MECHANISMS OF CELL INJURY

cell injury and adaptations

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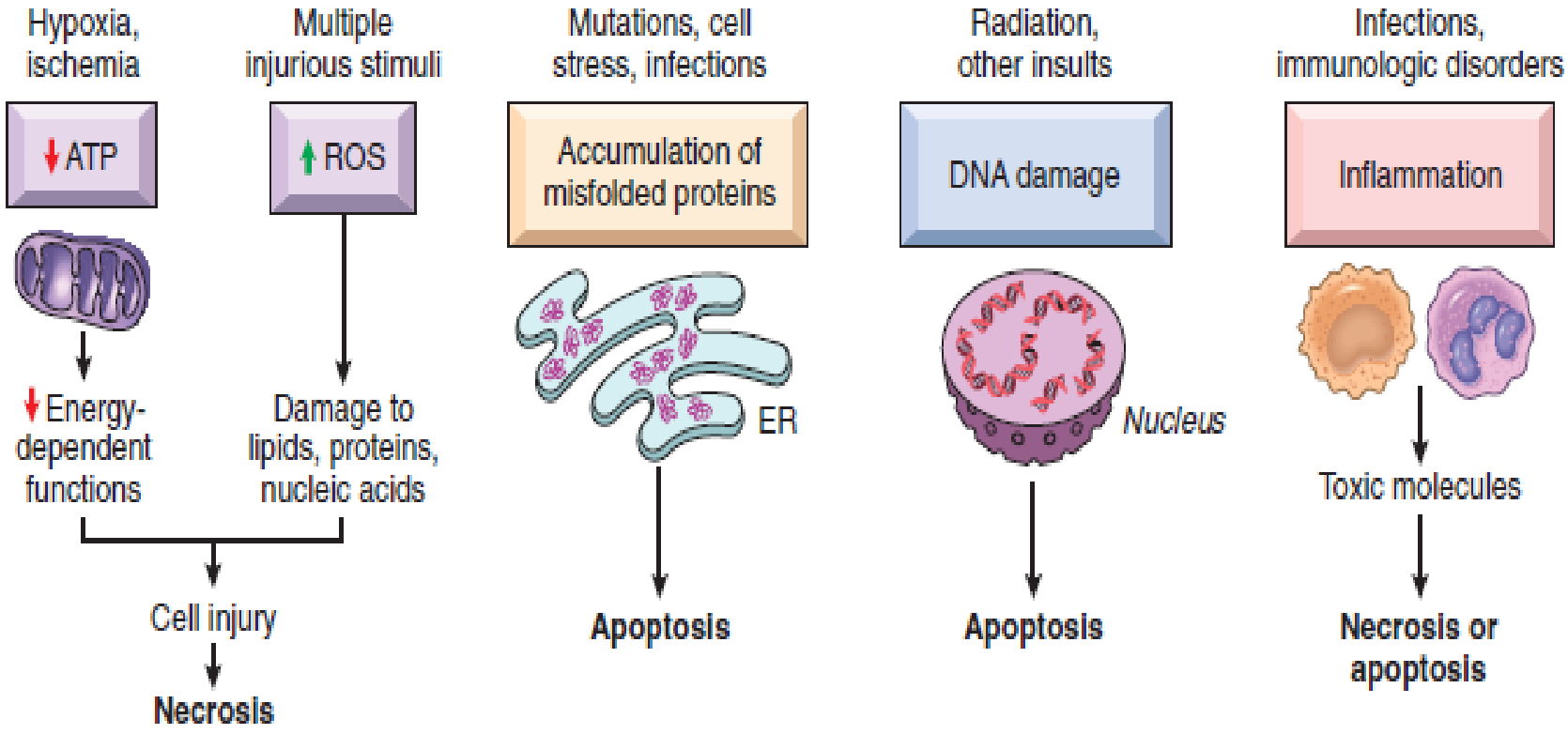
MECHANISMS OF CELL INJURY

Principles

- The cellular response to injury depends on:
  - type of injury
  - duration
  - severity
- The consequences of injury also depend on:
  - type,
  - status,
  - adaptability, and genetic makeup of the injured cell (precision medicine concept)

- Cell injury results from functional and biochemical abnormalities in one or more of several essential cellular components.
- Same injury may trigger more than one mechanism.

