Al muthanna University **Pharmacy college**
Lecturer Zainab sattar Ali **Theo. Pathophysiology lec.2**

Free Radicals

Are chemical species with a single unpaired in orbital, it Induced cell injury. In such chemical state are extremely unstable & readily react with inorganic & organic chemical

Sources OF Free Radicals

-1Redox reactions (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^-, hydrogen peroxide H_2O_2 & OH)

Nitric Oxide (NO)

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.

-2Absorption of radiant energy (uv light X-ray), these radiation can hydrolyze the water into OH & hydrogen free radicals (H(

-3During Enzymatic Metabolism of exogenous chemicals like CCL4

-4Free radicals can generate as a part of routine cellular activities like respiration process, defense mechanisms.

Mechanisms of cell Injury by FREE RADICALS

Free radicals can injured the cells by the following mechanisms:

Lipid peroxidation:

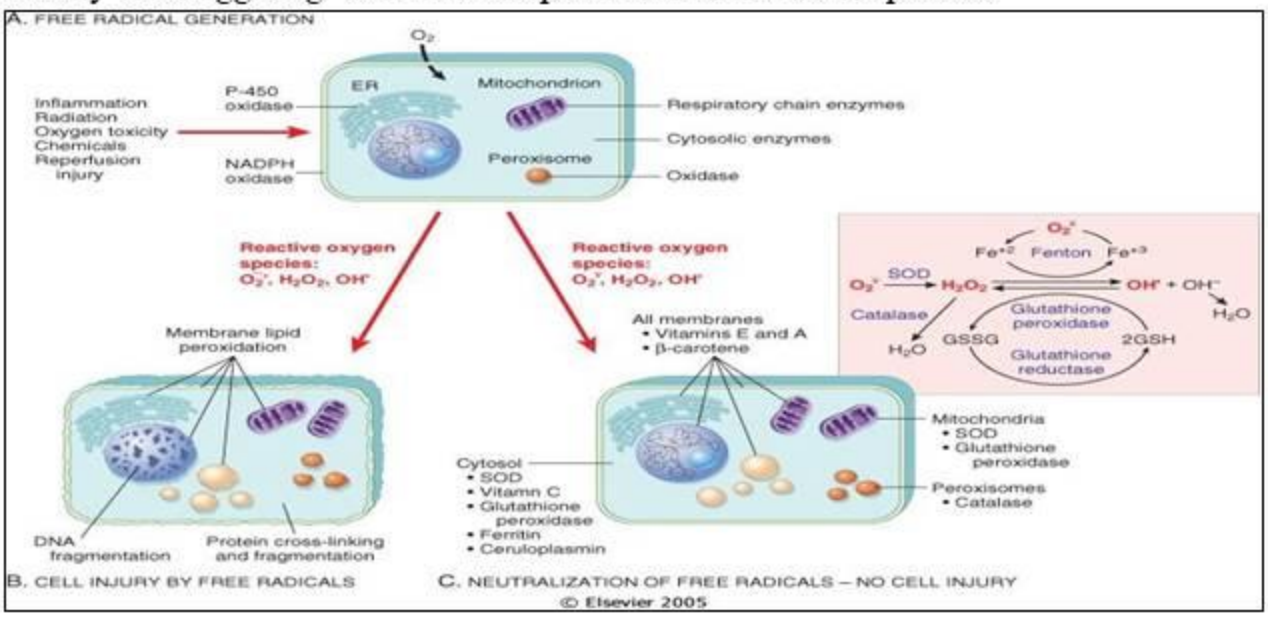
Free radicals attack the double bonds in lipid and polyunsaturated lipid in the membrane, which result formation of lipid peroxide (free radical causes cell injury.(

DNA. Fragmentation

Free radicals attack the Thymine base in the DNA of nucleus & mitochondria which result in Single Strand Breaks (SSB.(

Gross-Linkage of Proteins

Free radicals promote sulfhydryl-mediated protein crosslinking, also may directly cause polypeptide fragmentation resulting in enhanced degradation or loss of enzymatic activity and triggering the unfolded protein or called stress protein.



