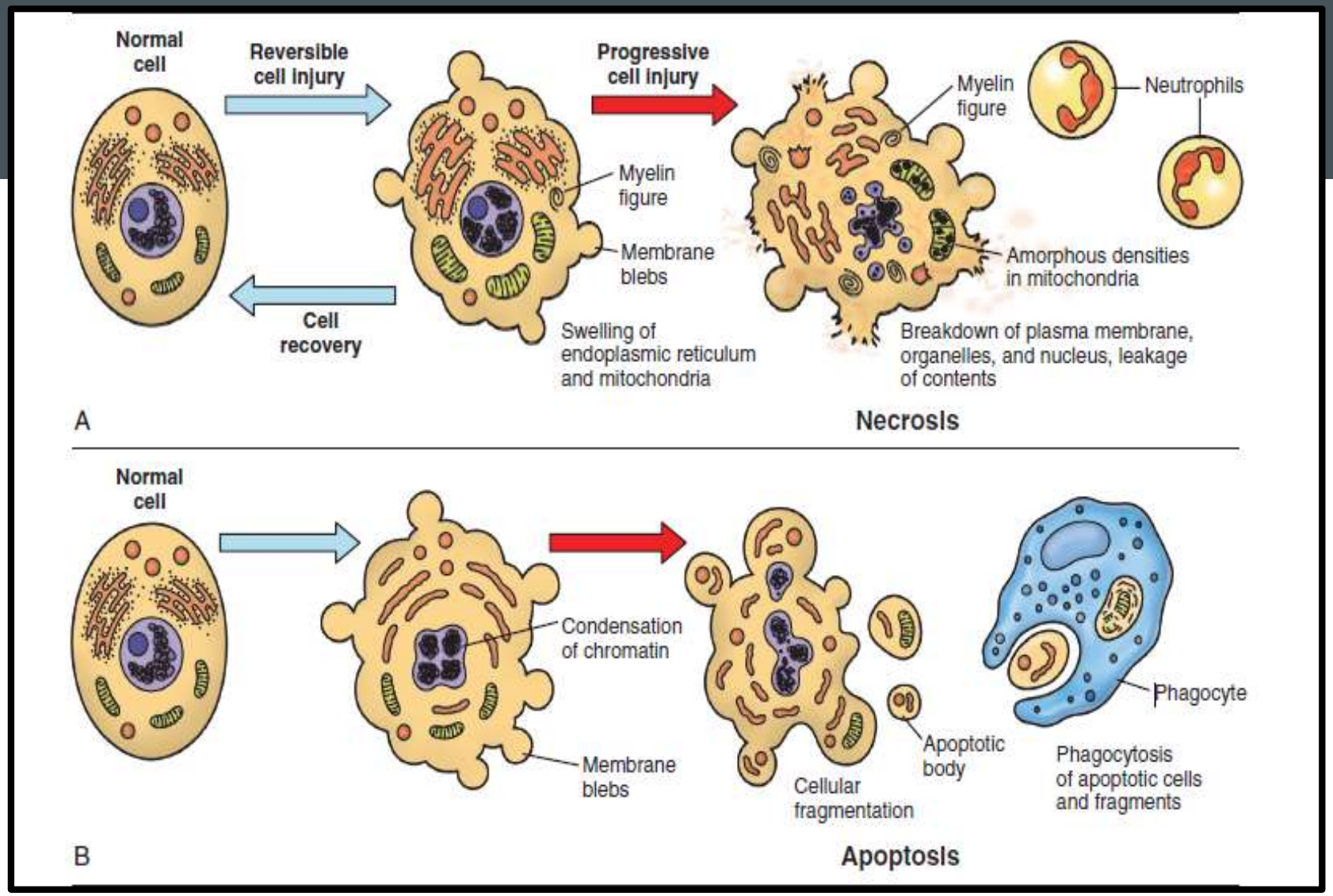
APOPTOSIS: PROGRAMMED CELL DEATH

- Apoptosis is the process of programmed cell death that serves as a regulated mechanism of growth and development within an organism.
- This process is also known as **"cellular suicide"** because the cell actively participates in its own death.
- The cell eliminates itself through a genetically regulated process rather than an uncontrolled or random event. This phenomenon may occur under both physiological and pathological conditions.

