**Pathogenesis of cell injury:**

Mechanism of cell injury include:

* Hypoxic-Ischemic cell injury
* Free-radical mediated cell injury
* Cell aging
* Chemical-mediated cell injury
1. **Hypoxic-Ischemic cell Injury**

Hypoxia is one of the major cause of ischemia and is a reversible cell injury and can be recovered by giving a sufficient amount of oxygen to cells and tissues.

Hypoxia leads to decreased production of ATP and it causes three consequences:

**Failure of sodium potassium pump**: Oxidative phosphorylation is inhibited in mitochondria and it causes:

* Inhibition of Na\K pump which causes net gain of 3 Na inside the cell and 2 K outside the cell causing increased concentration of Na inside the cell.
* Influx of Ca ions also increases due to inhibition of Na\K ATPase pump.
* This gain of Na and Ca causes water to move inside the cell.

**Clinical manifestation**

Signs and symptoms appear are

* Cell edema
* Endoplasmic reticulum swells
* Blebs form on the cell membrane

**Anaerobic glycogenolysis:** Decreased ATP level causes reduced level of glycogen and increased level of lactic acid which causes acidity and reduced pH in the cell

**Clinical manifestation**

* It results in clumping of chromatin material

**Detachment of ribosomes from endoplasmic reticulum**: When ATP decreases, there is detachment of ribosomes from ER which causes decreased production of protein synthesis.

**Irreversible cell injury:**

If ischemia persists for a longer period of time, it will cause irreversible cell injury, characterized by :

1. Injury to lysosomal membrane
2. Injury to cell membrane
3. Injury to mitochondrial membrane

**Injury to lysosomal membrane:**

Prolonged ischemia lead to to increase in anaerobic glycolysis that result in severe decrease in pH and cause rupturing of lysosomal membrane. This rupturing cause release of lysosomal enzymes. That produce different effects such as protein digestion, RNA digestion and nuclear changes.

 **Injury to cell membrane:**

It is the central step in pathogenesis in cell injury. It is caused by loss of phospholipids in cell membrane. This loss of phospholipids is due to activation of phospholipase A2 enzyme activated by calcium entry.

Degradation of phospholipids will result in formation of lipid breakdown products cause injury to cell membrane.

Cytoskeletal protein degradation will caused by activation of intracellular protease due to more influx of calcium to the cell. Production of reactive oxygen species by neutrophils infiltrate the ischemic tissues and cause the damage to cell membrane.

**Outcomes:**

Massive influx of calcium ions and other macromolecules into the cell

Release of creatinine kinase (special in case of myocardial infarction)

**Injury to mitochondrial membrane:**

Initially irreversible injury is associated with vacuolization of mitochondria.

Upon reperfusion, there is plasma membrane damage and cause more influx of calcium. Increase calcium inhibits mitochondrial enzyme.