The principal biochemical mechanisms and sites of damage in cell injury



Hypoxia and Ischemia

- One of the most frequent causes of injury.
- Defective oxidative phosphorylation >>Failure of ATP generation>>>depletion of ATP in cells
- Failure of energy dependent pathways (membrane transport, protein synthesis, lipogenesis and phospholipid turnover)

- Anaerobic glycolysis.
- Liver cells and skeletal muscle cells Vs brain and heart.

Hypoxia effects:

- Reduced activity of membrane ATP dependent sodium pumps>> cell swelling
- Lactic acid accumulation >> decreased PH>> failure of enzymes.
- Disruption of the ribosomes>> decreased protein synthesis.
- Accumulation of ROS
- Damage to mitochondrial and lysosomal membranes.
- Necrosis is the end result.
- Apoptosis can contribute.

Ischemia–Reperfusion Injury

- Paradoxical cell injury after restoration of blood flow to ischemic but viable tissues.
- After myocardial and cerebral ischemia.

- **Increased generation of ROS from:**
- Injured cells with damaged mitochondria & defective antioxidant mechanisms.
- Infiltrating new leukocytes.

- **Inflammation induced by influx of leukocytes, plasma proteins and complement**

Oxidative Stress

- Cellular abnormalities induced by ROS (free radicals)
- Chemical species with single unpaired electron (extremely unstable)

- **ROS generated in:**
- Chemical injury (CCL4)
- Radiation injury (UV, Xray)
- Hypoxia
- Cellular aging
- Inflammation
- Ischemia-reperfusion injury.

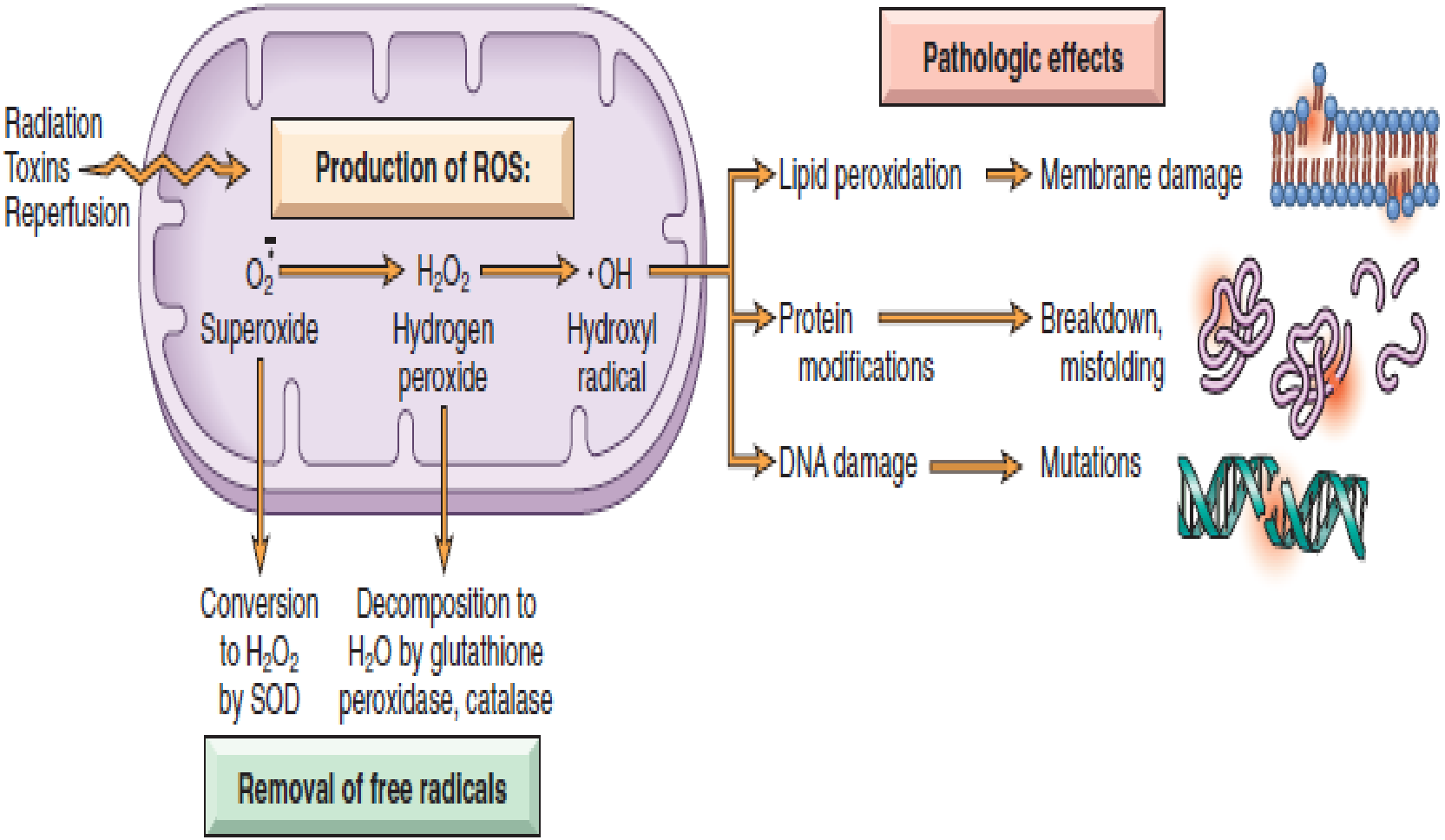
Generation and Removal of Reactive Oxygen Species

