MECHANISMS OF CELL INJURY

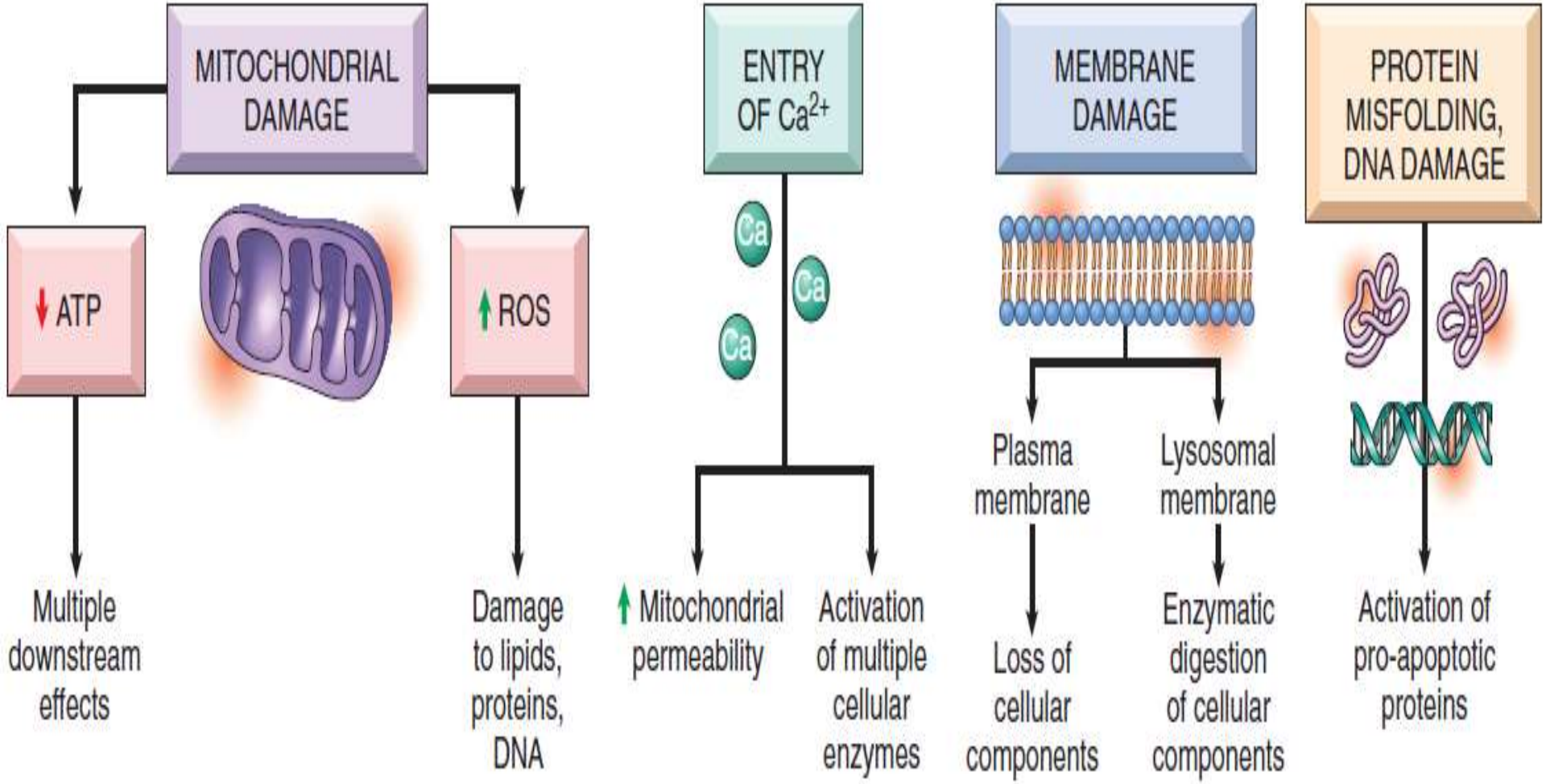
Manar Hajeer, MD, FRCPath.