Necrosis

Necrosis is a form of cell death in which cellular membranes fall apart, and cellular enzymes leak out. Necrosis elicits a local host reaction, **called inflammation**, that is induced by substances released from dead cells and which serves to eliminate the debris and start the subsequent repair process. The enzymes responsible for digestion of the cell are derived from lysosomes and may come from the dying cells themselves or from leukocytes recruited as part of the inflammatory reaction. The biochemical mechanisms of necrosis vary with different injurious stimuli. Necrosis is the result of two essentially concurrent processes:

.1Enzymatic digestion of the cell

.2Denaturation of proteins.

Morphological changes of Necrosis

.1 Cytoplasmic Changes. Include

i. Increased eosinophilia of cytoplasm.
ii. Glassy homogenous appearance of the cell (due to loss glycogen particles.(
iii. due to the cytoplasm becomes vacuolated (due to degradation of organelles by lysosomal enzyme

iv. Finally the fatty acids bind calcium salts, caused cells become calcified. Undergo calcification of the necrotic tissues can not digested by phagocytosis.

2. Nuclear Changes Include one the following three patterns

i. Pyknosis (shrinkage & condensation of DNA)
ii. Karyorrhexis (Fragmentation of chromatin).
iii. Karyolysis (breakdown of DNA by DNAase) & the nucleus is completely disappear within 1 to 2 days.

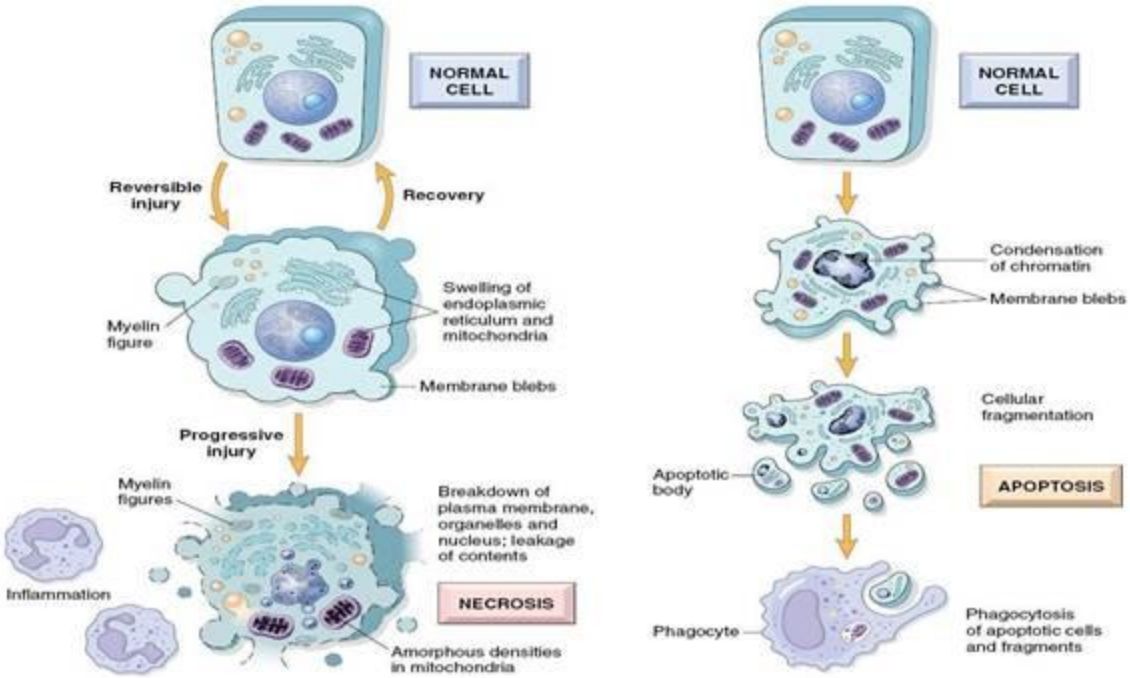


FIGURE 1–8 Schematic illustration of the morphologic changes in cell injury culminating in necrosis or apoptosis.

Types of necrosis:

There are many types of Necrosis depend on whether the enzymatic digestion is predominant or denaturation of proteins, these types include

1. Coagulative Necrosis
2. Liquilactive Necrosis:
3. Caseous Necrosis:
4. Gangrenous Necrosis:
5. Fat Necrosis.
6. Fibrinoid Necrosis.

