

MECANISMS OF CELL INJURY

lec no. 3,4

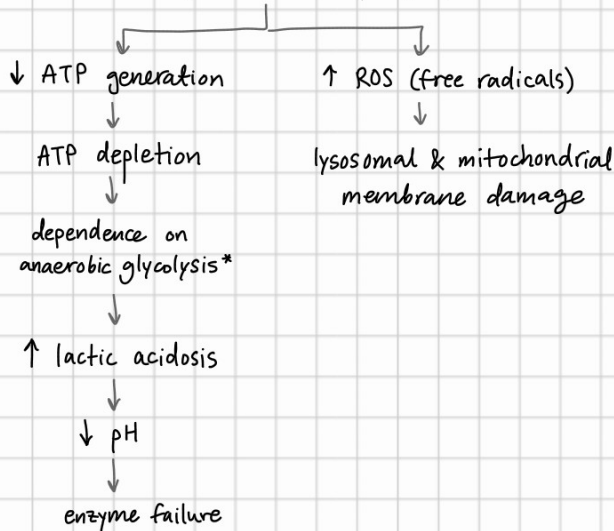
- Cellular response to injury depends on:
 - type of injury
 - duration (prolonged = irreversible injury...)
 - severity (hypoxia vs ischemia (more severe))
- Consequences of injury depend on:
 - type of injury
 - status (diseased vs healthy cell)
 - adaptability, and genetic makeup of the injured cell (precision medicine concept)
- Same injury may trigger more than one mechanism
- Each mechanism could be triggered by more than one type of cellular stress

SIMPLE
INTRO

↓ ATP

1. Hypoxia & Ischemia

- defective oxidative phosphorylation



- failure of energy dependent pathways due to ↓ATP (membrane transport, protein synthesis, lipogenesis & phospholipid turnover)
- disruption of ribosomes → ↓ protein synthesis (ER & mt swelling)

* Liver & SM / Brain & Heart
anaerobic glycolysis no anaerobic glycolysis

2. Ischemia Reperfusion Injury

- Paradoxical cell injury after restoration of blood flow
- After myocardial & cerebral ischemia/infarction
- ↑ ROS generation from
 - damaged mt & defective antioxidant mechanisms
 - infiltrating new leukocytes (they use ROS to kill pathogens)
- Inflammation due to influx of leukocytes, plasma proteins & complement proteins

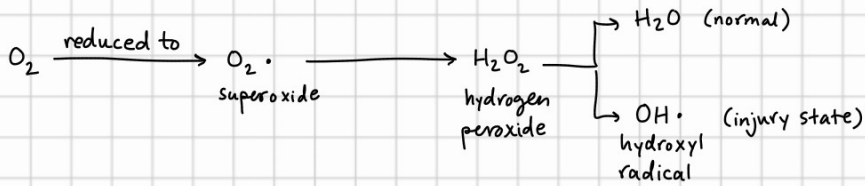
3. Oxidative Stress

- ↑ ROS (free radicals)
- chemicals with single unpaired electron (very unstable)
- free radicals cause cellular damage & produce more ROS
- ROS generated by:
 - chemical injury (CCL4)
 - Radiation injury (UV, Xray)
 - Hypoxia / Ischemic reperfusion
 - cellular aging
 - inflammation

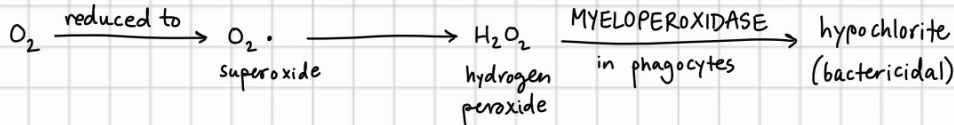
↑ ROS

1. Generation of ROS

A) Normally produced in small amounts during redox reactions



B) Produced in phagocytic leukocytes (neutrophils and macrophages) during inflammation



2. Removal of ROS

- Decay spontaneously (short-lived)
 - Superoxide dismutase (SOD) $\text{O}_2 \xrightarrow{\text{SOD}} \text{H}_2\text{O}_2$
 - 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)
- $$\text{H}_2\text{O}_2 \xrightarrow{\text{GSH / Catalase}} \text{H}_2\text{O}$$

3. Effects of ROS

- Lipid peroxidation of (plasma, lysosomal & mitochondrial) membranes
 - Crosslinking and other changes in proteins (degradation, fragmentation, loss of enzymatic activity & misfolding)
 - DNA damage/mutations (single strand breaks, mediate: apoptosis, aging, malignant transformation)
 - Killing of microbes & degradation of dead cells
- UV light / X-ray
- good effect

4. Toxins

- Environmental chemicals & substances produced by infectious pathogens

1. Direct-acting toxins

(They combine with a critical molecule)

- Mercuric chloride poisoning (contaminated seafood)
Mercury — sulfhydryl groups of membrane proteins
inhibit ATP-dependent transport & increase permeability (cell swelling)
- Chemotherapeutic agents (directly damage malignant cells)
- Toxins from microenvironments (cholera toxin / bacterial toxins)