MECHANISMS OF CELL INJURY

- Principles
- The cellular response to injury depends on:
  - type of injury
  - duration
  - severity
- The consequences of injury depend on:
  - type,
  - status,
  - adaptability, and genetic makeup of the injured cell

- Cell injury results from functional and biochemical abnormalities in one or more of several essential cellular components

The principal targets of cell injury are:



Depletion of ATP

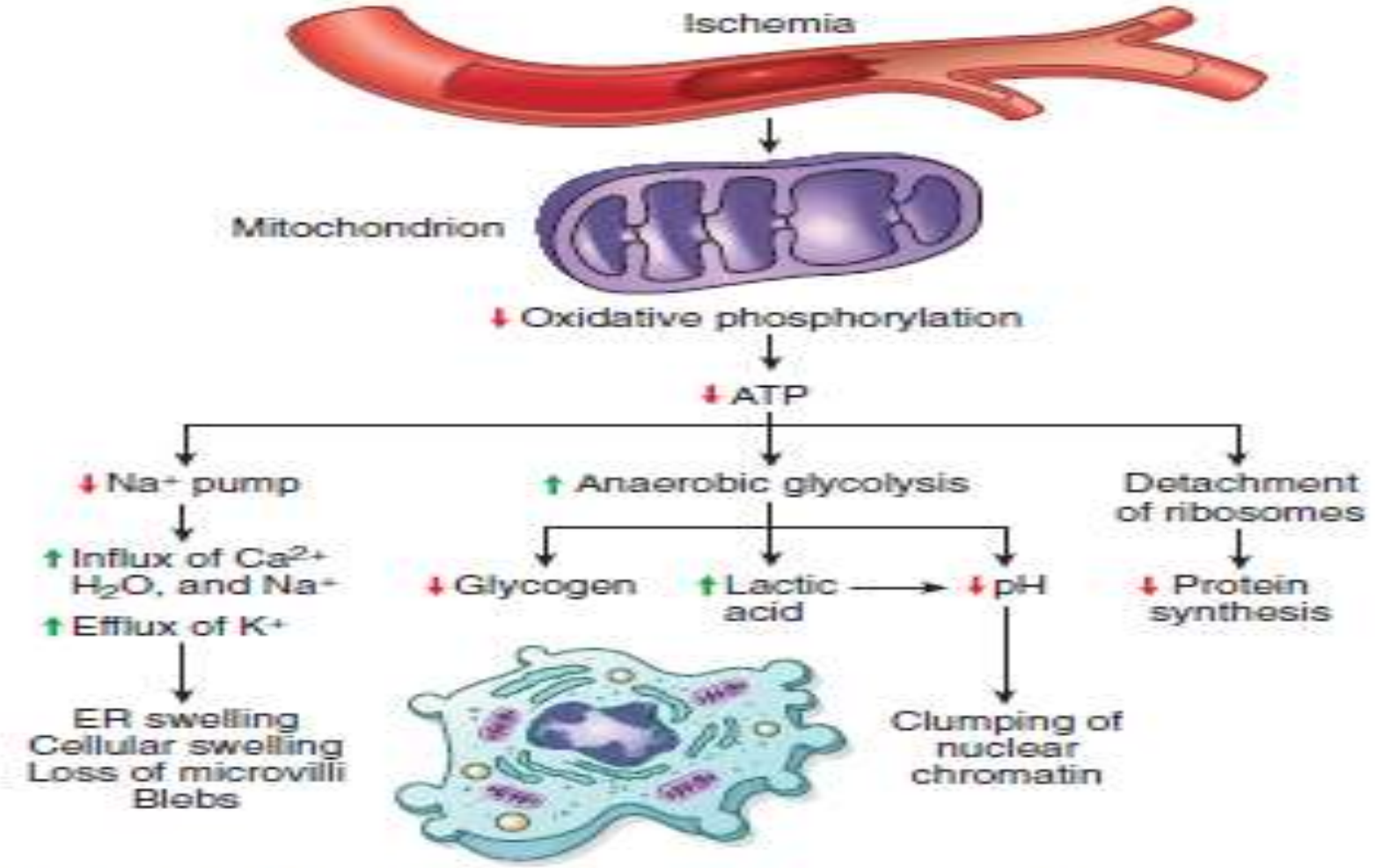


Figure 1–15 The functional and morphologic consequences of depletion of intracellular adenosine triphosphate (ATP). ER, endoplasmic reticulum.

