**LECTURE 5**

*~ b. kitavi ~*

**CELL INJURY**



**Definition**

Cell injury refers to the changes that occur in the cell when the cell has been exposed to abnormal or injurious stimuli or agents.

**CELLULAR INJURY**

**BASIC PRINCIPLES**

Cell damage/injury refers to different variety of changes due to stress that a cell might undergo due to external or internal changes.

These changes can be reversible with cellular response getting adaptive and restored to normal status or irreversible resulting into a cell death.

* Cellular injury occurs when a stress exceeds the cell's ability to adapt.
* The likelihood of injury depends on the type of stress, its severity, and the type of cell

affected.

* *Neurons are highly susceptible to ischemic injury; <>while skeletal muscle are relatively more resistant.*
* *Slow developing ischemia (e.g., renal artery atherosclerosis) results in atrophy.<>whereas, acute ischemia (e.g., renal artery embolus) results in injury*.
* Common causes of cellular injury include inflammation, nutritional deficiency or

excess, hypoxia, trauma, and genetic mutations.

**A. Hypoxia**

This refers to Low oxygen delivery to tissue; important cause of cellular injury

Oxygen is the final electron acceptor in the electron transport chain of oxidative

phosphorylation.

Decreased oxygen impairs oxidative phosphorylation,*(phosphorylation biochemical process that involves the addition of phosphates to an organic compound e.g. addition of phosphate to glucose to produce glucose monophosphates, addition of phosphate to adenosine diphosphate ADP to form ATP)* resulting in decreased ATP production.

Lack of ATP (essential energy source) leads to cellular injury.

Causes of hypoxia include ischemia, hypoxemia, and decreased O2-carrying capacity

of blood.

**B. Ischemia**

It is decreased blood flow to an organ or tissue.

Results from:-

1. Decreased arterial perfusion (e.g., atherosclerosis)

2. Decreased venous drainage (e.g., Budd-Chiari syndrome)

3. Shock - generalized hypotension resulting in poor tissue perfusion

**C. Hypoxemia**

It is a low partial pressure of oxygen in the blood (Pao2 < 60 mm Hg, Sao2 < 90%).

Commonly with:-

1. High altitude - Decreased barometric pressure results in decreased PAo2•
2. Hypoventilation - Increased PAco2 results in decreased PAo2•
3. Diffusion defect - PAo2 not able to push as much O2 into the blood due to a thicker diffusion barrier (e.g., interstitial pulmonary fibrosis)
4. V/Q mismatch*(ventilation perfusion mismatch)* - Blood bypasses oxygenated lung (circulation problem, e.g., right to-left shunt), or oxygenated air cannot reach blood (ventilation problem, e.g., atelectasis).
5. Decreased O2-carrying capacity arises with hemoglobin (Hb) loss or dysfunction.

Examples include:-

1. Anemia (decrease in RBC mass) Pao 80-100mmhg, normal; Sao >90% normal

2. Carbon monoxide poisoning

**GROWTH ADAPTATIONS, CELLULAR INJURY, AND CELL DEATH**

***Carbon Monoxide***

* CO binds hemoglobin more avidly than oxygen-PaO**2** normal; SaO**2** decreased (SpO2=partial oxygen saturation---oximeter, SaO2=oxygen saturation---BGA, Pa02==partial pressure of oxygen----BGA)
* Exposures include smoke from fires and exhaust from cars or gas heaters.
* Classic finding is cherry-red appearance of skin, lungs…
* Early sign of exposure is headache; significant exposure leads to coma and death.

***Methemoglobinemia***

* Iron in heme is oxidized to Fe**3**+,(ferric state) and not Fe2+(ferrous) which cannot bind oxygen-==PaO**2** normal;SaO**2** decreased
* Commonly caused by oxidant stress by (e.g., sulfa and nitrate drugs, some toxins) or in newborns
* Classic finding is cyanosis with chocolate-colored blood, headache, dizziness, dib, nausea, poor muscle coordination…
* Treatment is intravenous methylene blue, which helps reduce Fe3+ back to
* Fe**2**+state.