2. Latent toxins (indirect)

(no intrinsic activity)

- CCl₄ & acetaminophen (paracetamol overdose)
- membrane peroxidation
- ↓ enzyme & apoprotein synthesis
- no apoproteins to transport lipids in blood (accumulation in liver)
- fatty liver
- ↓ ATP production
- necrosis / apoptosis

inactive toxin

↓
metabolized in liver SER by cytochrome P-450

↓
formation of free radicals

↓
membrane phospholipid peroxidation (protein/DNA damage)

Accumulation of Misfolded Proteins

ER Stress

- Chaperones in ER control proper protein folding
- Unfolded Protein Response (UPR) (adaptive response to misfolded protein accumulation):

- ↑ chaperones production
- ↓ protein translation
- ↑ destruction

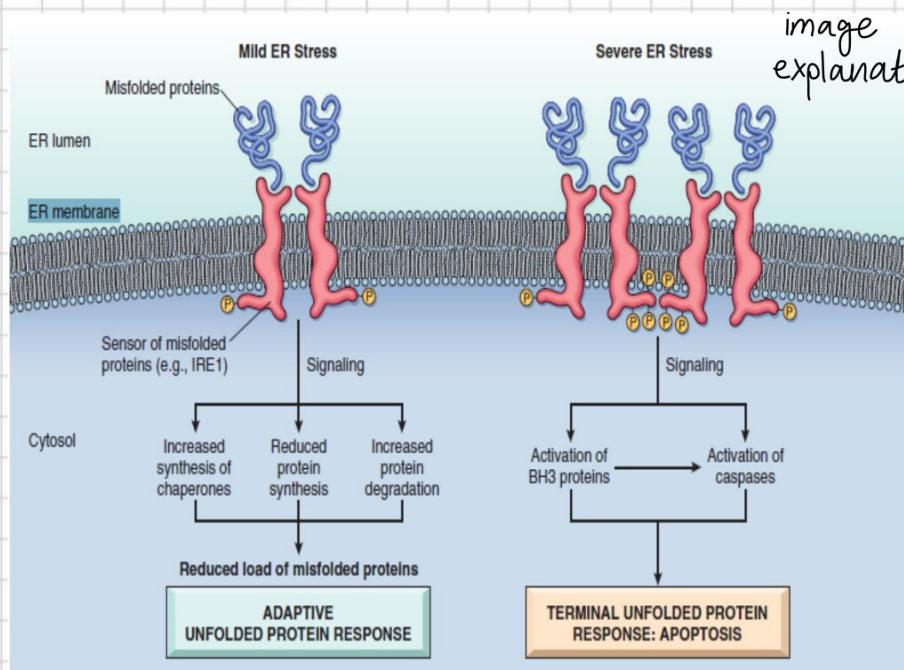
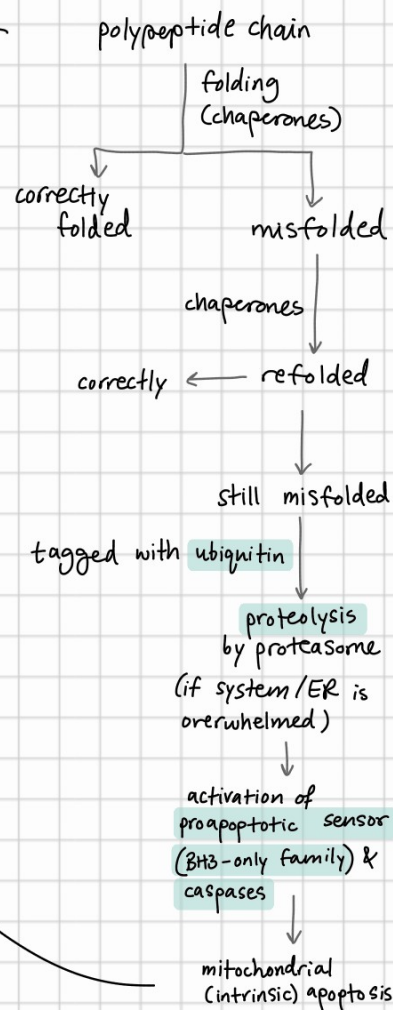


image explanation



Misfolding Causes

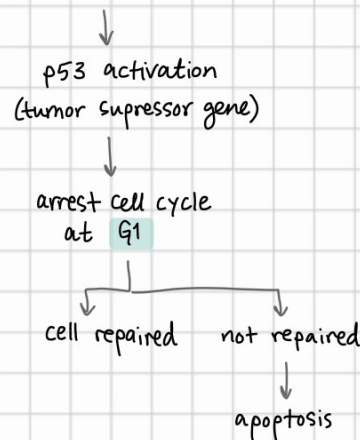
- Aging (↓ capacity to correct misfolding)
- Infections, especially viral infections (microbial proteins)
- ↑ demand for secretory proteins (ER stress) such as insulin in insulin-resistant states
- Changes in intracellular pH
- ↓ glucose and oxygen (ischemia/hypoxia)
- Gene mutations (misfolded proteins are degraded)
- Neurodegenerative diseases