Significant depletion of ATP has widespread effects on many critical cellular systems

- Plasma membrane ATP-dependent sodium pumps
- Increase in anaerobic glycolysis
- Failure of ATP-dependent Ca pumps leads to influx of Ca.
- Structural disruption of the protein synthetic apparatus.
- Irreversible damage to mitochondrial and lysosomal membranes, leading to necrosis.

Mitochondrial Damage and Dysfunction

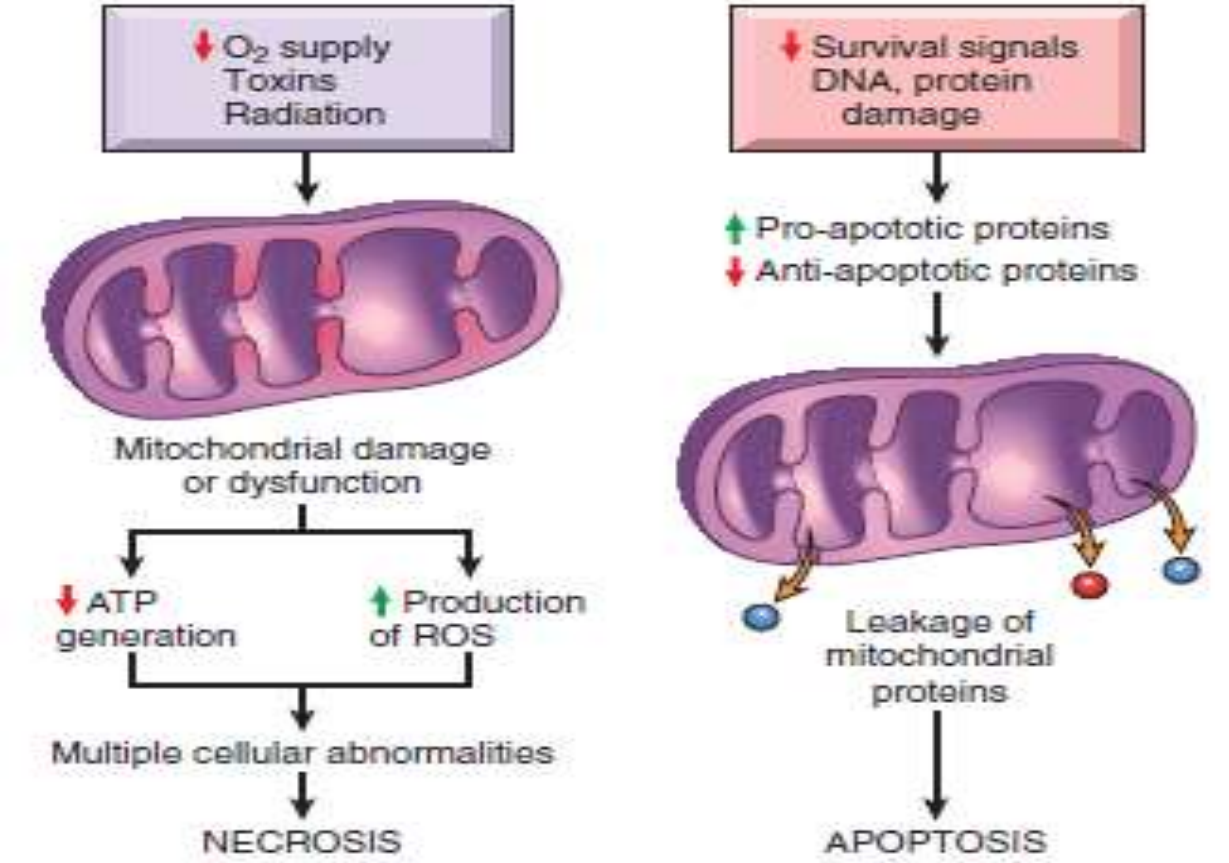
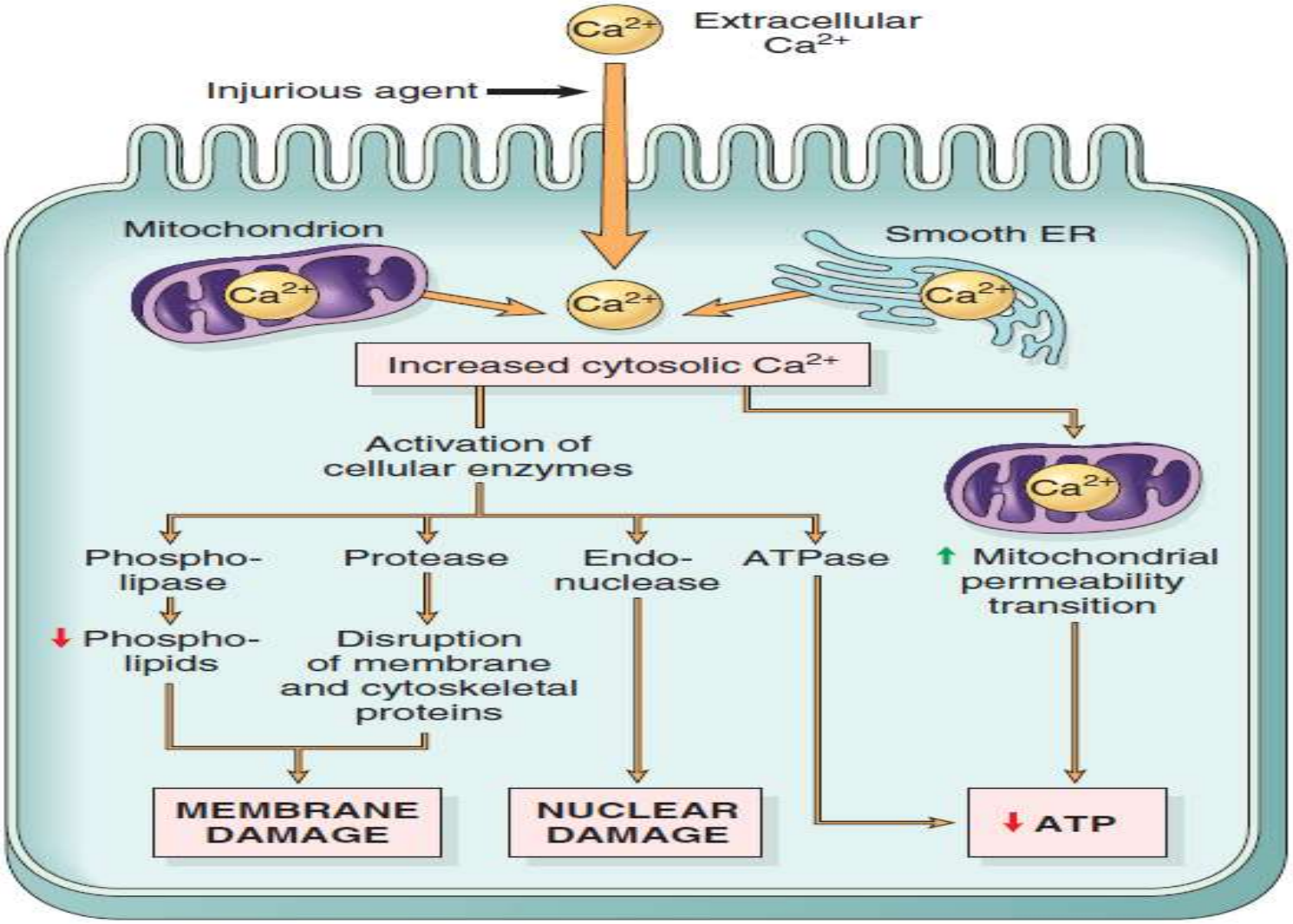


Figure 1–16 Role of mitochondria in cell injury and death. Mitochondria are affected by a variety of injurious stimuli and their abnormalities lead to necrosis or apoptosis. This pathway of apoptosis is described in more detail later. ATP, adenosine triphosphate; ROS, reactive oxygen species.