.1Coagulative Necrosis	.2Liquifactive Necrosis:
A. It is characteristics of Hypoxic or death in all tissues except the brain.	.1characteristic of bacterial fungal infections, also seen in hypoxic death of nervous system

B. The myocardial infarction is an excellent example for this type of necrosis. C. there is preservation of the general tissue architecture, with loss cellular details. **D.** Protein Denaturation is predominant in this type of necrosis	.2Brain infarction .3there is loss of both tissue architecture & cellular details **.4**Enzymatic digestion is predominant in this type of necrosis

3. **Caseous Necrosis**:

Is often present in infection with tuberculosis. Caseous means cheesy white gross appearance of the area of necrosis, unlike coagulative necrosis, the tissue architecture is completely obliterated a

- On microscopic examination, there is characteristic lesion which is called granuloma
- In this type of necrosis, both Enzymatic Digestion & Protein Denaturation are equally predominant,

4. Gangrenous Necrosis: This is occurs due to ischemia & superadded putrefaction.

Gangrene is classified into 3 types

a. Dry gangrene

b. Wet gangrene

c. Gas gangrene

Dry gangrene	**Wet gangrene**
-1distal part of the limb due to ischemia -2eg. toes and feet of an old patient due to atherosclerosis -3This gangrene slowly grows upwards (till reaches area of good blood supply.(-4A "Line of separation is well formed between the gangrenous part and the viable part (The affected part is dry, shrunken and	-1Usually occurs in the tissues and organs -2eg Diabetic leg patient due to Bedsores -3usually develops rapidly due to blockage of venous and less commonly arterial supply -4There is no clear demarcation of any line of separation -**5**Risk of development of

dark black(-5Risk of development of septicaemia is less than wet gangrene.	epticaemia is more

C. Gas gangrene: It is a special form of wet gangrene that is caused by a gas-forming Clostridia (Clostridia perfringens which a gram positive anaerobic(

It is seen in the open contaminated wounds and Compilation of operation on colon which usually contains the bacteria Clostridia. This type of gangrene is fatal due to septicemia

5 -Fat Necrosis:

There are two types of fat necrosis:

1. Traumatic fat necrosis.

2. Enzymatic fat necrosis

Traumatic fat Necrosis

occurred when a bruise or blow to the breast after surgery on the breast, and post radiotherapy on breast cancer. Clinically fat necrosis presented as painless, round, firm lumps (not malignant or increase risk of breast cancer). Microscopically characterized by foamy macrophages infiltrating in necrotic breast tissue.

Enzymatic Fat Necrosis:

Example: acute pancreatitis.

- There is release of pancreatic enzymes (mainly lipase) as a result of injury, into adjacent fatty tissue.
- These enzymes will liquefy fat cells membranes & hydrolyze triglycerides esters within these fat cells result in the formation of fatty acids combine with calcium.
- These combined fatty acids will produce grossly chalky white areas (Fat Saponification(
- Microscopically, there are shadow fat cells basophilic calcium deposits.

Fibrinoid necrosis:

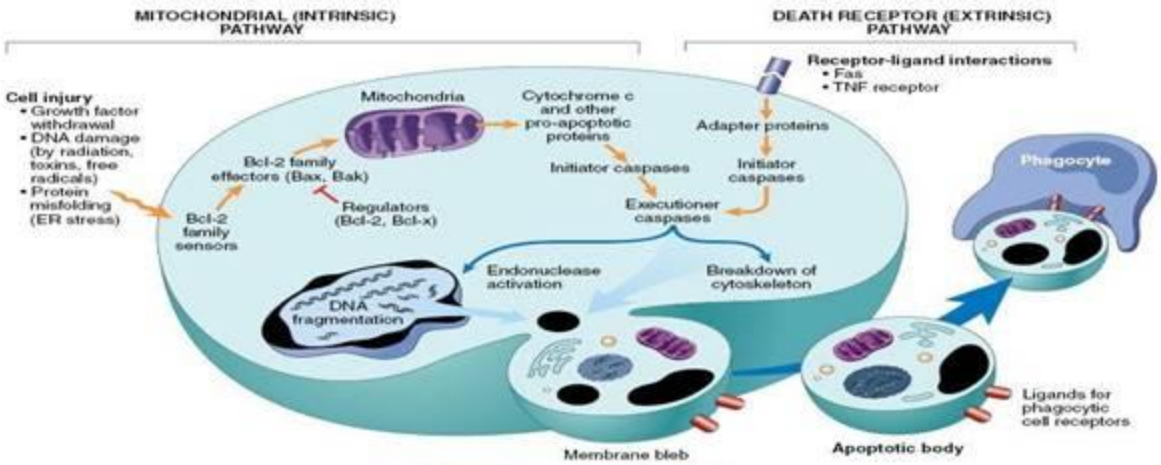
Usually occurs in immune reactions in which complexes of antigens and antibodies are deposited in the walls of blood vessels and plasma proteins that leak into the wall of damaged vessels produce a bright pink called fibrinoid. (The immunologically mediated diseases (e.g., polyarteritis nodosa), it also may occur in severe hypertension.

