

- Lack of oxygen supply disturbs the osmotic balance of cell which leads to swell up of cell organelles.
- Ribosomes detach from the endoplasmic reticulum and gets inactive which lead to decrease the synthesis of proteins.

DEPLETION OF ATP

Functional and morphologic consequences of decreased intracellular ATP during cell injury.



Irreversible cell injury Mechanism

- Long lasting ischemic or hypoxic effect lead to irreversible cell damage or cell death.
- **Mitochondrial damage**:

Increase in ca** damage mitochondrial wall---releases enzymes Phospholipase, endonuclease etc.---effects components like plasma membrane, nucleus, DNA.

- Phospholipase degrades plasma membrane which has phospholipids.
- Protease damages cytoskeleton of cell membrane
- Endonuclease damages nucleoprotein-damages nucleus and clumps nucleus, releases fragments of nucleus, dissolves the nucleus.
- Lack of oxygen activates enzymes like creatine kinase, RNAse, DNAse, Glycosidase that digest the cellular components leads to cell death.

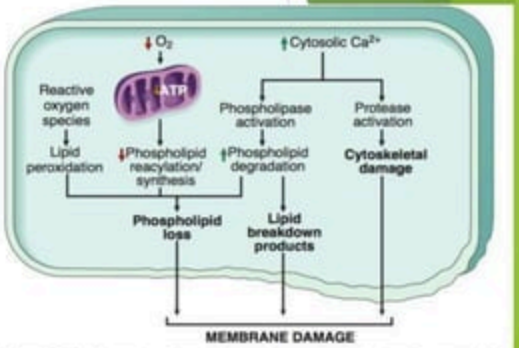


Figure 2-21 Mechanisms of membrane damage in cell injury. Decreased O_2 and increased cytosolic Ca^{2+} are typically seen in ischemia but may accompany other forms of cell injury. Reactive oxygen species, which are often produced on reperfusion of ischemic tissues, also cause membrane damage (not shown).

Pathogenesis of cell injury

- Cell membrane damage
- Mitochondrial damage
- Ribosome damage
- Nuclear damage
- ATP depletion or Hypoxia
- Loss of calcium

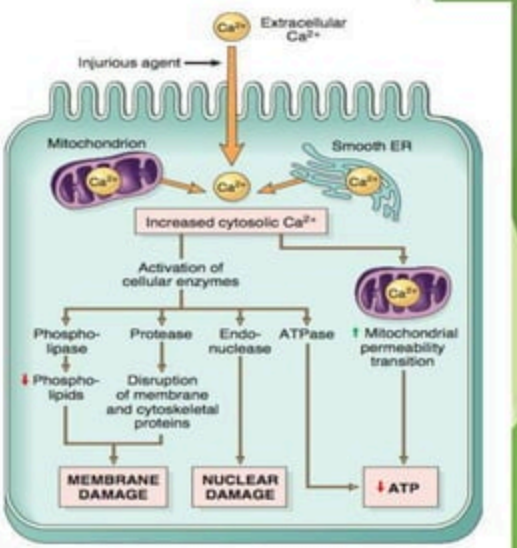


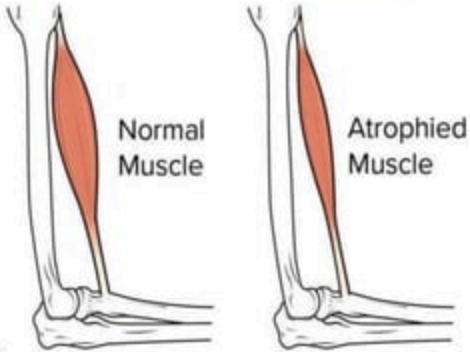
Figure 2-19 The role of increased cytosolic calcium in cell injury. ER, Endoplasmic reticulum.