Mitochondrial damage may result in several biochemical abnormalities

- Progressive depletion of ATP,
- Formation of reactive oxygen species
- Formation of a high-conductance channel in the mitochondrial membrane (mitochondrial permeability transition pore)
- Released of certain proteins into the cytoplasm to activate apoptosis

Influx of Calcium



- **Sources of intracellular calcium:**
  Intracellular stores (mitochondria and ER)
  Influx across plasma membrane(ATP dependent).
- Increased cytosolic Ca activates a number of enzymes,
- Calcium induces apoptosis by
  Direct activation of caspases
  Increasing mitochondrial permeability

Accumulation of Oxygen-Derived Free Radicals (Oxidative Stress)

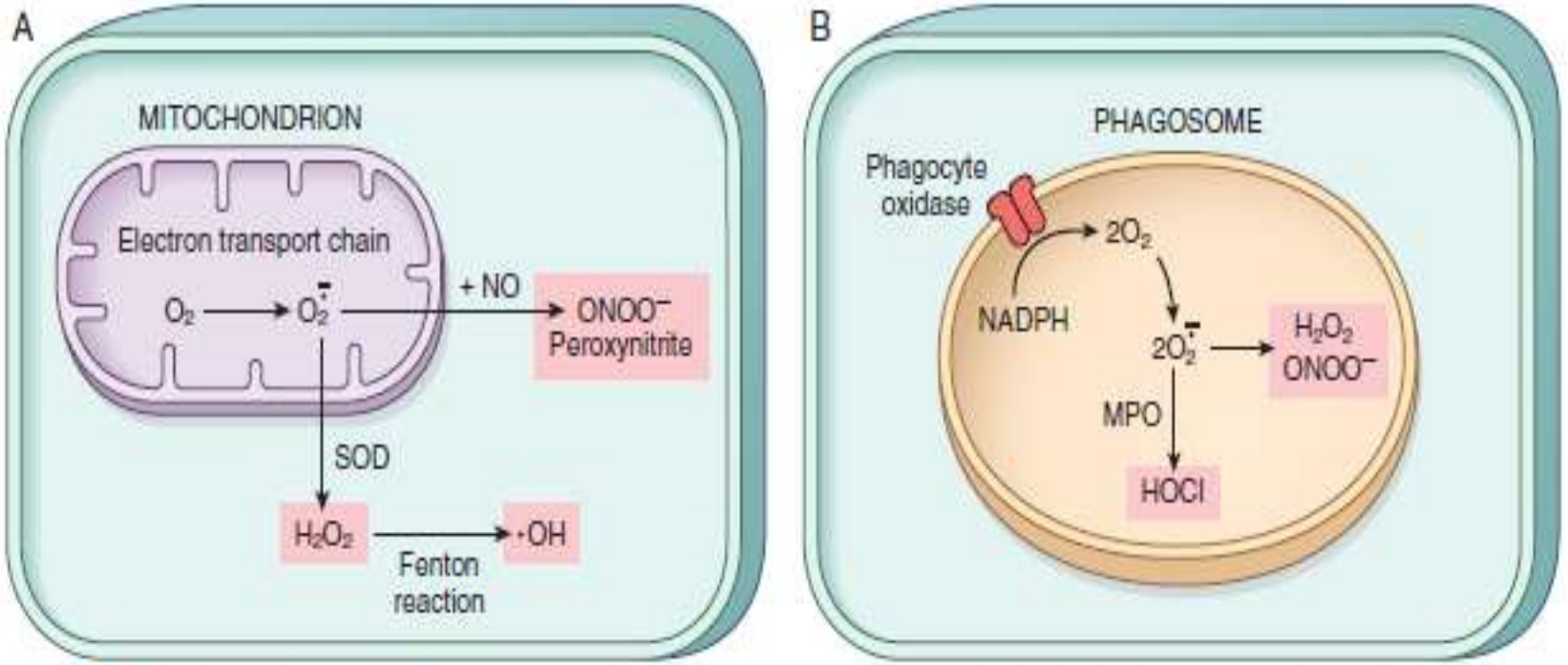


Figure 1–18 Pathways of production of reactive oxygen species. **A,** In all cells, superoxide ($O_2^{\cdot-}$) is generated during mitochondrial respiration by the electron transport chain and may be converted to H_2O_2 and the hydroxyl ($^{\cdot}OH$) free radical or to peroxynitrite ($ONOO^-$). **B,** In leukocytes (mainly neutrophils and macrophages), the phagocyte oxidase enzyme in the phagosome membrane generates superoxide, which can be converted to other free radicals. Myeloperoxidase (MPO) in phagosomes also generates hypochlorite from reactive oxygen species (ROS). NO, nitric oxide; SOD, superoxide dismutase.

Free radicals

- Chemical species with single unpaired electron (extremely unstable)
- Attack nucleic acids, cellular proteins and lipids.
- Molecules that react with free radicals are converted into free radicals.
- Involved in: **ischemia-reperfusion, chemical and radiation injury, toxicity from oxygen , cellular aging, microbial killing by phagocytes, and tissue injury in inflammation**.
- **The damage caused by them is determined by their rates of production and removal**

ROS are produced by two major pathways

- Normally in small amounts in all cells during (redox) reactions in the mitochondria.
- In phagocytic leukocytes (neutrophils and macrophages) for destroying microbes and inflammatory reactions.