- **1-Normally produced in small amounts in all cells during the redox reactions.**
- Oxygen is reduced to produce water.
- Small amounts of highly reactive but short-lived toxic intermediates are generated.
- Superoxide (O2 •), hydrogen peroxide (H2O2), hydroxyl radical •OH.

- **2-Produced in phagocytic leukocytes (neutrophils and macrophages) during inflammation.**
- In phagosomes and phagolysosomes to kill microbes.
- O2 >> superoxide >> H2O2 >> hypochlorite.
- Myeloperoxidase (H2O2 into hypochlorite).

Removal of free radicals

- Decay spontaneously
- Superoxide dismutase (SOD).
- Glutathione (GSH) peroxidases.
- Catalase (one of most active enzymes known)
- Endogenous or exogenous anti-oxidants (e.g., vitamins E, A, and C and β-carotene)


Radiation
Toxins
Reperfusion
Production of ROS:
$O_2^{\cdot-}$
Superoxide
H_2O_2
Hydrogen peroxide
·OH
Hydroxyl radical
Pathologic effects
Lipid peroxidation
Membrane damage
Protein modifications
Breakdown, misfolding
DNA damage
Mutations
Conversion to H_2O_2 by SOD
Decomposition to H_2O by glutathione peroxidase, catalase
Removal of free radicals

Effects or ROS:

- **1-Lipid peroxidation of membranes.**
- (plasma, lysosomal & mitochondrial membranes)
- **2-Crosslinking and other changes in proteins.**
- (degradation, fragmentation, loss of enzymatic activity & misfolding).
- **3-DNA damage.**
- Single strand breaks, mediate: apoptosis, aging, malignant transformation
- **4-Killing of microbes.**

Cell Injury Caused by Toxins

- Environmental chemicals & substances produced by infectious pathogens.

- **Direct-acting toxins**
- **Latent toxins.**

Direct-acting toxins

- Act directly by combining with a critical molecular component or cellular organelle.