Morphology of cell injury-Adaptive changes

- Most cells have the ability to adapt to changes in their environment by altering their morphology, pattern of growth and metabolic activity.
- These adaptive responses may be part of the normal physiology of a cell or tissue, or they may represent an attempt to limit the harmful effects of a pathological stress.
- physiologic signals such as hormonal stimuli can also cause tissues to change with similar patterns.
- Basic patterns of macroscopic change in cells can be induced by the physiologic stress or injury and sometimes physiologic stimuli as below:

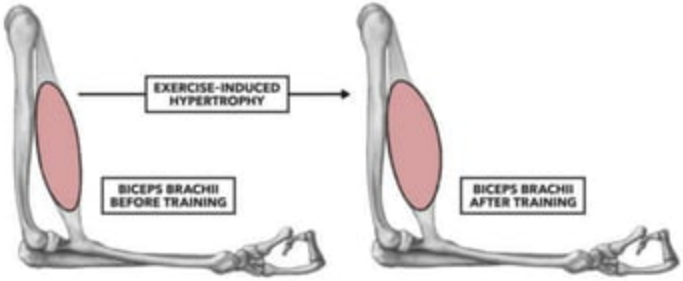
1. **Atrophy:**

- Decrease in cell size due to loss of cell substances.
- Causes are loss of blood flow, aging, decreased work load.
- When atrophy occurs simultaneously in a population of adjacent cells this can lead to decreased tissue or organ size.
- Types : Physiologic, pathologic, Local, Disuse atrophies.



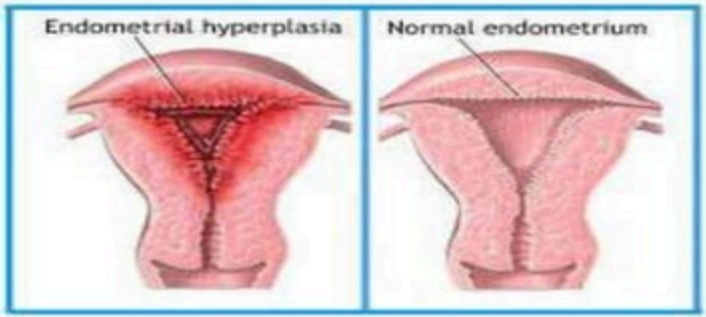
2. **Hypertrophy:**

- Increase in cell physical size a complete opposite to atrophy.
- Increased tissue size or organ size due to increased functional demand on the tissue or specific hormonal stimulation.
- Cells are increased in size due to increased synthesis of structural proteins and cell organelles.



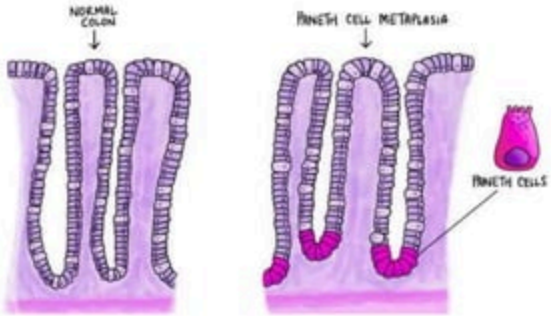
3. **Hyperplasia:**

- Increase in number of cells due to mitosis.
- The affected parts becomes but retains normal function.
- when the stimuli which induce hyperplasia are removed, cells will terminate their divisions.
- Cell division in the absence of stimuli is considered as neoplasia.
- Hyperplasia can be induced by specific hormonal stimuli, increased functional demand on the tissue or by injury to the tissue.



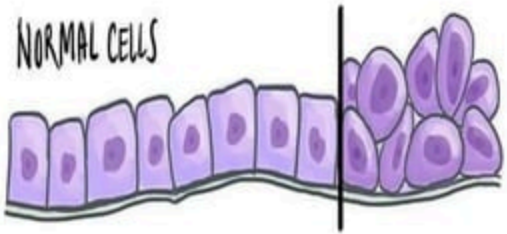
4. **Metaplasia:**

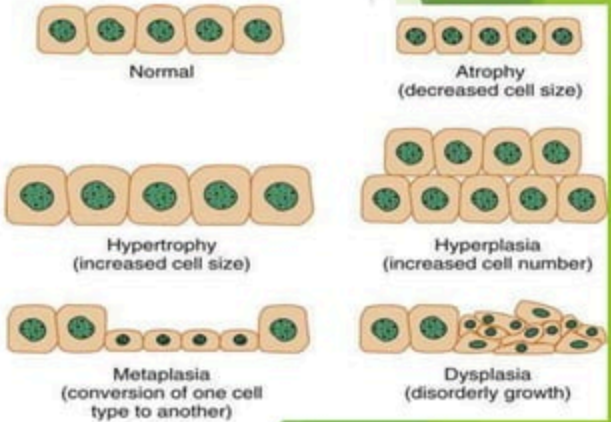
- A differentiated cell is replaced by another which is less differentiated than the original one.
- It is a reversible process for the adaptation of the cells.
- Although by definition metaplasia is a reversible adaptation, it frequently precedes and may represent the initial steps of malignant transformation.