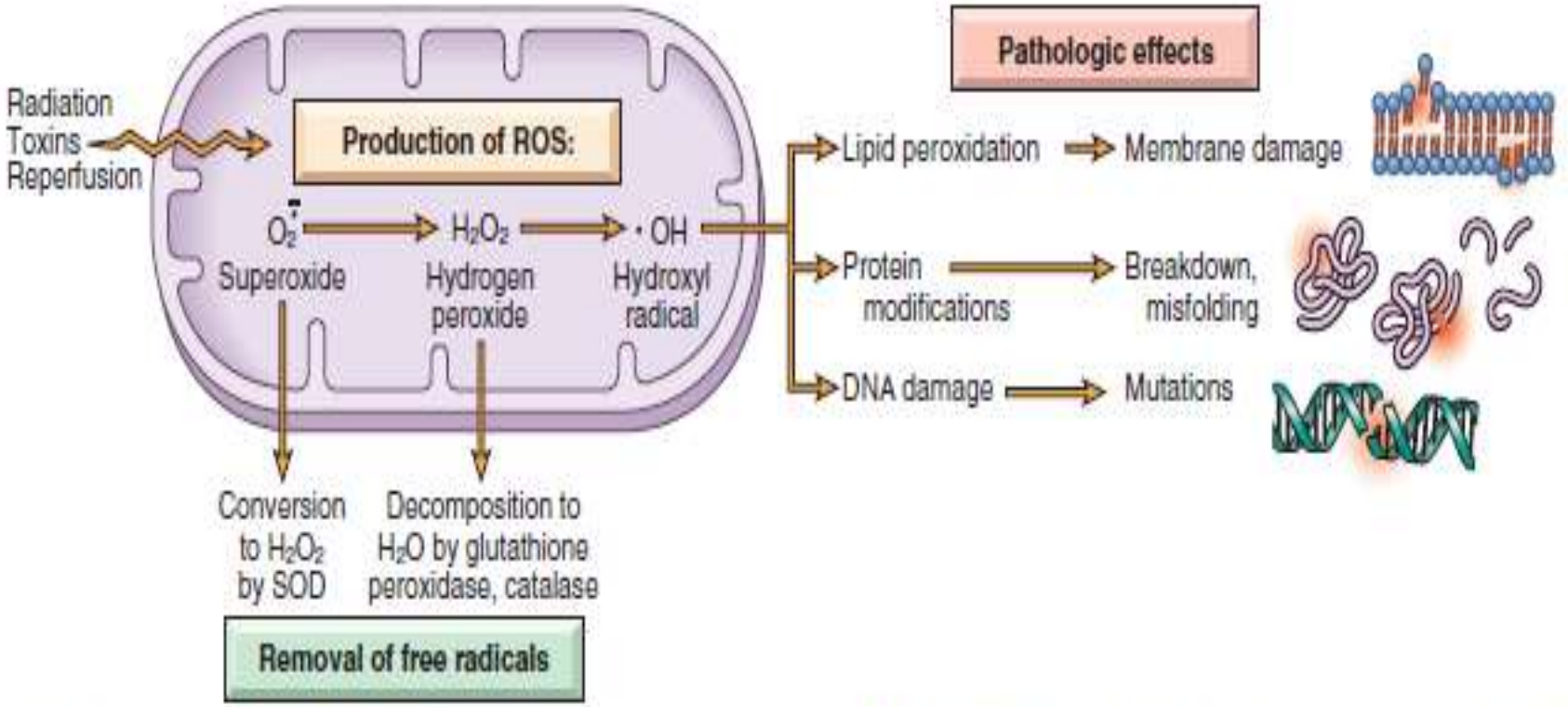
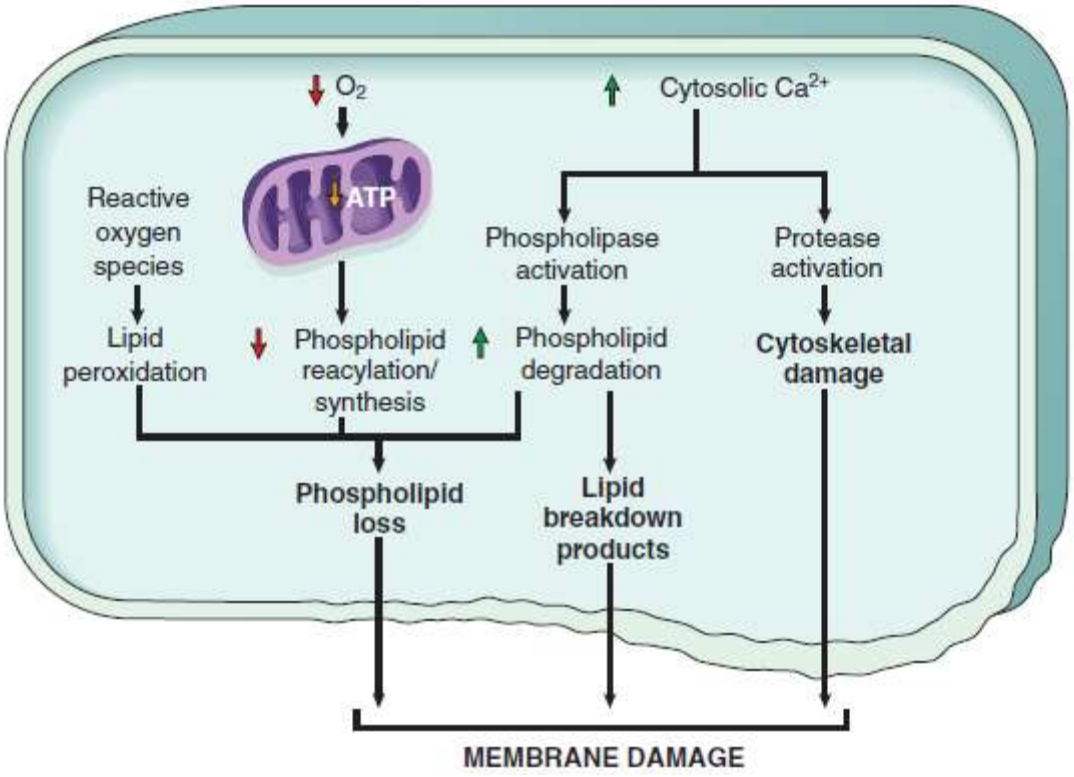


Figure 1–19 The generation, removal, and role of reactive oxygen species (ROS) in cell injury. The production of ROS is increased by many injurious stimuli. These free radicals are removed by spontaneous decay and by specialized enzymatic systems. Excessive production or inadequate removal leads to accumulation of free radicals in cells, which may damage lipids (by peroxidation), proteins, and deoxyribonucleic acid (DNA), resulting in cell injury.

