



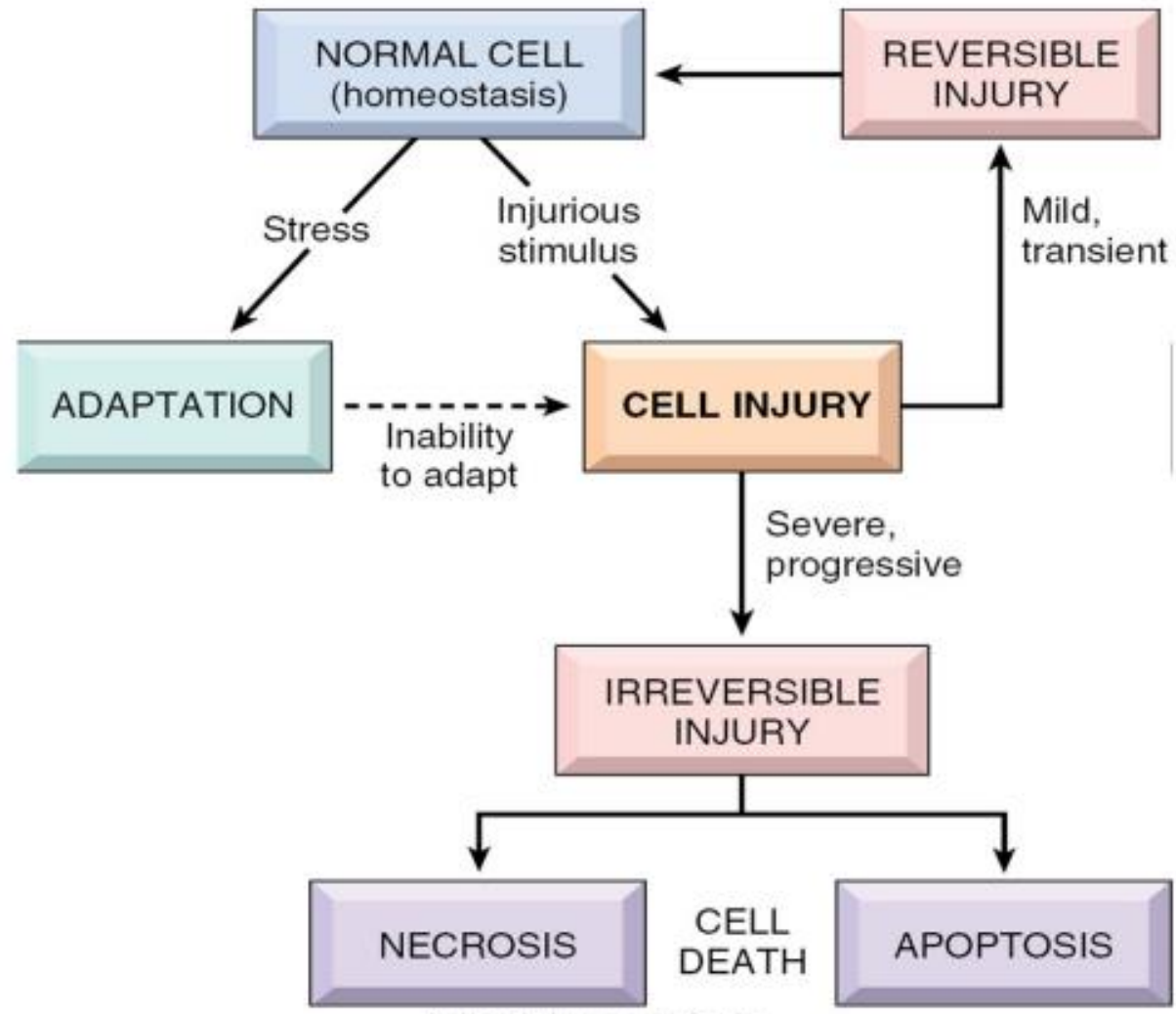
NOVA

Charting New Horizons in Education

Apoptosis

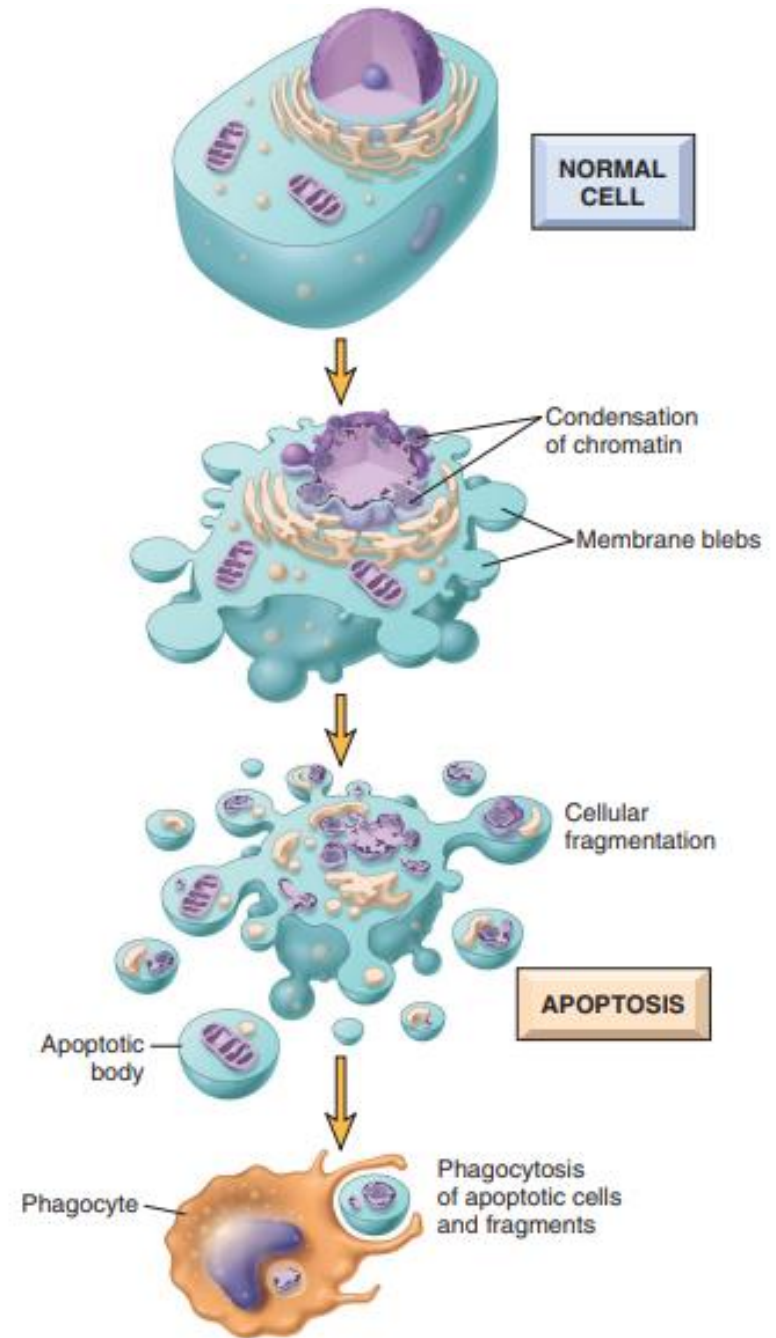
03

Pathology



Apoptosis

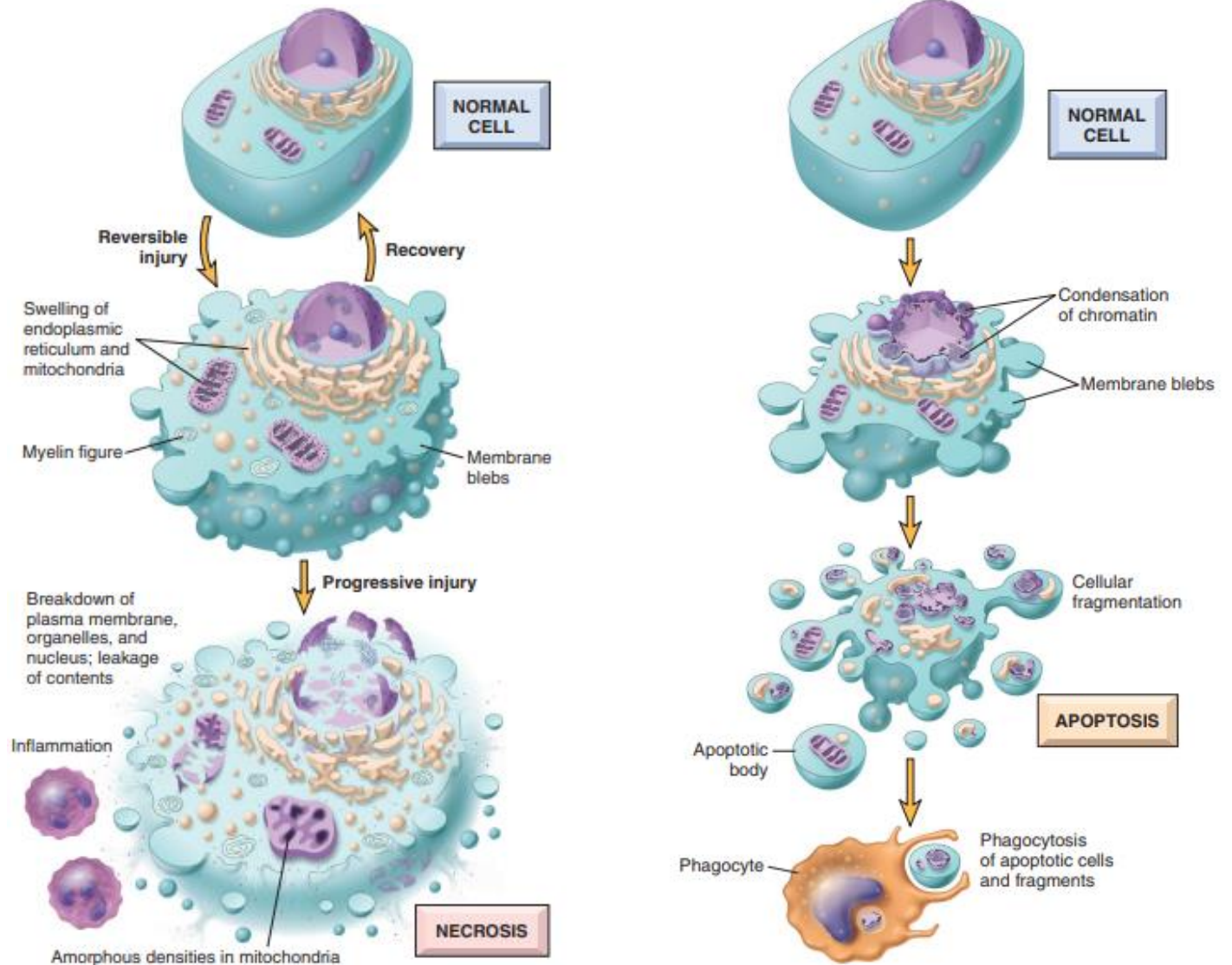
- **A**poptosis - suicide - **p**rogrammed cell death- regulated cell death.
- Is a pathway of cell death in which cells activate enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.
- Apoptosis = “falling off” Greek
- Can be **p**athologic and **p**hysiologic
- Doesn't elicit inflammation



Why apoptosis doesn't elicit inflammation



- The plasma membrane remains intact.
- Apoptotic bodies are formed, contain portions of the cytoplasm and nucleus and become targets for phagocytosis before their contents leak out.
- The apoptotic bodies are quickly recognized and engulfed by phagocytes, such as macrophages.



~ Physiologic Apoptosis:

