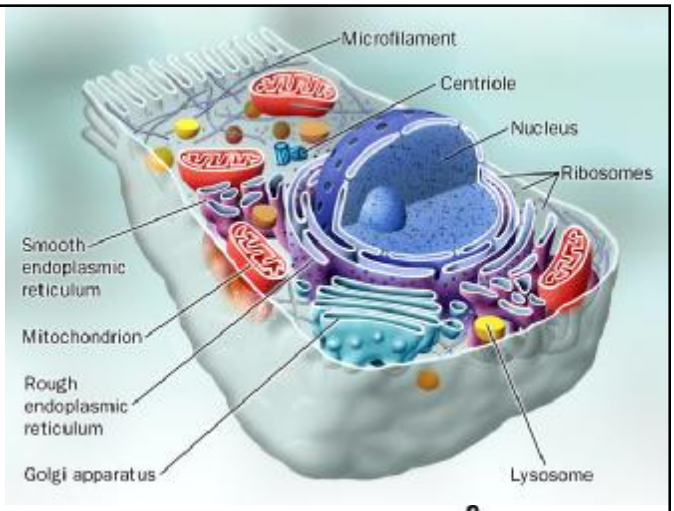
Apoptosis



Dr. Marwan Qubaja
Al-Quds University
Faculty of Medicine
Pathology Department

1

APOPTOSIS: PROGRAMMED CELL DEATH

Ø important type of cell death: cell commits suicide

Ø Physiological or pathological:

Ø Examples:

1. Programmed destruction of cells during embryogenesis

2. Hormone-dependent involution:

e.g. **physiological**, as in endometrium during menstrual cycle

e.g. **pathologic**, as in the prostate atrophy after castration

3.Cell deletion in proliferating tissues e.g. cell death in tumors

2

APOPTOSIS: PROGRAMMED CELL DEATH

Ø Examples:

4. Immune cell death:

e.g. deletion of autoreactive T-lymphocytes in thymus

e.g. cell death induced by cytotoxic T cells

5. Mild injurious stimuli:

e.g. mild heat, radiation, cytotoxic treatment.

6. Death of neurons in disease processes

e.g. Alzheimer disease

3

Mechanisms of apoptosis

The main players are:

ØCytosolic proteins called *Caspases*

ØMitochondrial proteins called *BCL-2* family

4

Mechanisms of apoptosis: Caspases

- Enzymes which are present in the cytoplasm and are key players in apoptosis
- Found in an inactive form in the cytoplasm.
- They are called Caspases from C; from Cysteine active site, "asp"; from cleavage after aspartic acid residue.

5

Mechanisms of apoptosis: Caspases

There are two types:

1. Initiators: signaling of these caspases results in commitment of cells to apoptotic cell death. These are found in certain cell types.
2. Effectors: these are proteases which bring about the structural degradation of the cells to give the classical morphology. They are present in all cell types.

6

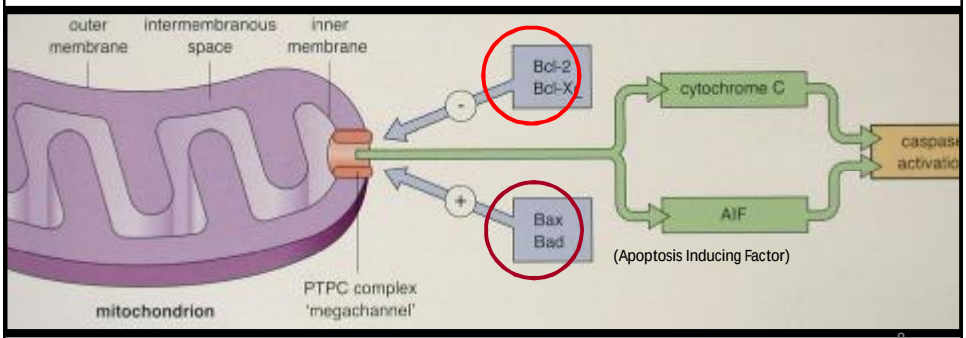
Mechanisms of apoptosis: BCL-2 family

- BCL-2 family are group of proteins that either:
  - suppress apoptosis, like BCL-2 / BCL-X_L
  - enhance apoptosis like Bax / Bad
- BCL-2 protects from apoptosis by stabilizing the mitochondrial membrane, thus preventing increase permeability, by binding and sequestering cytochrome-C, and stabilizing proteins like the Apaf, thus preventing its activation.

