Chemical and Biochemical Mechanism Of Cell Injury.

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Cell Injury
When the cell is exposed to an injurious agent or stress, a sequence of events follows that is loosely termed **cell injury**.

- Cell injury is **reversible** up to a certain point
- If the stimulus persists or is severe enough from the beginning, the cell reaches a point of no return and suffers **irreversible** cell injury and ultimately **cell death**.
- **Cell death**, is the ultimate result of cell injury

Causes of Cell Injury

1) **Oxygen Deprivation** (*Hypoxia*). It is a common cause of cell injury and cell death.
   - *Hypoxia* can be due to:
     A- inadequate oxygenation of the blood due to Cardio respiratory failure.
     B- loss of the oxygen-carrying capacity of the blood, as in anemia or carbon monoxide poisoning.
     • Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die.

2) **Physical Agents** :
   - Mechanical trauma,
   - Burns,
   - Deep cold,
   - Sudden changes in atmospheric pressure,
   - radiation, and electric shock,
3) **Chemical Agents and Drugs**
- oxygen, in high concentrations
- *poissons*, such as arsenic, cyanide, or mercuric salts
- environmental and air pollutants
- insecticides, herbicides, industrial and occupational hazards
- alcohol and narcotic drugs and therapeutic drugs

4) **Infectious Agents** e.g. bacteria, fungi, viruses and parasites, etc.

5) **Immunologic Reactions**

6) **Genetic Derangements**

7) **Nutritional Imbalances**

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4 weak points of the cell

- Cell membrane integrity, critical to cellular ionic and osmotic homeostasis
- ATP synthesis, largely via mitochondrial aerobic respiration
- Protein synthesis (RER)
- Integrity of the genetic apparatus (nucleus)

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- The structural and biochemical components of a cell are so integrally connected that regardless of the initial locus of injury, multiple secondary effects rapidly occur (Ripple effect).
Mechanisms of Cell Injury:
Two models:
  a. Ischemic injury
  b. Chemical injury

Ischemia vs Hypoxia
- Loss of blood supply
- ↓ed O2 as well as ↓ed delivery of other nutrients
- ↓ed removal of toxic waste products of the cells so there is accumulation of toxic substances, e.g. Lactic acid.
- Quicker and More severe injury than with just lack of Oxygen
- Lack of Oxygen in tissues
- Maybe due to ischemia or due to other causes like due to less RBCs in the blood, or less Oxygen in the atmosphere etc.
- Less severe injury than with Ischemia

MECHANISM OF CELL INJURY
1. Depletion of ATP
2. Mitochondrial Damage
3. Influx of intracellular calcium & loss of calcium homeostasis
4. Accumulation of oxygen-derived free radicals (oxidative stress)
5. Defects In Membrane Permeability

1. DEPLETION OF ATP
  ➢ ATP is required for many synthetic and degradative processes within the cell
  ➢ ATP depletion and decreased ATP synthesis are associated with both hypoxic and chemical (toxic) injury
ATP is produced in two ways.

- The major pathway is oxidative phosphorylation of ADP.
- The second is the glycolytic pathway, which generates ATP in the absence of oxygen using glucose derived from glycogen.

Effects of depleted ATP

- The activity of the plasma membrane energy-dependent sodium pump is reduced. It causes sodium to accumulate intracellularly and potassium to diffuse out of the cell causing cell swelling, and dilation of the endoplasmic reticulum.
- In ischemia (reduce O2 supply), oxidative phosphorylation ceases and cells rely on glycolysis for energy production (anaerobic metabolism) resulting in depletion of glycogen stores. Glycolysis results in the accumulation of lactic acid which reduces the intracellular pH, resulting in decreased activity of many cellular enzymes.

- Failure of the Ca2+ pump leads to influx of Ca2+, with damaging effects on numerous cellular components.
- Ribosome's detach from the RER and polysomes breakdown into monosomes, leading to reduction in protein synthesis.
- Ultimately, irreversible damage to mitochondrial and lysosomal membranes occurs, and cell undergoes necrosis.
- In cells deprived of oxygen or glucose, proteins may become misfolded, and trigger the unfolded protein response leading to cell injury and even death.
2. Mitochondrial Damage

- Mitochondria are important targets for all types of injury, including hypoxia and toxins

Mitochondria can be damaged by
A- Increases of cytosolic Ca2+
B- Oxidative stress
C- Breakdown of phospholipids, and by
D- Lipid breakdown products

Mitochondrial damage results, mitochondrial permeability transition, present in the inner mitochondrial membrane.

- In the initial phase it is reversible but once mitochondrial permeability transition is irreversible it becomes a deathblow to the cell
- Mitochondrial damage can also be associated with leakage of cytochrome c into the cytosol

3. Influx of intracellular calcium & loss of calcium homeostasis.

Ischemia causes an increase in cytosolic calcium concentration. Increased Ca2+ in turn activates a number of enzymes, e.g.
- ATPases (ATP depletion),
- Phospholipases (which cause membrane damage),
- Proteases (which break down both membrane and cytoskeleton proteins), and
- Endonucleases (which are responsible for DNA and chromatin fragmentation).
Effects of excess calcium in the cytosol
Cut-off point between reversible cell injury and cell death?

4. Accumulation of oxygen-derived free radicals (oxidative stress)

Free radicals are chemical species that have a single unpaired electron in an outer orbit.

- They are initiated within cells in several ways:
  a) Absorption of radiant energy (e.g., ultraviolet light, x-rays).
  b) Enzymatic metabolism of exogenous chemicals or drugs.
  c) The reduction-oxidation reactions that occur during normal metabolic processes normally produce small amounts of toxic intermediates, these include superoxide anion radical (O₂⁻), hydrogen peroxide (H₂O₂), and hydroxyl ions (OH).

- Transition metals such as iron and copper.
- **Nitric Oxide** (NO), an important chemical mediator generated by various cells, can act as a free radical.

- Effects of these reactive species are
  - Lipid peroxidation of membranes: result in extensive membrane, organelle, and cellular damage.
  - Oxidative modification of proteins, resulting in protein fragmentation.
  - Lesions in DNA. This DNA damage has been implicated in cell aging and malignant transformation of cells.
Mechanism of chemical injury:

Most chemicals do not produce cell injury directly by themselves, but once they are metabolized in the body, the metabolites are the injurious agent:
Example is Carbon tetrachloride poisoning