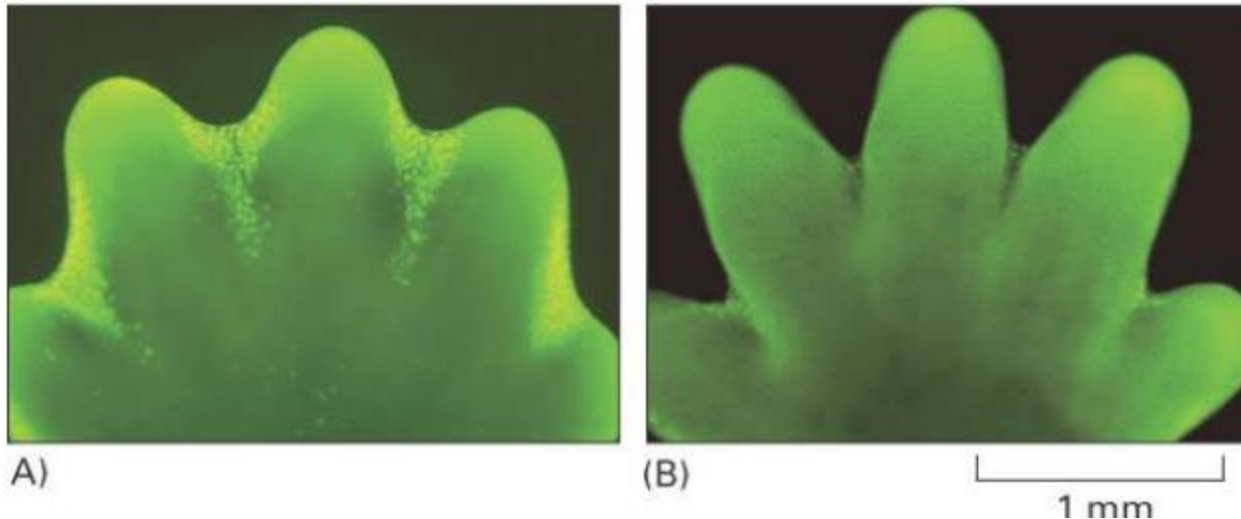


Condition	Mechanism of Apoptosis
Physiologic	
During embryogenesis	Loss of growth factor signaling (presumed mechanism)
Turnover of proliferative tissues (e.g., intestinal epithelium, lymphocytes in bone marrow, and thymus)	Loss of growth factor signaling (presumed mechanism)
Involution of hormone-dependent tissues (e.g., endometrium)	Decreased hormone levels lead to reduced survival signals
Decline of leukocyte numbers at the end of immune and inflammatory responses	Loss of survival signals as stimulus for leukocyte activation is eliminated
Elimination of potentially harmful self-reactive lymphocytes	Strong recognition of self antigens induces apoptosis by both the mitochondrial and death receptor pathways

~ Physiological apoptosis



- Embryogenesis Processes: during key developmental stages like implantation, organogenesis (the formation of organs), and developmental involution (where certain structures are reduced or disappear), apoptosis is crucial.
- Specifically, the separation of digits in the limbs (fingers or toes) is a result of programmed cell death, which removes the tissue between digits, forming distinct fingers.

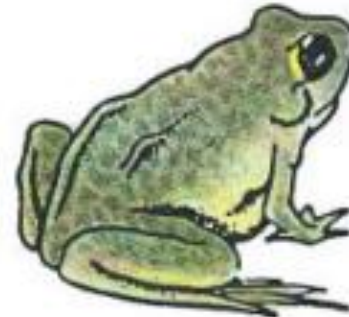
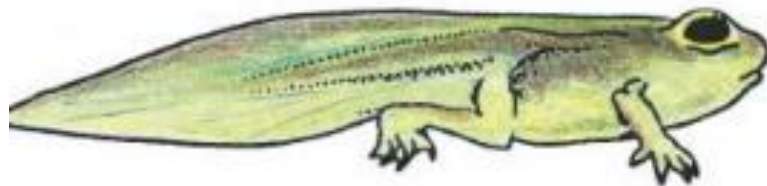


- Image A shows a developing limb with webbed tissue between the digits.
- Image B shows the same limb after the tissue between the digits has been removed, thanks to apoptosis, leaving separated digits.