7

Mechanisms of apoptosis: BCL-2 family

- Factors that influence mitochondrial membrane permeability are important players in regulating apoptosis in the cells.



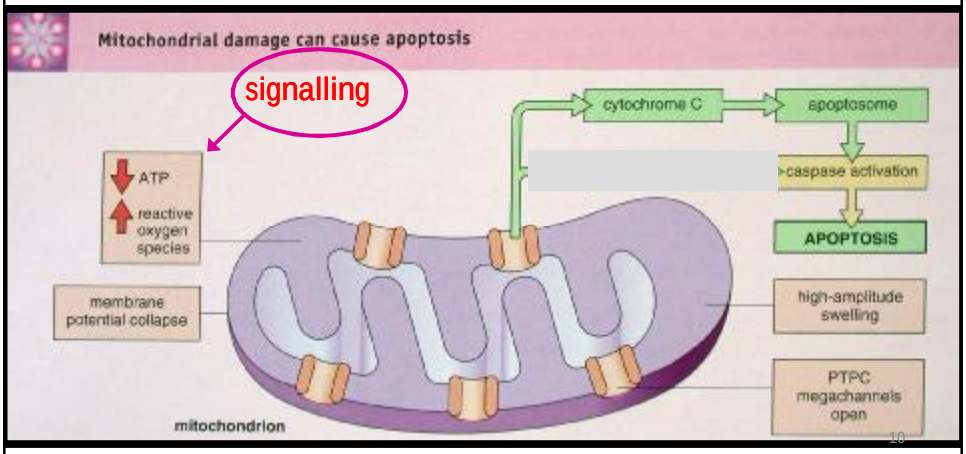
8

Mechanisms of apoptosis: mitochondrial damage

- Stimuli like toxins, or signalling will open permeability transition pore complex (PTPC), or mega channels, which will release material mainly cytochrome-C from the mitochondria to cytosol.
- Cytochrome-C will bind to Apaf "pro-apoptotic protease-activating factor" and activate effector caspases.

9

Mechanisms of apoptosis: mitochondrial damage



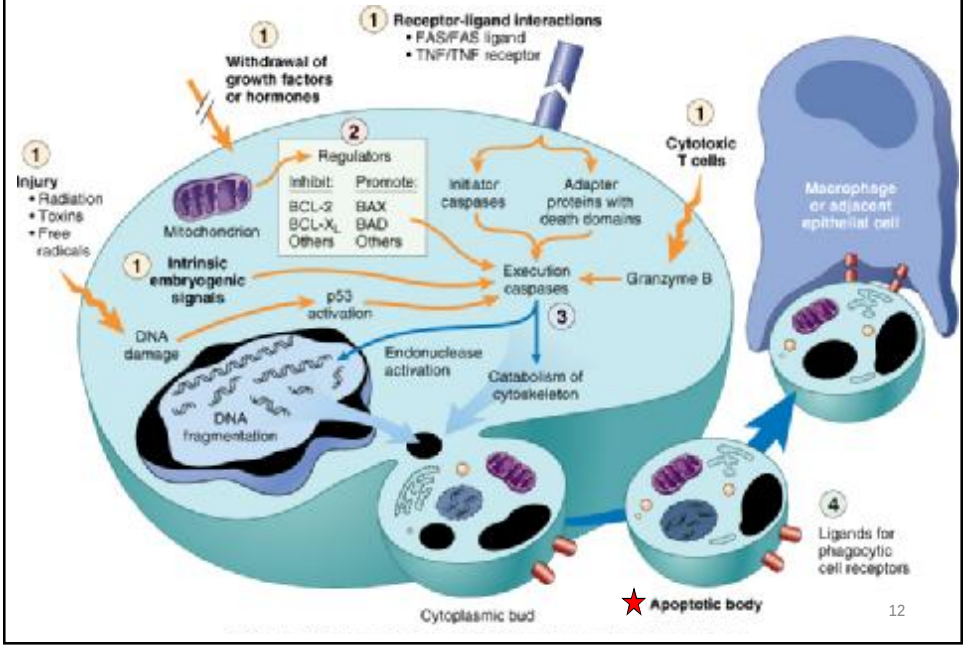
10

Mechanisms of apoptosis

1. Signaling: intrinsic or extrinsic **triggers** to induce apoptosis
2. Control and integration: by the **BCL-2** family that can either inhibit or promote cell death.
3. Execution: by **caspases** that activate cytoplasmic endonuclease and proteases that degrade cytoskeletal & nuclear proteins which results in breakdown of cytoskeleton and fragmentation of nuclear chromatin.
4. Removal of dead cells: the formation of apoptotic bodies containing various intracellular organelles; they express new ligands that mediate phagocytic cell binding and uptake.