- **Mercuric chloride poisoning**
- Contaminated seafood
- Mercury binds to sulfhydryl groups of membrane proteins>>inhibit ATP-dependent transport and increase permeability.
- **Chemotherapeutic agents**
- **Toxins from microorganisms.**

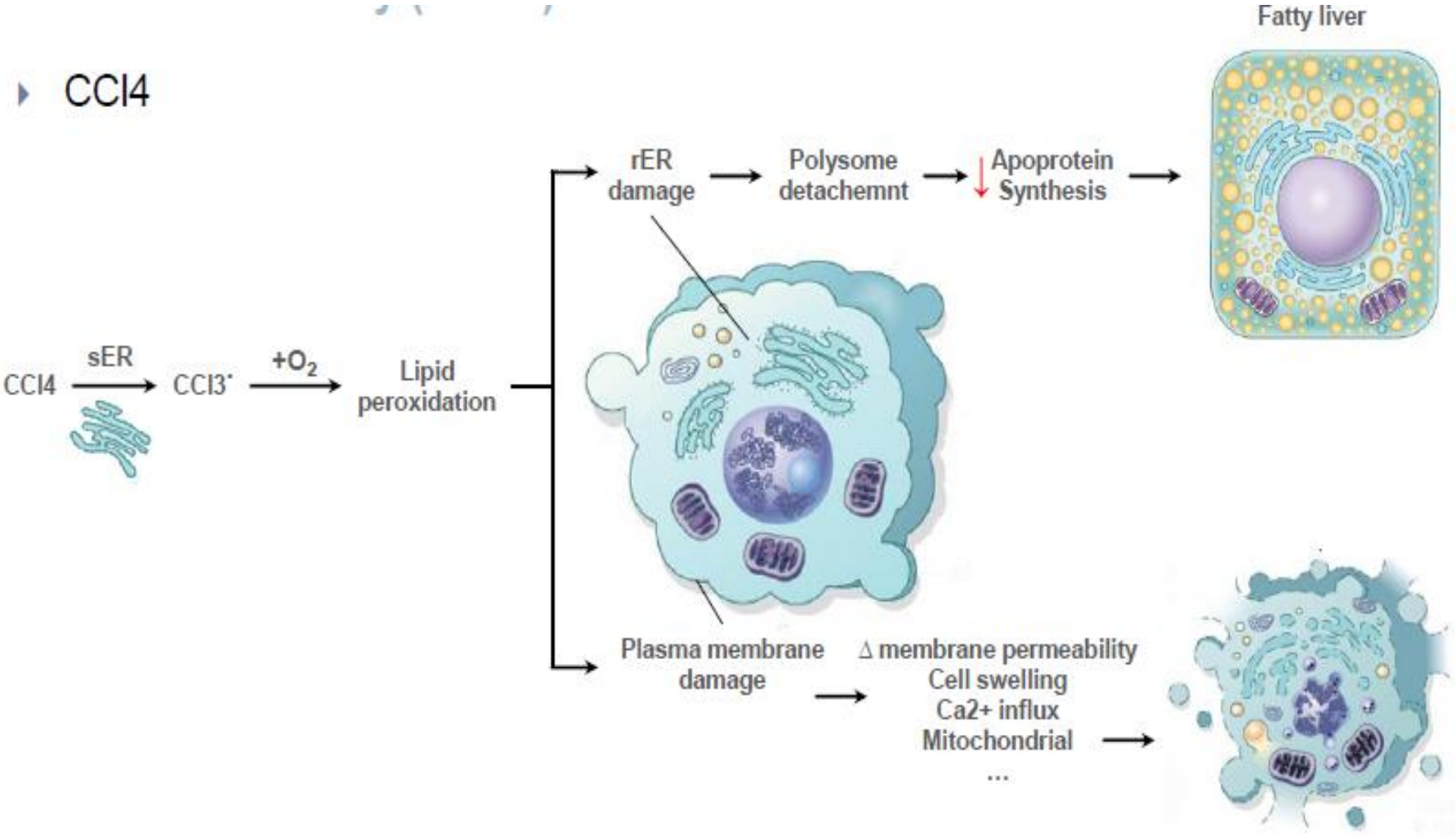
Latent toxins

- Not intrinsically active
- Must be converted to reactive metabolites, then act on target cells.
- Via cytochrome P-450 in SER of the liver.
- Damage mainly by formation of free radicals>>membrane phospholipid peroxidation.

