Pathology # Cell injury

LEC. 2

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Types of cell injury: is either

1-**Reversible Cell injury** the cells return back to their stable baseline state after removal the cause of cell injury. This is called **Degeneration.**

2- Irreversible Cell injury cells cannot return to their baseline state after removal the cause of cell injury. This is called **Cell death** & **Necrosis**

Causes of Cell Injury:

1- Hypoxia (O_2 Deprivation)

- This is the common cause of cell injury & cell death.
- It means the interference with aerobic respiration of cells
- Hypoxia should be differentiate from **ischemia** (loss of blood supply) .
- So, it means that any case of ischemia associated with hypoxia, while not any case of hypoxia associated with ischemia
- **Causes of Hypoxia (O_2 Deprivation).**
  - **a.** Ischemia (decrease O_2 supply)
  - **b.** Anemia (decrease O_2 carrying capacity of blood)
  - **c.** Co poisoning (displace O_2 from Hb)

Ischemia cause more rapid and severe cell and tissue injury than does hypoxia in the absence of ischemia **because ischemia cease both the aerobic & anaerobic generation of energy** and compromises the delivery of substrates for glycolysis. In ischemic tissues, not only is aerobic metabolism compromised but anaerobic energy generation also stops after glycolytic substrates are exhausted, or glycolysis is inhibited by the accumulation of metabolites that would otherwise be washed out by flowing blood, **while hypoxia will cease only the aerobic pathway** and **energy** production by **anaerobic glycolysis can continue**.

2-**Physical agents**, including trauma, heat, cold, radiation, and electric shock

3- **Chemical agents and drugs**, including therapeutic drugs, poisons, environmental pollutants, and alcohol and narcotics.

4- **Infectious agents**, including viruses, bacteria, fungi, and parasites

5- Immunologic reactions ,including autoimmune diseases and cell injury following responses to infection, hypersensitivity reaction to some drugs like penicillin.

6- **Genetic derangements,** such as chromosomal alterations and specific gene mutations.

7- **Nutritional imbalances**, including protein–calorie deficiency or lack of specific vitamins, as well as nutritional excesses(obesity).

8-Aging Can result in diminished ability of cells to response to exogenous stimuli & injury& eventually cell death.

General principles for most forms of cell injuries

Four intracellular systems are particularly vulnerable for cell injury

a. **Cell membrane.** b. **Protein synthesis** c. **ATP production by mitochondria.** d. **DNA**

Mechanisms of Cell injury (Reversible)

1) ATP deprivation. 2) Generation of Free Radicals. 3) Loss of Ca+2 homeostasis. 4) Defect in plasma membrane permeability. 5) Mitochondrial damage

Mechanisns of Cell injury (biochemical changes) reversible

1) **ATP deprivation:**

- ATP is important virtually in every processes in the cell like (protein synthesis, cellular osmolarity & transport processes)

- ATP production is either by aerobic cellular respiration (mitochondria) & anaerobic glycolysis.
- Loss of ATP results in rapid shutdown of most critical cellular systems:

• The activity of plasma membrane ATP-dependent **sodium pumps** is reduced, resulting in intracellular accumulation of sodium and efflux of potassium. The net gain of solute is accompanied by iso-osmotic gain of water, causing cell **swelling** and dilation of the ER and other organelles.

• There is a compensatory **increase in anaerobic glycolysis** in an attempt to maintain the cell's energy sources. As a consequence, intracellular **glycogen stores** are rapidly **depleted**, and **lactic acid accumulates**, leading to **decreased intracellular pH** and **decreased activity of many cellular enzymes.**

2) **Loss of Ca^{+2} homeostasis**.

- Normally, the extra cellular concentration of Ca^{+2} is higher than the cytosolic free Ca^{+2} (this is maintain by ATP dependent transport)
- Also the Ca^{+2} normally is stored intracellular at mitochondria & endoplasmic Reticulum.
- In the cell injury (ischemia, toxins) failure of ATP-dependent Ca2+ pumps leads to influx of Ca2+ and then release of Ca^{+2} from intracellular stores & this result in increased cytosolic Ca^{+2}, will mediate cell injury by activation of many enzymes which include
  a. ***Phosphlipases.*** cause cell membrane damage.
  b. ***Proteases.*** catabolizing the structural & membrane proteins.
  c. ***ATPase.*** accelerating ATP depletion.
  d. ***Endonuclease***. fragmented the genetic material.

