Cell Injury

General Principles of Cell Injury

- The cellular response to injurious stimuli depends on:
  - the type of injury, its duration, and its severity

- The consequences of cell injury depend on:
  - the type and adaptability of the injured cell

- Cellular function is lost far before morphologic changes of cell
- The "*point of no return*" at which cell death has irreversibly occurred is difficult to determine

Possible Biochemical Mechanisms of Cell Injury

1) ATP depletion.

2) Generation of reactive oxygen free radicals.

3) Loss of ca^{++} homeostasis.

4) Defect in plasma membrane permeability.

5) Mitochondrial damage.

1-ATP depletion

- ATP is essential for every cellular process :

-Maintanance of cell osmolarity

-Transport processs

-Protein synthesis

Therfore loss of ATP results in rapid shutdown of most critical homeostatic pathways

2-Free Radical Mediation of Cell Injury

- **Definition Of Free Radicals**

  Extremely unstable, highly reactive chemical species with a single unpaired electron in an outer orbital

- In cells they attack and degrade nucleic acids, proteins, lipids and carbohydrates

- They initiate autocalytic reaction, i.e. molecules that react with free radicals are converted into free readicals

- Examples Of Free Radicals
  - Hydroxyl ($OH^{\cdot}$)
  - Hydrogen ($H^{\cdot}$)
  - Superoxide ($O_2^{\cdot -}$)

Free Radical Mediation of Cell Injury

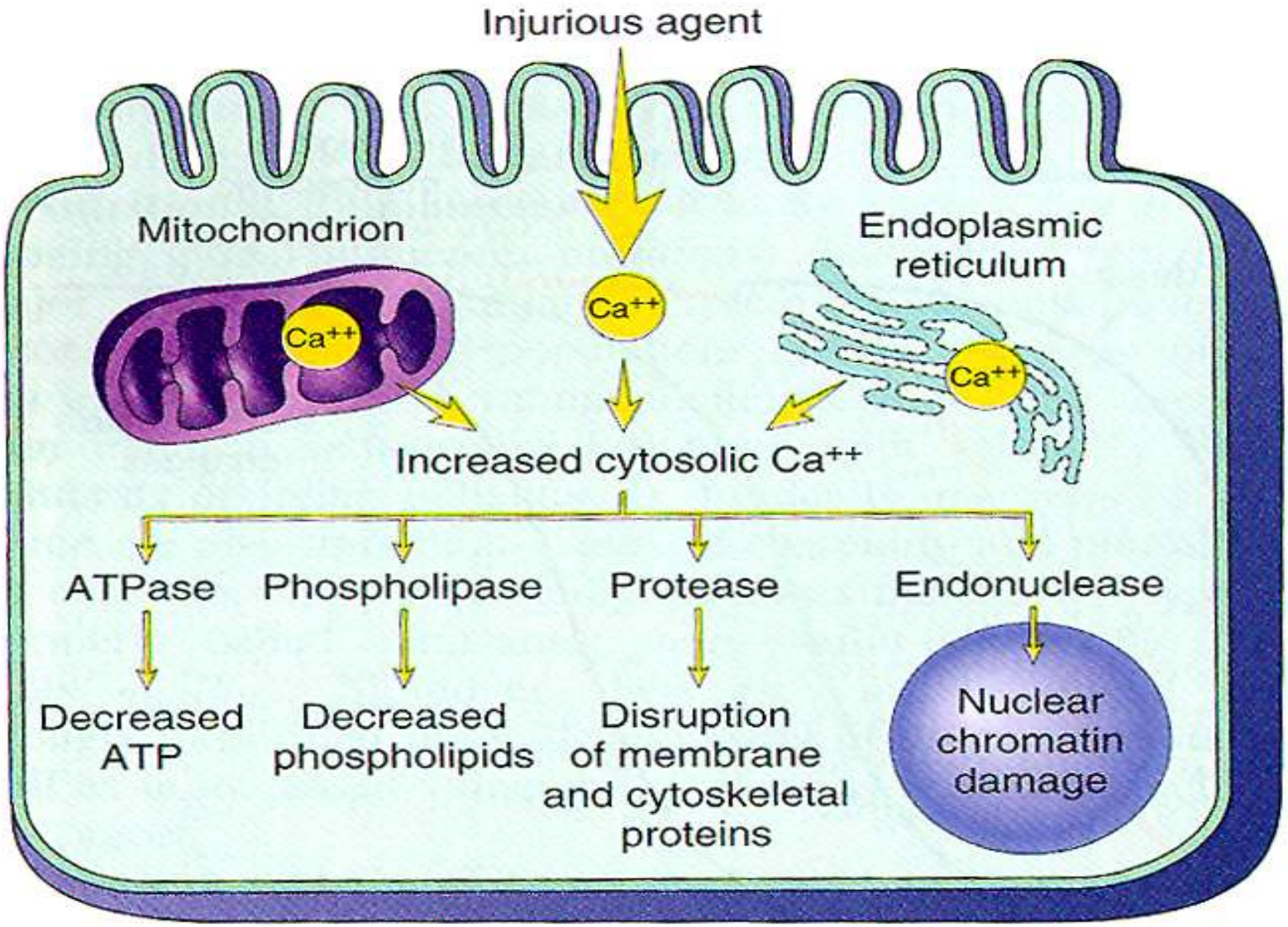
- Free radicals constitutes an important mechanism of cell injury

- It Contributes To:
  - Chemical and radiation injury
  - Oxygen and other gaseous toxicity
  - Cellular aging
  - Microbial killing by phagocytic cells
  - Inflammatory damage
  - Tumor destruction by macrophages
  - Others

3-Increased Cytosolic Calcium:

- Sources
  - mitochondria
  - endoplasmic reticulum
  - external to the cell
- Consequences (activates enzymes)
  - ATPase
    - decreased ATP
  - phospholipase
    - decreased phospholipids
  - protease
    - disruption of membrane and cytoskeletal proteins
  - endonuclease
    - nuclear chromatin damage

Increased Cytosolic Calcium, source and consequences



4-Defects in Plasma membrane permeability:

- Causes :

1. Direct damage by toxins (bacterial, viruses,complement,physical or chemical injury)
2. Damage secondary to ATPase loss or from calcium-mediated phospholipase activation

- Effects:

Loss of Mb barriers →breakdown of the concentration gradient of metabolites

5-Mitochondrial damage

- Mitochondrial integrity if cruicial for cell survival

Causes:

Increase Cytosolic calcium, free radicals

Effects:

No ATP generation

Release of cytochrome c into cytoplasm

Mechanisms of Cell Injury

1) ISCHEMIC & HYPOXIC INJURY

- Reversible injury
- Irreversible injury

Ischemic and Hypoxic Injury

Reversible Injury

Mechanism:

1) Decreased oxidative phosphorylation
2) Increased anaerobic glycolysis
1) Detachment of ribosomes/reduced protein synthesis
3) Worsening mitochondrial function
4) Increasing membrane permeability
5) Cytoskeleton dispersion
6) Swelling of mitochondria, endoplasmic reticulum, and entire cells