It is an energy-dependent process and requires caspase activation.

- **Intrinsic pathway**
- **Extrinsic pathway**



Pathologic Basis of Veterinary Disease, 6th Ed., Ed.: Zachary JF, (2017) Elsevier, St. Louis, Missouri.

In apoptosis, the cell:

- Shrinks
- Its cytoplasm condenses
- Its chromatin condenses (pyknosis)
- The nucleus breaks down (karyorrhexis)
- The cell membrane generally retains its integrity
- The cell divides into apoptotic bodies
- These bodies are phagocytosed by macrophages or neighboring cells. Therefore, apoptosis usually occurs without creating an inflammatory reaction.

APOPTOTIC MECHANISM

1. Intrinsic (mitochondrial) pathway

- Activated by intracellular stress:
- DNA damage
- Oxidative stress
- Growth factor deficiency
- Misfolded proteins

In this pathway:

- BCL-2 family proteins determine balance
- Proapoptotic proteins: BAX, BAK, BIM
- Antiapoptotic proteins: BCL-2, BCL-XL
- Cytochrome c is released from the mitochondria, followed by the formation of a complex with apaf-1
- Caspase-9 is activated
- Executor caspases (caspase-3, -6, -7) become involved

APOPTOTIC MECHANISM

2. Extrinsic (death receptor) pathway

- It begins via plasma membrane receptors as well as death receptors (DRs) on the cell surface:

- Fas (CD95) – Fas ligand
- TNF receptor

- Activation of these receptors:

- Recruits adapter proteins
- Leads to caspase-8 or caspase-10 activation
- Then executive caspases are activated

2. FERROPTOSIS

- This is a type of regulated cell death different from apoptosis.
- Its main characteristic is the damage to polyunsaturated fatty acids (especially phospholipid PUFAs) in the cell membrane through lipid peroxidation.
- The formation of ROS is catalyzed by the Fenton reaction, triggered by lipid peroxidation.
- The Fenton reaction is a fundamental oxidative reaction catalyzed by iron ions and leading to the formation of highly reactive hydroxyl radicals (•OH). It is one of the most important sources of cellular oxidative stress mechanisms.

2. FERROPTOSIS

In this reaction:

- Fe^{2+} (ferro iron) acts as a catalyst
- H_2O_2 (hydrogen peroxide) is the substrate
- The result is the formation of a hydroxyl radical (•OH).
- The hydroxyl radical is one of the strongest oxidants in biological systems and can cause:
- Lipid peroxidation
- Protein oxidation
- DNA damage.

2. FERROPTOSIS

Iron-dependent.

Increased intracellular free iron increases the oxidative load via Fenton-type reactions and free radical formation, which fuels lipid peroxidation.

Therefore, ferroptosis should be considered not only as "oxidative stress" but specifically as iron-related membrane lipid oxidation.

Feroptosis = iron excess + antioxidant defense collapse + lipid peroxidation → cell death.

II. Mechanistically, the most critical axis is the System Xc−/GSH/GPX4 pathway.

System Xc− takes cystine into the cell.

Cystine is used for glutathione (GSH) synthesis.

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GPX4 detoxifies lipid hydroperoxides using GSH. If this axis is disrupted, lipid peroxides accumulate and ferroptosis develops.

3. PYROPTOSIS

- This is a type of programmed cell death associated with inflammation. Unlike apoptosis, it generates a strong pro-inflammatory response and usually occurs in cases of infection or cellular stress.

- Pyroptosis is characterized by three main features:
- Caspase activation, particularly caspase-1, but also caspase-4, caspase-5 (human), and caspase-11 (mouse).
- Gasdermin activation: Gasdermin-D (GSDMD) is cleaved by caspase-1, creating pores in the membrane.
- Release of pro-inflammatory cytokines, particularly:
- IL-1β
- IL-18
- This process increases the permeability of the cell membrane, and the cell dies through lysis.