MORPHOLOGY OF REVERSIBLE CELL INJURY

Two patterns of morphologic changes are characteristic for reversible cell injury; include **Cellular swelling & Fatty change.**

Cellular Swelling:

- Is the first manifestation of almost forms of injury to cells, occur due to ***incapability of cells to maintain ionic & fluid homeostasis.***
- It is more apparent at the level of whole organ (Gross) than at cellular level (light microscope).
- Cellular Swelling also called *Hydropic change, vacuolar degeneration.*

Gross: Increased weight, increased pallor of the organ.

Mic: Small, clear vesicles within the cytoplasm (distended endoplasmic reticulum)

Fatty change:

- **Causes**: various types of cell injury include hypoxic, toxic or metabolic injury.
- **Site**: Mainly occur in cells participating in fat metabolism e.g hepatocytes & myocardial cells.
- Micro. : Lipid vacuoles in the cytoplasm of the cells.
- **Ultrastructural(electron microscope) features of REVERSIBLE injury**

.mitochondrial swelling &presence of Ca rich small densities cause decrease in mitochondrial function.

- Increase membrane permeability cause generalized cellular swelling.
- Loss of microvili.
- Formation of cell surface blebs.
- Swelling of endoplasmic reticulum with dispersion of ribosomes.
- Clumping of nuclear chromatin.
- If oxygen restores, the cell return back to normal

Ischemia / Reperfusion injury.

- **Is the tissue damage caused when blood supply returns to tissue (re-perfusion) after a period of ischemia or lack of oxygen (anoxia or hypoxia).**

Restoration of blood flow in reversibly injured cells but still viable can promote recovery but it may also paradoxically exacerbate the injury result in further injury of the cells or even cause cell death by following mechanisms.

- **1- Oxidative stress**. Re oxygenation increase generation of reactive oxygen and nitrogen species, *as a result of incomplete reduction of oxygen by damaged mitochondria and/or* ***cellular antioxidant defense mechanisms may be compromised by ischemia, favoring the accumulation of free radicals.***

2-Increase intracellular Ca+2 due to influx of calcium resulting from cell membrane damage

3- Inflammation: production of free radicals by the inflammatory cells at the perfusion area.

4-Activation of the complement system.

Free Radicals induced cell injury:

Free radicals are chemical species with a **single unpaired electron in outer orbital.** In such chemical state are extremely unstable & readily react with inorganic & organic chemicals. They initiate autocatalytic reactions, molecules that react with free radicles are in turn converted into free radicles.

Sources of Free Radicals.

1. **<u>Redox reactions</u> (reduction – oxidation reaction)**
    - This reaction normally occurs in the mitochondria.
    - During this reaction small amount of toxic intermediate species are formed include (*superoxide $O_2^{\cdot -}$, hydrogen peroxide H_2O_2 & $OH^{\cdot}$)*
2. **<u>Nitric Oxide (NO)</u>**.
    - Nitric oxide is normally synthesized by a variety of cell types which then act as free radicals by itself or by conversion to highly reactive Nitrite species.
3. **<u>Absorption of radiant energy (U.V light, X-ray)</u>**, these radiation can hydrolyze the water into $OH^{\cdot}$ & hydrogen free radicals ($H^{\cdot}$).
4. **<u>During Enzymatic Metabolism of exogenous chemicals like</u>** CCL_4.
5. Free radicals can generate as a part of routine cellular activities like **<u>respiration process, defence mechanisms.</u>**

<u>Mechanisms of Cell Injury by (FREE RADICALS</u>)

Free radicals can injured the cells *by the following mechanisms.*

1. <u>Lipid Peroxidation</u>. 2-**<u>DNA Fragmentation</u>**. 3- **<u>Cross – Linkage of Proteins.</u>**

<u>Inactivation of Free Radicals:</u>

Inactivation of free radicals can achieve by the following mechanisms.

1. Enhancement the rate of spontaneous decay of free radicals by **SuperOxide Dismutase (SOD)** which is present in many cell types of body

$$2O_2^{\cdot -} + 2H \longrightarrow H_2O_2 + O_2$$

2. **Glutathione (GSH) Peroxide**, which catalyzing the free radicals by the following equation

$$2OH^{\cdot -} + 2GSH \longrightarrow H_2O_2 + GSSG \text{ (glutathione homodimer)}$$

3. **Catalase,** which direct the degradation of hydrogen superoxide as the following equation

$$2H_2O_2 \longrightarrow 2H_2O + O_2$$

4. **Endogenous or Exogenous antioxidants** (Vitamins A, E, C) these act either by block the formation of free radicals or removed them as they are formed.
5. **Plasma Transporting proteins e.g. *Transferrin, Ceruloplasmin*.**
   Free iron and copper can catalyze the formation of reactive oxygen species (ROS). Under normal circumstances, reactivity of these metals is minimized by their binding to storage and transport proteins (e.g., transferrin, ferritin and ceruloplasmin) which prevents these metals from participating in reactions that generate reactive oxygen species (ROS).