Apoptosis

Is a pathway of cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins. Fragments of the apoptotic cells then break off. The plasma membrane of the apoptotic cell remains intact, but the membrane is altered in such a way that the fragments, called apoptotic bodies, leading to their rapid consumption by phagocytes, so apoptotic cell death does not elicit an inflammatory reaction. **DOES NOT INDUCE INFLAMMATION."**

Mechanisms of Apoptosis:

- **Mitochondrial (intrinsic) induction** –activation of pro-apoptotic proteins and/or down regulation of anti-apoptotic proteins leads to loss of mitochondrial membrane integrity and release of CytC and other pro-apoptotic factors.
  Death receptor (extrinsic) induction –cell receptors respond to signals (either secreted or by direct contact with other cells) to directly induce apoptosis.
  Removal of dead cells –ligands expressed on surface membrane (e.g. phosphatidylserine and/or glycoproteins) signal phagocytosis by macrophages.



Causes of Apoptosis may be Physiologic or Pathologic:

Physiologic

- Embryogenesis and fetal development.
- Hormone dependent involution. Prostate glandular epithelium after castration. Regression of lactating breast tissue after weaning.

- Cell loss in proliferating cell populations e.g Immature lymphocytes epithelial cells in the GI tract
- Elimination of self-reactive lymphocytes.
- Death of cells that have served their function. Neutrophils, Lymphocytes

Pathologic

- DNA damage due to radiation, chemotherapy.
- Accumulation of misfolded proteins leads to ER stress which ends with apoptosis.
- Cell death in viral infections that induce apoptosis such as HIV and Adenovirus or by the host immune response such as hepatitis.
- Organ atrophy after duct obstruction.

Inflammation

It is a protective response a living body initiates against local tissue damage. It takes the form of a complex reaction of blood vessels, certain plasma components and blood cells, which acts to eliminate the cause of cell injury**. Inflammation is combined with repair process.**

Inflammation can be divided into two basic types:

-1A cut inflammation (short duration few hours to few days(
-2Chronic inflammation (long duration days to rears.(

Acute inflammation:

Is the immediate & early response to injury that serves to deliver leukocytes and plasma proteins such as antibodies, to sites of injury and remove the causes of injury.

The process of acute inflammation has two major parts:

- **1Vascular changes.**

2Cellular changes

- These vascular & cellular changes are responsible for the as classic local sings of acute inflammation.
- These changes of acute inflammation are regulated by release of chemical mediators

Classical local sings of inflammation

-1 Heat (Calor.(
-2 Redness (Rubor).
-3 Swelling (Tumor.(

- These three signs are a result of integration between vascular & cellular changes of acute inflammation.

-4 Pain.
-5 Loss of function.

- These two sings of acute inflammation are due to release of chemical mediators from leukocytes.

Vascular Changes of acute inflammation

Include the followings:

.1Changes in the caliber of vessels & flow:

i. Immediate vasoconstriction (transient, not significant(
ii. Then arteriolar vasodilatation (increase local blood flow to capillary bed& result in hotness & redness of area(
iii. Movement of protein rich fluid into extravascular areas, (increase viscosity& slowing the circulation & this called Stasis(
iv. After stasis migration of neutrophils and accumulate along the vascular endothelial surface.(