The cellular response to injury depends on
- Type of injury
- Duration
- Severity

The consequence of injury depends on
- Type of injury
- Status
  Whether the cell was healthy or diseased before
- Adaptability && genetic makeup

Mechanisms of cell injury

Depletion of ATP

Because of

Hypoxia

➢ One of the most frequent causes of injury.
➢ Results on
1…Defective oxidative phosphorylation —> Failure of ATP generation—> depletion of ATP in cells
Reduced activity of membrane ATP dependent sodium pumps —> cell swelling
2… Failure of energy dependent pathways (membrane transport,protein synthesis, lipogenesis and phospholipid turnover)
3… Anaerobic glycolysis in Liver cells and skeletal muscle cells
Lactic acid accumulation —> decreased PH—> failure of enzymes
But in brain and heart They cannot survive long periods of hypoxia without suffering irreversible damage.
4… Disruption of the ribosomes —> decreased protein synthesis.
5… Accumulation of ROS
6… Damage to mitochondrial and lysosomal membranes

Necrosis is the end result
Apoptosis can contribute

Ischemia-Repurfusion injury

➢ Paradoxical cell injury after restoration of blood flow to ischemic but viable tissues.
➢ Results on :-
1… **Increased generation of ROS** from:
> Injured cells with damaged mitochondria & defective antioxidant mechanisms.
> Infiltrating new leukocytes.(blood during reperfusion has many WBCs that generate ROS as immunological response.
2… **Inflammation induced by influx of leukocytes, plasma proteins and complement**

Necrosis is the end result
Apoptosis can contribute

Defects in membrane potential:-
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

Oxidative stress

➢ Oxidative Stress occurs when there is an imbalance between the production of ROS and the body's ability to neutralize or detoxify these reactive molecules.

➢ **Causes lead to production of ROS:-**
~ Chemical injury (CCL4)
~ Radiation injury (UV, Xray)
~ Hypoxia
~ Cellular aging
~ Inflammation
~ Ischemia-reperfusion injury

➢ **Generation of ROS:-**
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.
Ex:- Superoxide ($O_2^{\bullet}$), hydrogen peroxide (H_2O_2),hydroxyl radical ($^{\bullet}OH$)
2- Produced in phagocytic leukocytes (neutrophils and
macrophages) during inflammation.
=> In phagosomes and phagolysosomes to kill microbes.
=> O_2 —> superoxide —> H_2O_2 —> hypochlorite.
Myeloperoxidase (H_2O_2 into hypochlorite ClO^-)

➢ **Removal of ROS:-**
1- Decay spontaneously
2- Superoxide dismutase (SOD).($O_2^{\bullet-}$ ~> H_2O_2)
3- Glutathione (GSH) peroxidases.
4- Catalase (one of most active enzymes known)
(H_2O_2 ~> H_2O) in both enzymes
5- Endogenous or exogenous anti-oxidants (e.g., vitamins E, A and C and β-carotene

➢ **Effects of 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

Necrosis occurs

Toxins

➢ Environmental chemicals & substances produced by infectious pathogens

Direct

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

Latent

➢ 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
Examples:-
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

Necrosis occurs

ER 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
- increase destruction.
➢ If failed —> proapoptotic sensor activation (BH3-only family)
+ direct activation of caspases—> apoptosis by the mitochondrial pathway

Apoptosis occurs

Protein 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

=> diseases caused by protein misfolding:-
~ 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

Apoptosis occurs

DNA damage

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

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

Apoptosis occurs

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

Necrosis or Apoptosis occurs

Mitochondrial dysfunction

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

Apoptosis occurs