<u>Irreversible Cell injury (Necrosis)</u>

- **Persistent or excessive injury** causes cells pass into **irreversible cell injury.**
- **Two important events indicate that the cells reach(point <u>of no return) or reach cell death or irreversible cell injury</u>, these include**

1. **Irreversible <u>Mitochondrial damage</u> (lack of ATP production)**
2. **Profound damage & disturbances in <u>cell membrane</u> function (this is the central factor in development of irreversible cell injury).**

- **<u>Clinical correlation to cell membrane damage</u>**

Leakage of intracellular proteins through the damaged cell membrane and ultimately into the circulation provides a means of detecting tissue-specific cellular injury and necrosis using blood serum samples.

- **e.g. : <u>Cardiac muscle</u> :**enzyme **<u>creatine kinase</u> and <u>troponin</u>**.
- **liver hepatocytes contain transaminases.**
- Irreversible injury and cell death in these tissues are reflected in increased levels of such proteins in the blood, and **<u>measurement of these biomarkers is used clinically to assess damage to these tissues</u>**.

- **<u>Necrosis</u>** is sequence of morphologic changes that follow **cell death in living tissue.** The morphologic appearance of necrosis is the **result of two essentially concurrent processes**
- **Enzymatic digestion** of the cell (sources of these enzymes are either from the dead cells themselves or from lysosomes of invading inflammatory cells like neutrophils and macrophage)
- **Denaturation of proteins.**
- **<u>Morphology of Necrosis:</u>**
- **<u>Cytoplasmic Changes.</u>** Include
- **<u>1- Increased eosinophilia</u>** (due to increased binding of eosin to denaturated intracytoplasmic proteins).
- 2-The cells become more **<u>glassy homogenous appearance</u>** than the normal cell (due to loss glycogen particles).
- 3-The **<u>cytoplasm becomes vacuolated</u>** (due to degradation of organelles by lysosomal enzymes).
- 4- Finally the **<u>cells become calcified</u>**.
- **<u>Nuclear Changes.</u>** Include one the following three patterns
- **<u>1-Pyknosis</u>** (nuclear shrinkage & condensation) due to DNA condenses into small shrunken mass.
- **<u>2-Karyorrhexis</u>** (Fragmentation of chromatin)
- **<u>3-Karyolysis (</u>**breakdown of DNA by DNA ase) then the nucleus is completely disappear within 1 to 2 days.
- **<u>Types of Necrosis:</u>**
- There are many types of NECROSIS depend on whether the enzymatic digestion is predominant or denaturation of proteins, these types include:
- **<u>Coagulative Necrosis</u>**:
- It is characteristics for of **Hypoxic** cell death in **all tissues except the brain**.
- The myocardial infarction is an excellent example for this type of necrosis
- **Mic.** :In the coagulative necrosis, there is **preservation** of the general tissue **architecture,** with **loss of cellular details** (acidophilic, coagulated, anucleated cells)
- **Protein denaturation** is predominant in this type of necrosis

- **Liquifactive Necrosis:**
  - **1-Suppurative infections** characterized by the formation of **pus** (liquefied tissue debris and neutrophils) in some focal **bacterial** or, occasionally, **fungal** infections (due to the action of inflammatory cells).
- 2-For unclear reasons, **hypoxic** death of cells within the **CNS** often evokes liquefactive necrosis.
- Liquefaction completely digests the dead cells. The end result is transformation of the tissue into a liquid viscous mass.
- **Enzymatic digestion** is predominant in this type of necrosis.
- In the liquefactive necrosis, there is **loss of both tissue architecture & cellular details**

- **3.Caseous Necrosis**:
- A distinctive form of necrosis is often present in foci of tuberculous infection.
- The term caseous is derived from the **cheesy white gross appearance** of the area of necrosis.
- **Combination** of **coagulative and liquefactive necrosis**
- In this type of necrosis, both Enzymatic Digestion & Protein Denaturation are equally predominant.
- Unlike coagulative necrosis, the tissue architecture is completely obliterated.
- On microscopic examination, (composed of fragmented, coagulated cells and amorphous granular debris) surrounded by characteristic lesion which is called **granuloma.**
- Characterized by the presence of soft, dry, cheesy homogenous necrotic material but It is **NOT** liquefied.