- **CCl4 and acetaminophen**.
- Membrane peroxidation>>>>damage
- ER membranes >> detachment of ribosomes>>decline in synthesis of enzymes and proteins +decreased synthesis of apoproteins >> fatty liver
- Mitochondrial membranes>> decreased ATP >> cell swelling >> cell death.

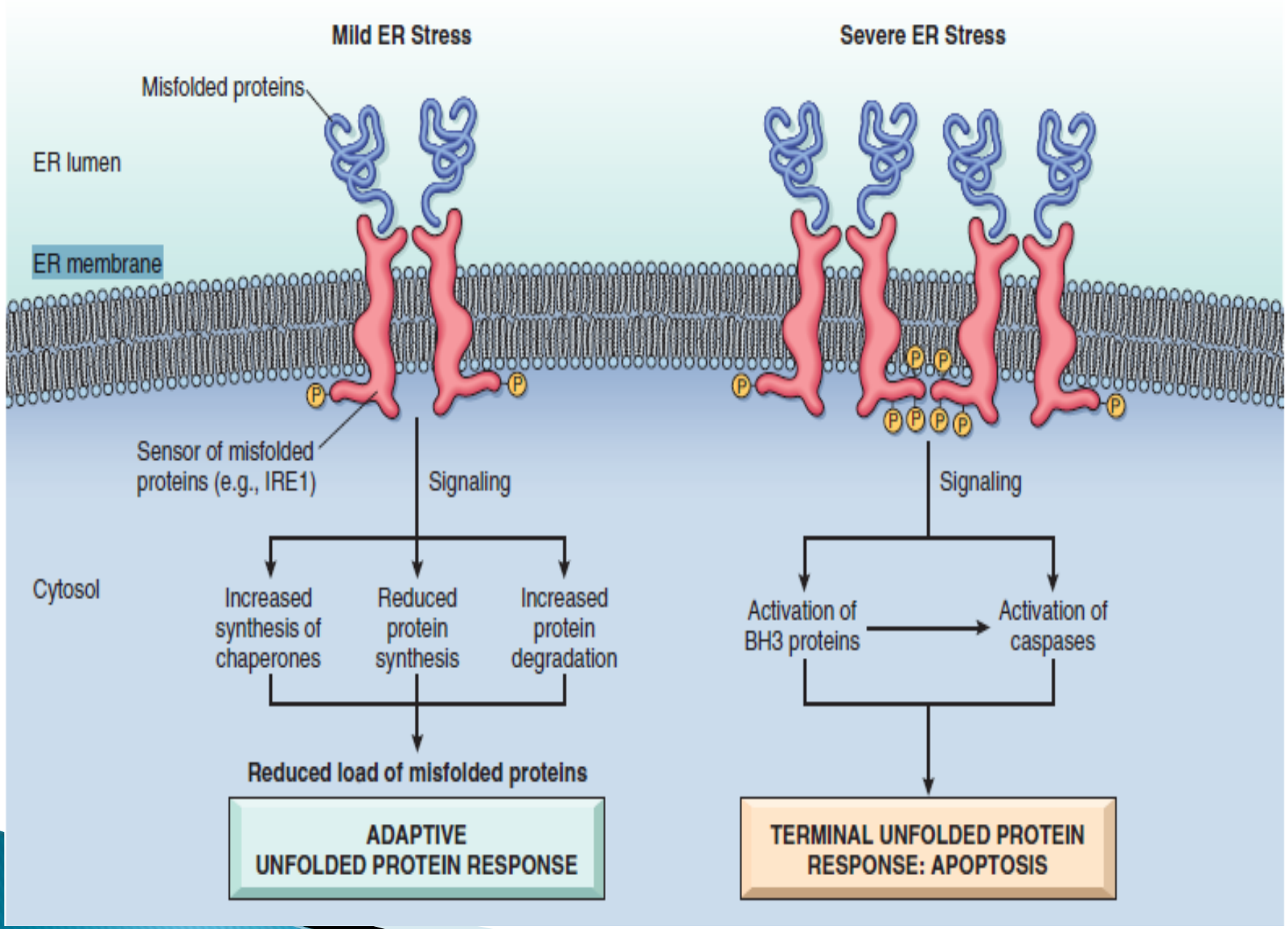
CCL4 toxicity

- CCl4



Endoplasmic Reticulum Stress

- Chaperones in ER control proper protein folding
- Misfolded proteins >> ubiquinated >> targeted to proteolysis
- **Unfolded protein response (adaptive response):**increase chaperones production, decrease protein translation and increase destruction.
- If failed >> proapoptotic sensor activation (BH3-only family) + direct activation of caspases >>**apoptosis by the mitochondrial pathway.**