DNA Damage

Causes

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

DNA DAMAGE



* p53 mutated

↓

mutated cells keep replicating

↓

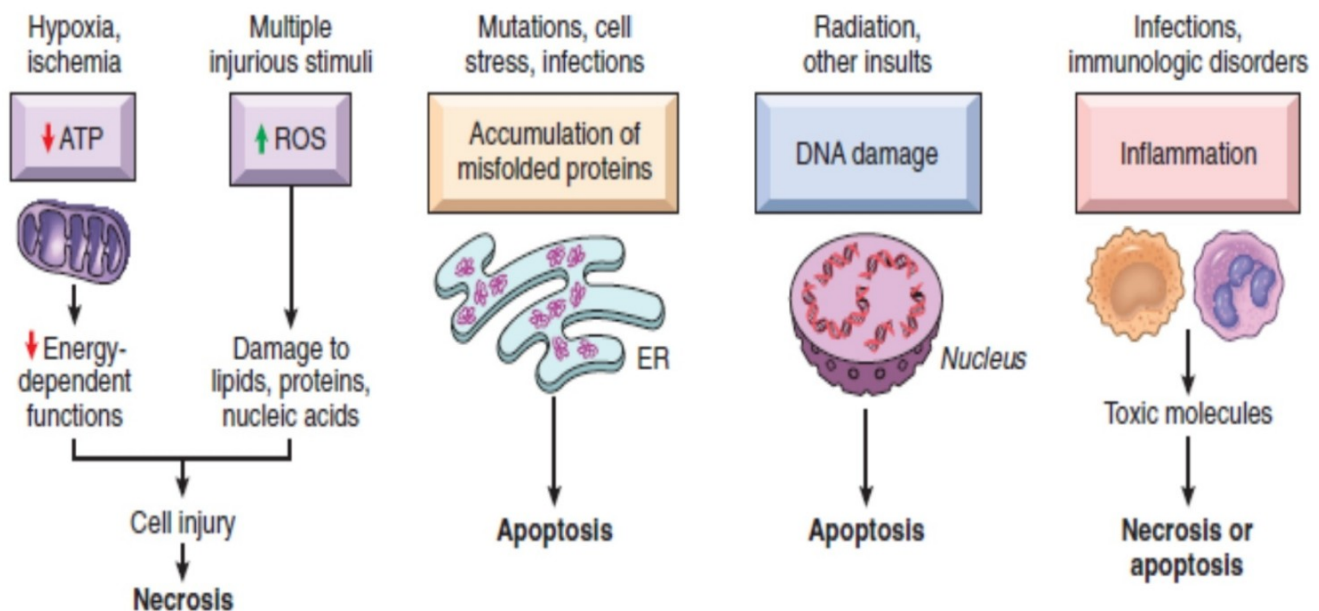
neoplastic change (tumor development)

Pathological Mechanism	Cellular Fate	Clinical Example
Gene mutations	Degradation	Cystic fibrosis
Induced apoptosis	Cell death	Neurodegenerative disease (Alzheimer's, Huntington's, Parkinson's) Prion diseases Type 2 diabetes
Both	Degradation & Toxicity	α-1-antitrypsin Deficiency
Extracellular Accumulation of misfolded proteins	Insoluble aggregates	Extracellular Amyloidosis

Inflammation

- Pathogens
- Necrotic cells
- Dysregulated immune responses (autoimmune diseases and allergies)
- Inflammatory cells (neutrophils, macrophages, lymphocytes) secrete products (like ROS) that destroy microbes and damage host tissues

This image visualizes all the previous info



Common Events in Cell Injury

BY: EMAN AIAMMOURI

❏ Mitochondrial dysfunction

- hypoxia/toxins/radiation
- Necrosis & apoptosis

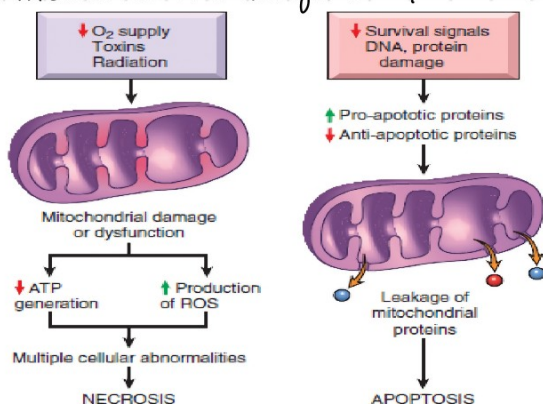
Consequences:

- Failed oxidative phosphorylation ($\downarrow$ ATP, $\uparrow$ ROS)
- Mitochondrial permeability transition pores (loss of membrane potential)
- Cytochrome c released $\rightarrow$ activation of caspases $\rightarrow$ apoptosis

❏ Defects in mitochondrial membrane permeability

- Mitochondrial membrane damage ($\downarrow$ ATP)
- Plasma membrane damage (loss of osmotic balance, influx of fluids, leak of contents)
- Lysosomal membrane damage (leakage of enzymes $\rightarrow$ cellular digestion)

Mitochondrial Damage & Dysfunction



ATP Depletion