11

Mechanisms of apoptosis



12

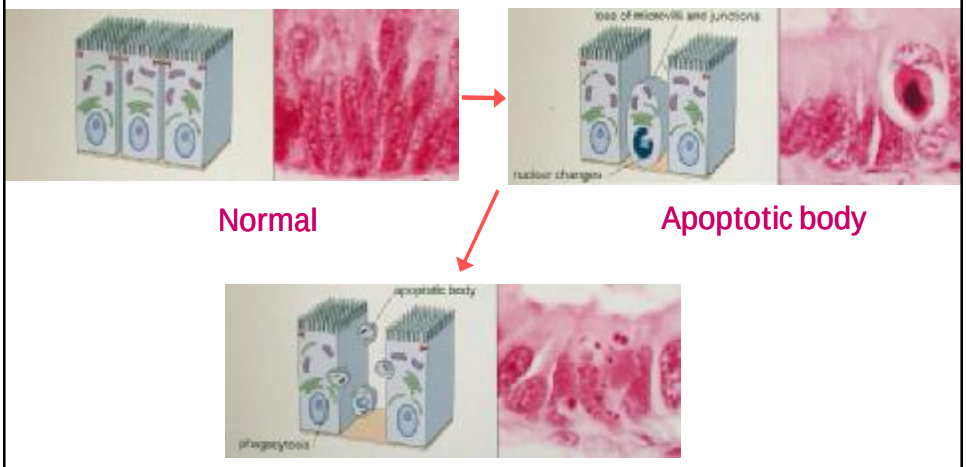
Apoptosis: Morphology

- Single cells or groups of cells
- Cells show intensely eosinophilic cytoplasm and condensed pyknotic nucleus
- Cells are not surrounded by inflammatory cells
- Rapidly removed by fragmentation and engulfment by cells

Pyknosis: increased basophilia due to shrinkage of the nucleus

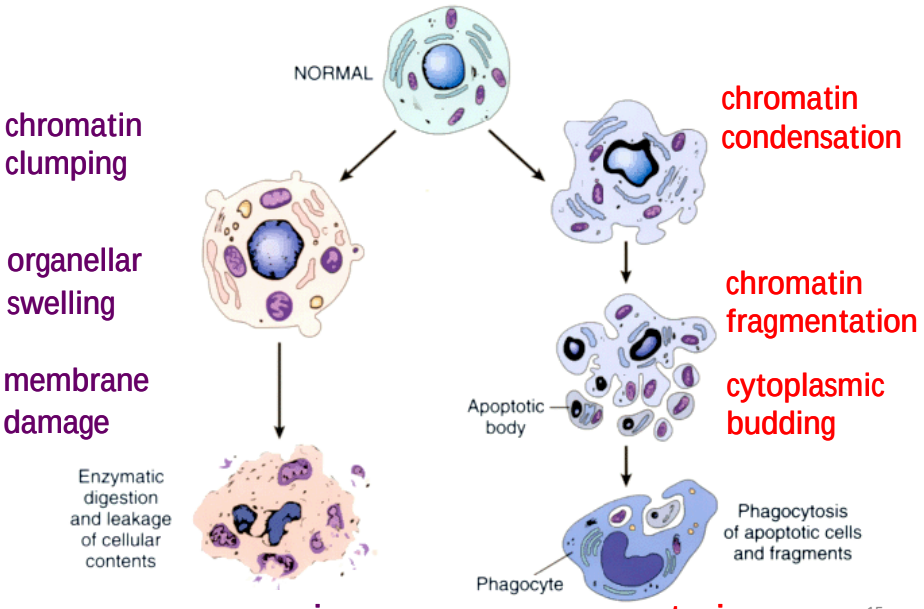
13

Apoptosis: Morphology



14

Ultrastructural changes in necrosis & apoptosis



15

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucelus	Pyknosis karyorrhexis karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

16