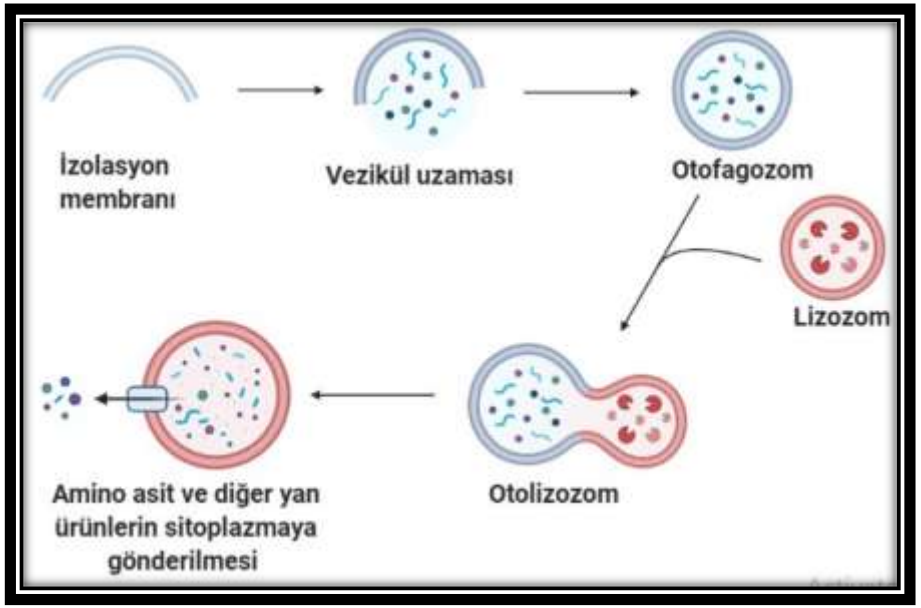
4. ENTOSIS

- This is a non-apoptotic cell death mechanism characterized by the active internalization of a cell by another living cell (cell-in-cell phenomenon).

- It was first identified in epithelial tumor cells. In this process, a cell enters a neighboring cell and often dies through lysosomal destruction.

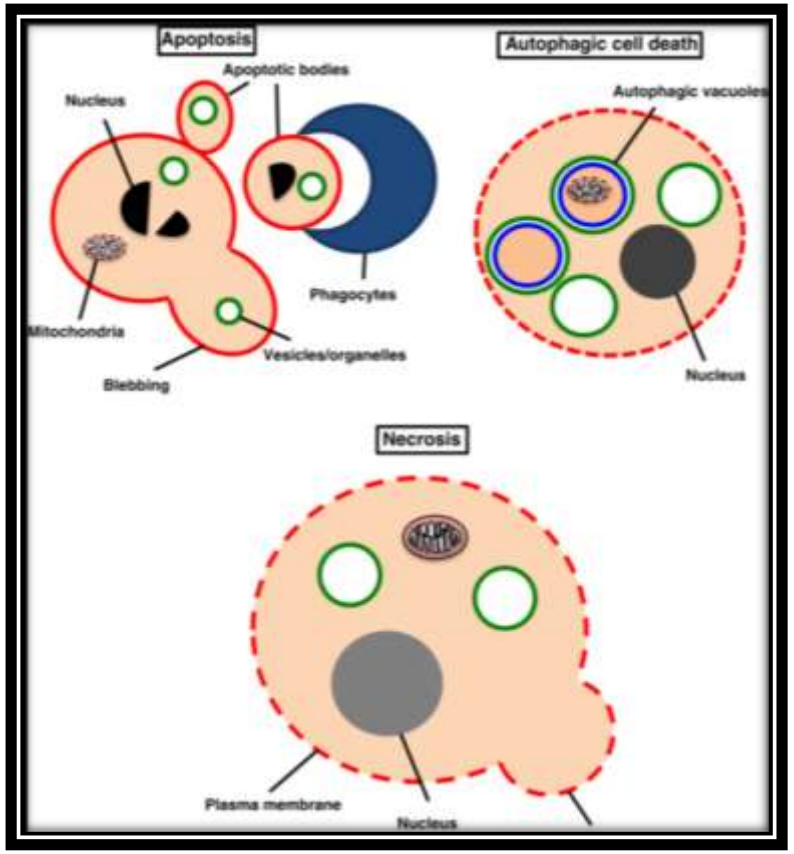
Autophagy

Autophagy (or "self-eating") is the body's way of clearing out damaged cells to make way for new, healthier cells.



Heterophagia

The process by which a cell digests the substance it takes in through phagocytosis.



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