**N/B:**

*REVERSIBLE STATE*

**Hypoxia** impairs oxidative phosphorylation resulting in decreased ATP.

Low ATP disrupts key cellular functions including;-

* Na+- K+pump, resulting in sodium and water buildup in the cell
* Ca2+pump, resulting in Ca2+ buildup in the cytosol of the cell
* Aerobic glycolysis, resulting in a switch to anaerobic glycolysis.
* Lactic acid buildup results in low pH, which denatures proteins and precipitates DNA.

The initial phase of injury is reversible. The hallmark of reversible injury is *cellular*

*swelling.*

Cytosol swelling results in loss of microvilli and membrane blebbing.

Swelling of the rough endoplasmic reticulum (RER) results in dissociation of

ribosomes and decreased protein synthesis.

The two major reversible changes may involve swelling or fatty changes

*IRREVERSIBLE STATE*

Eventually, the damage becomes irreversible. The hallmark of irreversible injury is

membrane damage.

* Plasma membrane damage results in Cytosolic enzymes leaking into the serum (e.g., cardiac troponin)
* Additional calcium entering into the cell

Mitochondrial membrane damage results in

* Loss of the electron transport chain (inner mitochondrial membrane)
* Cytochrome C oxidaseleaking into cytosol *(activates apoptosis)*
* Lysosome membrane damage results in hydrolytic enzymes leaking into the cytosol, which, in turn, are activated by the high intracellular calcium.
* The end result of irreversible injury is ***cell death either by necrosis or apoptosis***

**Necrosis**

Necrosis results from organelle breakdown leading to cell death.

Necrosis stages include;-

Pyknosis—clumping of chromosomes

Karyorrhexis--- fragmentation of nucleus

Karyolysis—dissolution of cell nucleus

Cytosolic componentspour out of the cellinto extracellular space triggering inflammatory response.

The types of necrosis are:- coagulative,liquefactive,fat necrosis, caseous necrosis, fibroid & gangrenous necrosis.

**Apoptosis**

This is a programmed cell death

It is energy dependent process

The dying cells shrink and condense into apoptotic fragments which can under go phagocytosis.

Inhibition of apoptosis can result into a number of cancers, autoimmune disorders,inflammatory disorders…

Abnormal apoptosis (hyper-apoptosis) can result into conditions such as in SCD,

**REPAIR**

When dead cells are dissolved, there is a replacement with another cells for functional and structural continuity.

***Regeneration*** is growing back of cells which are making the bulk of the lost or damaged cells

***Replacement;*** can occur by replacing the parenchymal (major cells) cell with stromal cells(basal cells)

***DNA repairs*** can be done through5 major pathways:-

1. Nucleotide excision repair
2. Base excision repair
3. Mismatch repair
4. Non-homologous end joining
5. Homologous Recombinational repair (HRR)

**Causes of cell injury**

1. Physical agents. Directly damage the cell (e.g. trauma, electrical stimulation, irradiation)
2. Chemical agents. Disrupt cellular balance (e.g., therapeutic drugs, poisons, toxic substances).
3. Microorganisms. Include bacteria (secrete endo-and exotoxins), Viruses (hamper cellular metabolism) and fungi (may produce toxins).
4. Hypoxia. Reduced oxygen supply to a tissue. Lack of oxygen causes to go into anaerobic respiration with release of lactic acid (eg shock, localized loss of blood supply, and hypoxemia).
5. Genetic defects. Various metabolic problems or malformations may result.
6. Nutritional imbalance: under-nutrition (e.g. protein and vitamin deficiencies), over-nutrition (e.g. hyperlipidaemias, obesity).
7. Immunologic agents. Cellular injury resulting from immunologic phenomena (e.g. hypersensitivity reactions, autoimmune disorders, immune deficiencies).

-------------------------END OF LECTURE 5-----------------------------