Mild ER Stress
Severe ER Stress
Misfolded proteins
ER lumen
ER membrane
Sensor of misfolded proteins (e.g., IRE1)
Signaling
Signaling
Cytosol
Increased synthesis of chaperones
Reduced protein synthesis
Increased protein degradation
Activation of BH3 proteins
Activation of caspases
Reduced load of misfolded proteins
ADAPTIVE UNFOLDED PROTEIN RESPONSE
TERMINAL UNFOLDED PROTEIN RESPONSE: APOPTOSIS

Causes of misfolding

- Gene mutations
- Aging (decreased capacity to correct misfolding)
- Infections, especially viral infections (microbial proteins)
- Increased demand for secretory proteins such as insulin in insulin-resistant states
- Changes in intracellular pH
- Neurodegenerative diseases
- Deprivation of glucose and oxygen in ischemia and hypoxia.

Protein misfolding causes disease by:

- **Deficiency of an essential protein due to degradation**
- Cystic fibrosis
- **Inducing apoptosis of the affected cells**
- Neurodegenerative disorders (Alzheimer disease, Huntington disease & Parkinson disease), type 2 diabetes and prions disease.
- **Inducing both:**
- Alpha 1 antitrypsin deficiency.
- **Improperly folded proteins accumulation in extracellular tissues**
- Amyloidosis

DNA Damage

- Radiation
- Chemotherapeutic agents
- Intracellular generation of ROS
- Mutations

- DNA damage >> p53 activation >>arrest cell cycle at G1 phase for repair >> if repair is impossible >> apoptosis.
- In P53 mutations >> mutated cells replicate >> neoplastic change.

Inflammation

- Pathogens
- Necrotic cells,
- Dysregulated immune responses (autoimmune diseases and allergies)

- Inflammatory cells (neutrophils, macrophages, lymphocytes) secrete products that destroy microbes and damage host tissues.

Common Events in Cell Injury From Diverse Causes

- Mitochondrial Dysfunction
- Defects in Membrane Permeability

Mitochondrial Dysfunction

- Energy factory
- Hypoxia, toxins, radiation.
- In necrosis and apoptosis.

- **Consequences:**
- Failure of oxidative phosphorylation, ATP depletion.
- Abnormal oxidative phosphorylation, formation of ROS
- Mitochondrial permeability transition pores, loss of membrane potential.
- Release of cytochrome c >> apoptosis