- **Generation of free radicals**
- Radiant energy
- Exogenous chemicals
- Inflammation
- **Removal of free radicals:**
- SPONTANIOUS DECAY
- Superoxide dismutases (SODs)
- Glutathione (GSH) peroxidases.
- Catalase.
- Endogenous or exogenous antioxidants (vitamins E, A, and C and β-carotene

Defects in Membrane Permeability



Cell membranes, lysosomal membranes, mitochondrial membranes.

Damage to DNA and Proteins

- Cells have mechanisms that repair damage to DNA.
- If damage is too severe, trigger apoptosis.
- Improperly folded proteins have similar effect

CLINICOPATHOLOGIC CORRELATIONS: EXAMPLES OF CELL INJURY AND NECROSIS

- Ischemic and Hypoxic Injury

- Ischemia injures tissues faster than hypoxia
- Reduced generation of ATP
- Functional consequences (heart muscle)
- If oxygen is restored, disturbances are reversible.
- If ischemia persists, irreversible injury and necrosis .

Hypoxia
Ischemia

2

*

1

↓ Oxidative phosphorylation

↓ ATP

↓ Protein synthesis

↓ Glycogen

↑ Lactic acid

Pump failure cell swelling

↓ pH

↑ Influx of Ca^{2+}

↑ Mitochondrial permeability transition

+

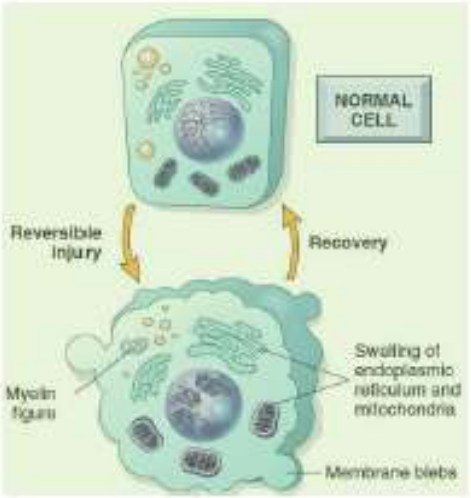
Activation of cellular enzymes

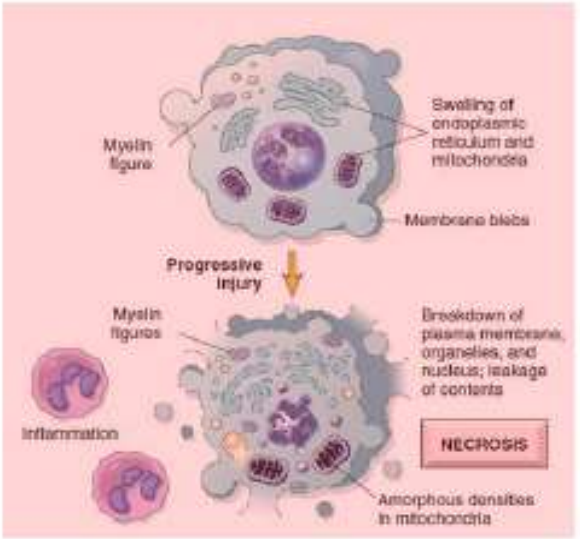
Accumulation of ROS

↓

Phospholipid loss

3





* Some apoptosis may also occur due to leakage of pro-apoptotic molecules

Ischemia-Reperfusion Injury

- Restoration of blood flow to ischemic but viable tissues results, in the death of cells that are reversibly injured.

- Mechanism:
- By generation of ROS from parenchymal, endothelial cells and leukocytes
- By influx of leukocytes and plasma proteins (complement)

Chemical (Toxic) Injury

- **Direct toxicity**: combining molecular component or cellular organelle
- The greatest damage is usually to the cells that use, absorb, excrete, or concentrate the chemicals.
- Examples: mercuric chloride poisining (seafood), chemotherapeutic drugs.

- **Indirect toxicity**: converted to reactive toxic metabolites, involves the formation of free radicals. (cytochrome P-450)
- Examples: Carbon tetrachloride (CCl4), acetaminophen

CCL4 toxicity

- CCl4