[A QUICK SUMMARY]

[pathology, 3rd lec]

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PRINCIPLES & CONCEQUENCES:

The **cellular response** to injury

Depends on:

1. **type** of injury
2. **duration**
3. **severity**

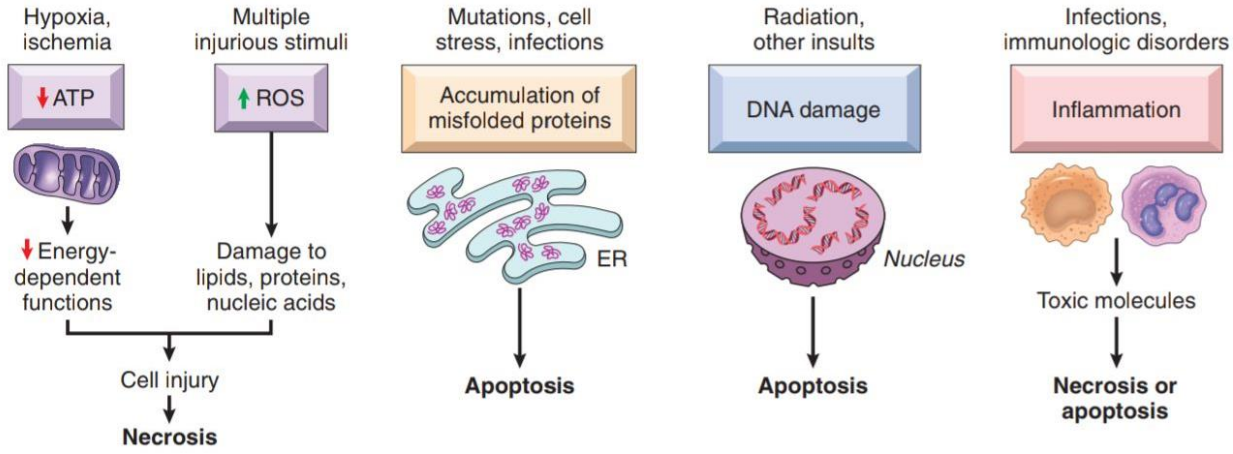
The **consequences** of injury

Depend on:

1. **Type** of cell
2. **status** (whether the cell is diseased from beginning or not)
3. **adaptability** and **genetic makeup** of the injured cell **(cells among different individuals may develop different consequences to the same toxin/drug)**

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

Pharmacogenetics : Understanding the role of generating polymorphisms in response to drugs and toxins



Mechanisms of cell injury

1 Hypoxia and Ischemia

Reduction in O_2 supply to the cell

↓

detective **oxidative phosphorylation** in the mitochondria

↓

failure of ATP generation

↓

depletion of ATP in cells failure of **E-dependent pathway**

↓

Adoption: anaerobic glycolysis (less efficient then oxidative phosphorylation {2ATP / lactic acid accumulation muscle fatigue})

Lead to decreased:

- -plasma membrane transportation (Na+/K+ pump)
- -protein synthesis
- -lipogenesis (production of lipids)
- -phospholipid turnover

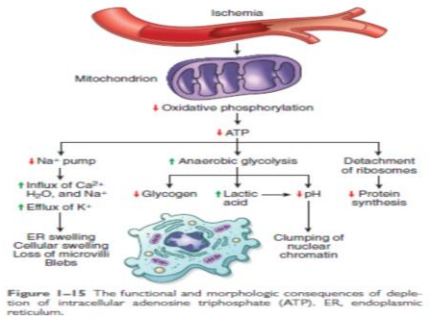


Figure 1–15 The functional and morphologic consequences of depletion of intracellular adenosine triphosphate (ATP). ER, endoplasmic reticulum.

The effects of hypoxia:

*Reduced activity of membrane ATP-dependent sodium pumps >sodium and water accumulation inside the cell >cellular swelling.

*Lactic acid accumulation >> decreased PH>> failure of enzymes.

*Disruption of the ribosomes from the RER membrane> decreased protein synthesis

*Accumulation of ROS

*Damage to mitochondrial and lysosomal membranes and leakage of destructive lysosomal enzymes to the cytosol of the cell.