Mitochondrial Damage and Dysfunction

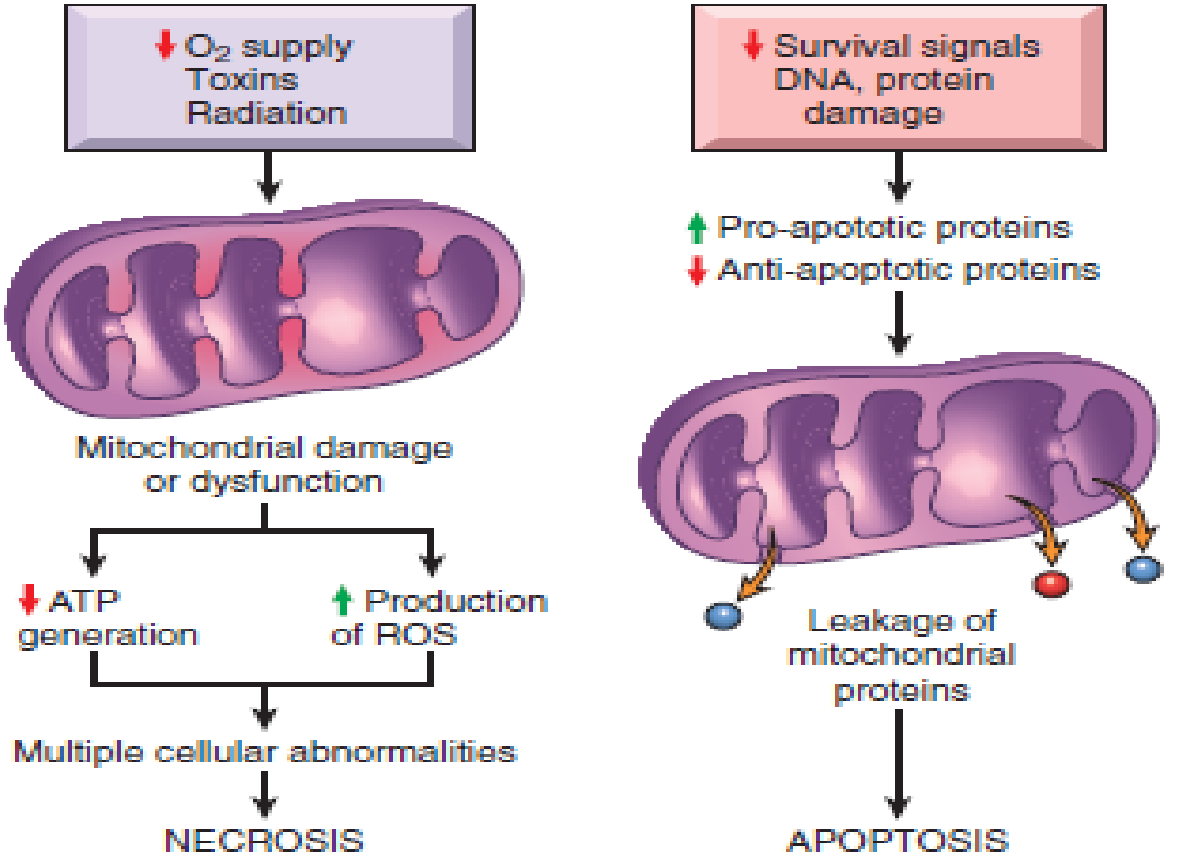


Figure 1–16 Role of mitochondria in cell injury and death. Mitochondria are affected by a variety of injurious stimuli and their abnormalities lead to necrosis or apoptosis. This pathway of apoptosis is described in more detail later. ATP, adenosine triphosphate; ROS, reactive oxygen species.

