Dr. Sedjelmaci nesrine
Lecturer in Toxicology

Mechanisms of Toxic Action – Necrosis and Apoptosis

1. Alterations at the molecular (biochemical) level

- Attack of macromolecules: enzymes, receptors, DNA, etc.
- Inhibition of mitochondrial energy function
- Alteration of cellular structure and lipid peroxidation of membranes
- Alteration of function and metabolism through changes in enzymatic activity

2. Alterations at the cellular level

These occur via two fundamentally different mechanisms: necrosis and apoptosis.

a. Necrosis

Accidental (uncontrolled) cell death caused by a biological agent (bacteria, virus, etc.), physical factors (radiation, etc.), or chemical agents (toxic substances, drugs, etc.). It is characterized by:

- Swelling of cells and organelles
- Chromatin fragmentation into irregularly contoured clumps
- Rupture of membranes
- Release of cellular debris into the extracellular environment ⇒ Inflammation

b. Apoptosis

Programmed cell death regulated by DNA; it may be physiological (death of interdigital cells, thymic involution) or occur following an insult. It is characterized by:

- An active process (requires ATP) of programmed cell death
- Dependence on gene expression
- Condensation of nuclear and cytoplasmic components
- DNA fragmentation
- Formation of apoptotic bodies (vesicles)
- Phagocytosis ⇒ no inflammation

3. Cellular Targets

a. Mitochondria

Functions: energy production, heme synthesis, regulation of calcium homeostasis, etc.

- **a.1. Inhibitors of the mitochondrial respiratory chain (MRC):** block electron transfer through carriers (e.g., CO, CN)
- **a.2. Uncoupling of oxidative phosphorylation:** inhibits ATP synthesis (e.g., salicylates, arsenic)

b. Endoplasmic Reticulum (ER)

The endoplasmic reticulum is the main site of protein synthesis (including enzymes) and metabolic activity (microsomes).

Enzymatic activity can be affected in two ways:

1. **Enzyme induction:** acute ethanol intake, barbiturates
2. **Enzyme inhibition:** cimetidine

Consequences:
Depend on the toxicity of the parent compounds or their metabolites

c. Microtubules

Blocking intracellular contractile structures causes depolymerization, leading to inhibition of cell division.

- Example: colchicine produces an antimitotic effect

d. Lysosomes

Spherical vesicles containing numerous lytic enzymes (hydrolases).

- Example: bacterial toxins, asbestos (disintegration of lysosomes and release of their enzymatic content ⇒ damage to neighboring cells)

e. Nucleus

Cell division occurs through the process of **mitosis**.
Damage may lead to genotoxicity characterized by mutations or cancer.

- Examples: colchicine, KCN (condensation of chromosomal filaments by coiling)