Lead to :

Necrosis

Function consequences depend on:

- duration of the detection
- -severity
- the type of the tissue (heart+brain **VS** liver+muscles)

2 Ischemia-Reperfusion injury

When blood supply returns to a tissue after a period of ischemia or lack of oxygen (ischemic but viable tissues (didn't undergo irreversible cell injury**))**

E.G: myocardial or cerebral ischemia

↓

restoration(reperfusion) of blood flow

↓

Paradoxical cell injury

Cause:

Increased generation of ROS from:

- **Injured cells with damaged mitochondria & defective antioxidant mechanisms.** (incomplete reduction of oxygen in oxidative phosphorylation >>production of ROS (free radicals)
- **Infiltrating new leukocytes.**

Inflammation induced by influx of leukocytes, plasma proteins and complement

3 OXIDATIVE STRESS

Cellular abnormalities induced by ROS

Leads to Necrosis

ROS = chemical species with single unpaired electron (unstable, high E), that can bind to any organic/inorganic molecule and convert them to a free radical too >>> damage to cellular proteins/lipids and nucleic acids

ROS generated in:

-Chemical injury (CCL4)
-Radiation injury (UV, Xray)
- Hypoxia

-Cellular aging

-Inflammation

-Ischemia-reperfusion injury.

Generation of ROS

Normally

-produced in small amounts
-in all cells
-short-lived
-during the redox rxn

O2

Reproduce to produce

(O2 •)
(H2O2)
(•OH)

Small amounts of highly reactive but short-lived toxic intermediates are generated

H2O

During inflammation

-produced in phagocytic leukocytes (neutrophils and macrophages)

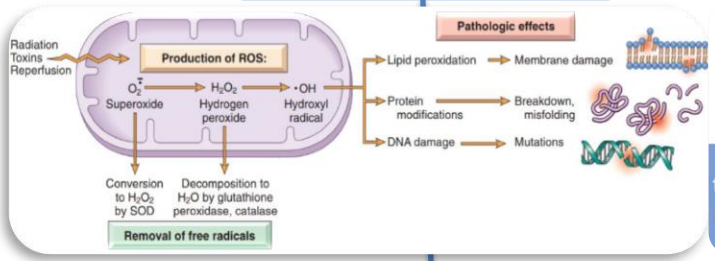
Mechanism

- leukocytes use phagosomes & phagolysosomes in attempt to kill the microbes /phagocytose the bacteria.

-the reaction of free-radicals production is the same, but H_2O_2 is converted to HYPOCHLORITE in phagocytes, this process is catalyzed by Myeloperoxidase.

[O2>Super oxide >H2O2> hypochlorite]

Removal of ROS



***Decay spontaneously**

***Superoxide dismutase** (catalyzes the conversion of O2• into H2O2)

***Glutathione (GSH) peroxidases [GSH type 1]** (catalyzes: H2O2 >>> water)

***Catalase** (catalyzes: H2O2 >>> water)

*** Endogenous or Exogenous anti-oxidants** (e.g., vitamins E, A and C and β-Carotene), antioxidants either block **or** scavenge free radicals' production

effects

the net effect of ROS (free radicals)

Depends on the rate of their production and removal

Determines the extent of the damage they perform on the cell

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

Necrosis

4

TOXINS CELL INJURY

Environmental chemicals & substances produced **by infectious pathogens**

Necrosis

mechanisms

Direct-acting toxins

- **They act directly**

-by combining with: critical molecular component or **cellular organelle** or **cellular membrane component** > مما يؤدي إلى حدوث تغيرات

E.g:

1. ***Chemotherapeutic agents*** [antineoplastic drugs]
2. ***Mercuric chloride poisoning*** [ingestion of contaminated seafood]:

Mercury binds to sulfhydryl groups of membrane proteins >> inhibit ATP-dependent transport + increase permeability

Latent-acting toxins

- **The indirect acting toxins**
- **Not intrinsically active by themselves**

شو بتعمل :

Latent toxins>> convert via cytochrome p450 in SER (مثل liver) to reactive metabolites >>>act on targeted cells >>>cause cells damage by formation of free radicals >>>membrane phospholipid peroxidation

E.g:

1. ***CCL4***
2. ***Acetaminophen***

Their effects:

***membrane peroxidation >>damage in the cell**

***ER membrane damage >> decrease enzymes and proteins + decrease apoproteins >>fatty liver**

***mitochondrial injury >> decrease ATP >> cell swelling>> cell death**

Produced in the liver (carrying & excreting lipids from the hepatocytes to circulation)

***decrease in apoproteins >> increase of accumulating of lipids and triglyceride inside the hepatocytes**

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ER STRESS

Leads to: Apoptosis (mitochondrial pathway)

Chaperons in ER control proper protein folding

Misfolded proteins >> ubiquitinated causes >> targeted to proteolysis

Causes off misfolded proteins :

- **Gene mutation >>** production of proteins that can't be folded properly.
- **Aging** >> decrease the cell's ability to produce chaperons>> decrease the cell's capacity to fold proteins.
- **Infections [** viral infections**]**
- **Increased demand for secretory proteins such as insulin in insulin-resistant states**}
- **Changes in intracellular pH (in ischemia and hypoxia)**
- **Neurodegenerative diseases**

diseases caused by misfolded proteins

1)Deficiency of an essential protein due to degradation [[[*Cystic fibrosis***]]]**

➡ Genetic mutation effects on **CFTR** protein **(membrane transporter)**>> degrade + deficiency of this misfolded protein

2) Inducing apoptosis of the affected cells

➡ Neurodegenerative disorders

{Alzheimer disease, Huntington disease & Parkinson disease}

➡ type 2 diabetes

3)Improperly folded proteins accumulation in extracellular tissues

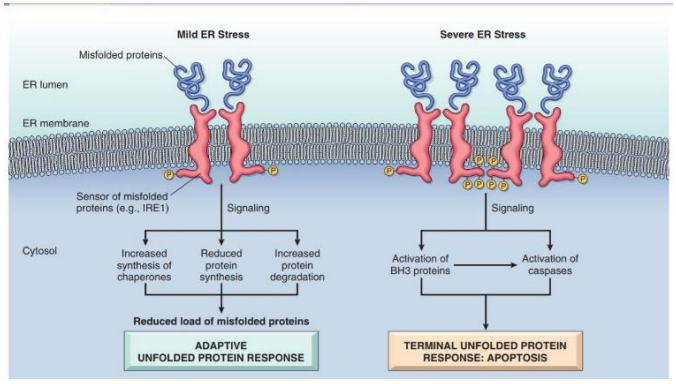
➡ Amyloidosis

response against misfolded proteins

small amount >> proteolysis

high amount>> unfolded protein response [adaptive response] >>> increase Chaperons products + increase proteins destruction + decrease proteins translation

if the adaptive response failed >> proapoptotic sensor activation (by BH3 protein family)>> direct activation of caspase>> apoptosis by the mitochondrial pathway



6 DNA DAMAGE → Lead to Apoptosis (mitochondrial pathway)

Causes:

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

how cells deal with it:

if there is DNA damage >> P53 is activated >> cell arrest in cell cycle at G1 phase for repair, after repair cells will continue replication

-if repair is impossible, apoptosis is induced.

-If p53 is mutated, abnormal cells will be produced leading to skin cancer (basal/squamous cell carcinoma)

7 INFLAMMATION

Causes:

- pathogens
- necrotic cells
- dysregulated immune response

(autoimmune diseases and allergies)

Mechanism:

inflammation >> accumulation of inflammatory cells (neutrophils, macrophages, lymphocytes)>> secreting products that destroy microbes + damage host tissues

COMMON EVENTS IN CELL INJURY FROM DIVERSE CAUSES

Result from

Hypoxia
toxins
radiation

Mitochondrial dysfunction

necrosis or apoptosis

defects in membrane permeability

necrosis

Consequences

- **failure of oxidative phosphorylation>> ATP depletion >> necrosis**
- **abnormal oxidative phosphorylation >> formation of ROS >> necrosis**
- **mitochondrial permeability transition pores >> loss of membrane potential >> apoptosis**
- **release of cytochrome C from the mitochondria to the cytoplasm >> activation of caspase >> apoptosis**

- **Plasma** membrane damage:
  loss of osmotic balance+ influx of fluids due to attraction of water + leak of contents
- **Mitochondrial** membrane damage:
  decreased ATP
- **Lysosomal** membranes:
  leakage of enzymes into cytosol >> leading to cellular digestion