Depletion of ATP

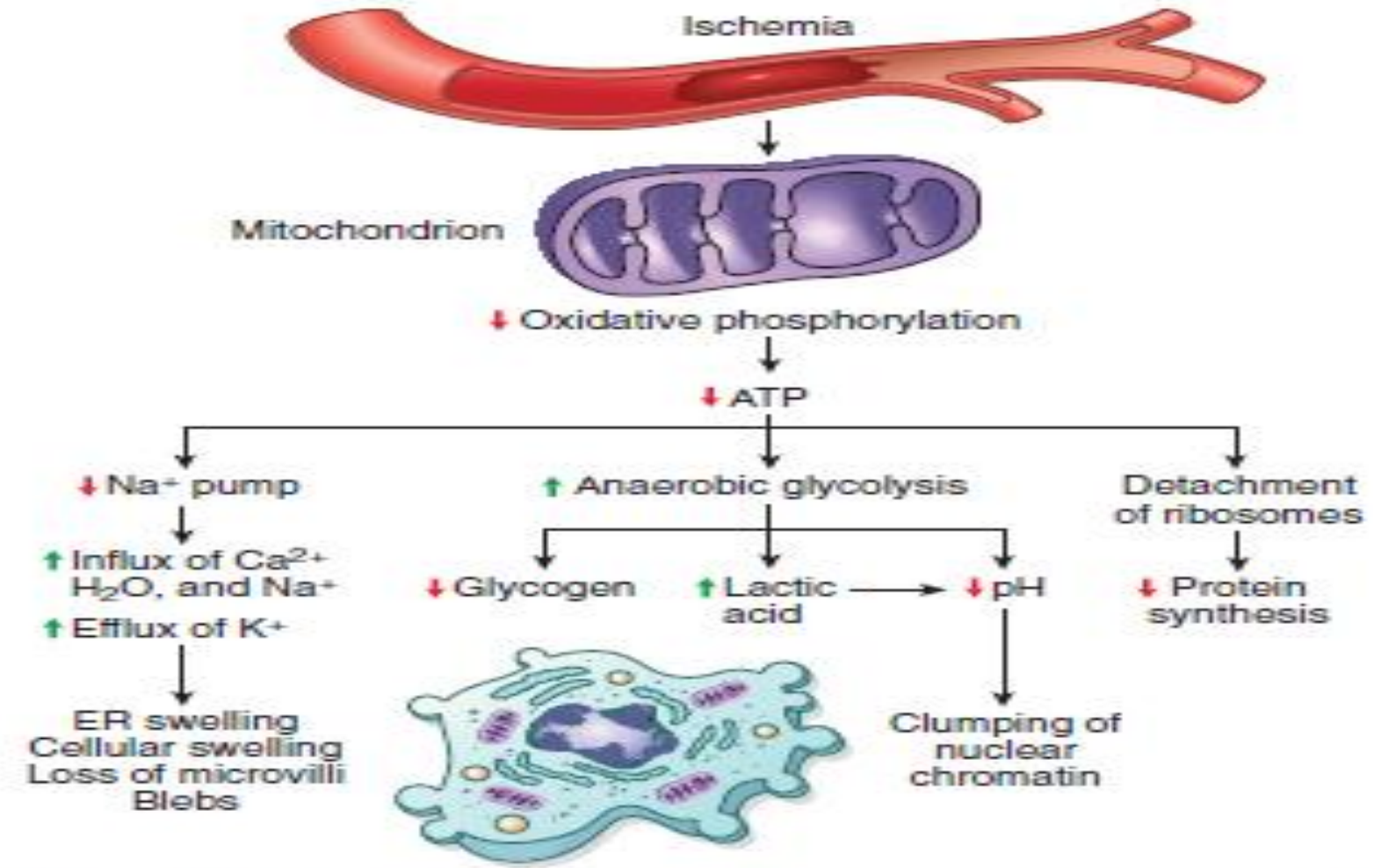


Figure 1–15 The functional and morphologic consequences of depletion of intracellular adenosine triphosphate (ATP). ER, endoplasmic reticulum.

Defects in Membrane Permeability

- Mitochondrial membrane damage: decreased ATP
- Plasma membrane damage: loss of osmotic balance, influx of fluids, leak of contents
- Lysosomal membranes: leakage of enzymes >> cellular digestion.

- A 20 year old male is involved in a motor vehicle accident. The left femoral artery is lacerated resulting in extensive blood loss.He is hypotensive for hours during transport to the ER. Which of the following tissues is most likely to withstand the impact of these events with the least damage?
-
- A Intestinal epithelium
- B Skeletal muscle
- C Retina
- D Cerebral cortex
- E Renal tubules

- A 50 year old female suffers an acute myocardial infarction. Thrombolytic agents are used to restore coronary blood flow. In spite of this therapy, the degree of myocardial fiber injury may increase because of which of the following cellular abnormalities?
-
- AIncreased production of ATP
- B Decreased intracellular pH from anaerobic glycolysis
- C Increased free radical formation
- D Mitochondrial swelling
- E Decreased phospholipid peroxidation

- In an experiment, cells are subjected to oxidant stress. There are increased numbers of free radicals generated within the cells. Generation of which of the following enzymes within these cells is the most likely protective mechanism to reduce the number of free radicals?
-
- A B Phospholipase
- C Endonuclease
- D Glutathione peroxidase
- E Myeloperoxidase
- Cytochrome p450.

- A cellular mutation results in a protein that does not fold properly. The misfolded protein remains within the cell and is not excreted. Activation of which of the following cytoplasmic enzymes is most likely to occur?
-
- A NADPH oxidase
- B Glutathione peroxidase
- C Ribonuclease
- D Caspase
- E Telomerase