5. **Dysplasia**:

- Dysplasia means abnormal changes in cellular size , shape and organisation.
- Hyperplasia and Dysplasia may or may not become cancer.
- The number of adult and mature cells decreases while the number of immature cells increases.
- The microscopic changes which occur in reversible cell injury are cellular swelling (organelle changes) and fatty changes.



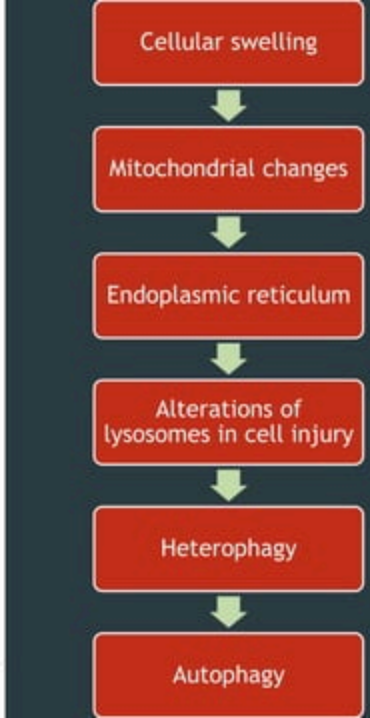


Cell swelling

- The plasma membrane forms a barrier against excessive amounts of Na^+ with in the extracellular fluid from entering the cell.
- However the membrane is slightly leaky to Na^+ allowing the minimal amounts of sodium to move gradually in to the cell.
- To compensate this, there is a perpetually active Na+/K+ATPase pump, which move Na+ out of the cell constantly, in exchange for K+ into the cell.
- depletion of ATP which leads to accumulation of Na+ intracellularly creating osmotic pressure which causes cellular swelling.

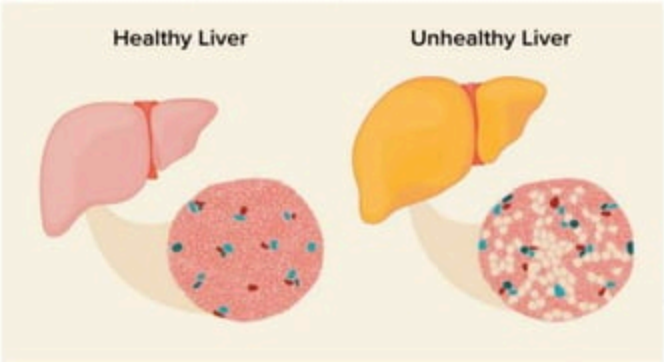
Ultra structural changes during cell swelling:

1. Cellular swelling: decrease in ATP increase in Na^+ and water inside the cell due to hypoxia and ischemia.
2. Due to ischemia Ca^+ deposits increase leads to abnormality in proteins and lipids.
3. Detachment of ribosomes and decreased protein synthesis.
4. Lysosomes rupture causing leakage of lysosomal enzymes.
5. Phagocytosis by the materials of external environment like leucocytes
6. Phagocytosis by lysosomes.



Fatty Change (Steatosis):

- This steatosis is caused in hypoxic, toxic and metabolic injuries and is related to a dysfunction in the cell's regulation of synthesis and elimination of triglycerides.
- Excess lipids accumulate within the cells, usually parenchymal cells that form numerous vacuoles that displace the cytoplasm.
- If these vesicles are large enough to displace and distort the nucleus, it is referred to as macro vesicular steatosis.
- Fatty change is commonly seen in liver, heart.



Free fatty acids from Adipose tissue or ingested food

↓

Transported to hepatocytes

↓

Esterified to triglycerides

↓

Further converted to cholesterol, phospholipids

↓

Or oxidized to ketone bodies

Excess accumulation of triglycerides leads to defects at any step in fatty liver condition.