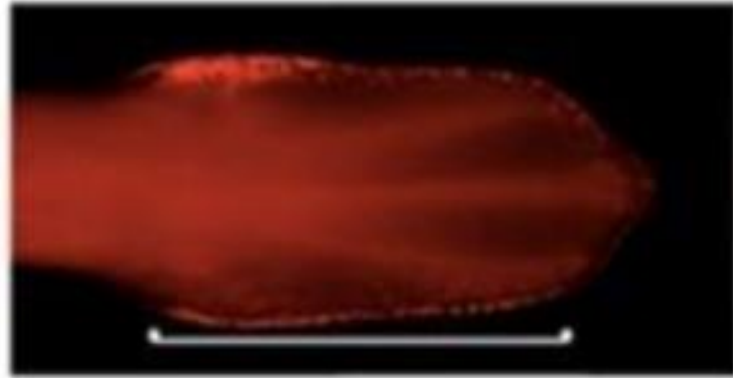
⚡ Physiological apoptosis



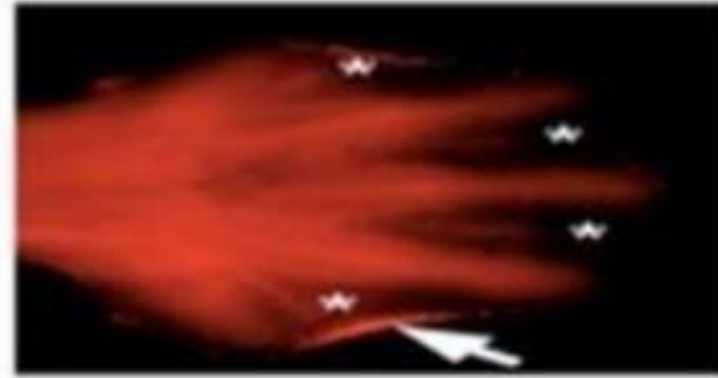
- **In Adult Multicellular Organisms:** apoptosis is not limited to embryonic development.
- It continues throughout life in adult organisms, where cell death is a regular occurrence to maintain tissue health and balance.
- The image of a **tadpole** transitioning into a **frog** further emphasizes the role of apoptosis in development.
- In this case, apoptosis is responsible for the loss of the tadpole's tail during metamorphosis as it develops into an adult frog.



~ Physiological apoptosis



a. Embryonic day 12.5



b. Embryonic day 13.5



c



d

~ Physiological apoptosis



- (a) and (b) Development of mouse limbs and sequential passage of time of digits.
- Red dots show cells undergoing apoptosis.
- Consequences of inappropriate apoptosis in developing human embryo.
- (c) Deficient apoptosis causes fusion of digits (syndactyly) leading to less digits (oligodactyly).
- (d) Excessive apoptosis results in extra digits (Polydactyly).

~ Physiological apoptosis



Pathologic	
DNA damage	Activation of proapoptotic proteins by BH3-only sensors
Accumulation of misfolded proteins	Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
Infections, especially certain viral infections	Activation of the mitochondrial pathway by viral proteins Killing of infected cells by cytotoxic T lymphocytes, which activate caspases

⚡ Mechanisms of Apoptosis



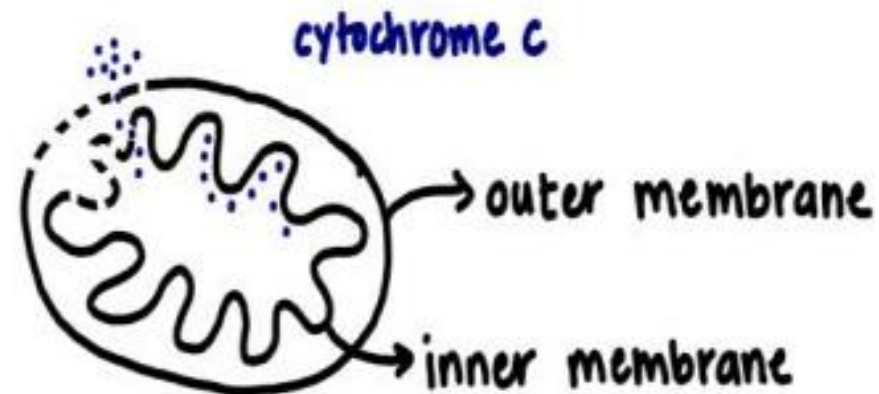
- Normally, there is a biochemical pathways that control the balance of death- and survival-inducing signals.
- Apoptosis is regulated by these pathways → Activation of enzymes called caspases through two main pathways:
 1. Mitochondrial pathway (intrinsic)
 2. Death receptor pathway (extrinsic)



~ Intrinsic pathway; mitochondrial pathway

- In most physiologic & pathologic situations.
- Mitochondria contain several proteins capable of inducing apoptosis → Cytochrome c.
- ↑ mitochondrial permeability → permeable membrane → cytochrome c leaks → triggering caspase 9 → activate apoptosis

apoptosis → ↑ permeability → cyt c release



~ Intrinsic pathway; mitochondrial pathway



A family of more than 20 proteins (prototype is Bcl-2) controls the permeability of mitochondria.

+ **proapoptotic** members of the family are **Bax & Bak**.

+ **Activated by BH3 proteins** (sensor)

+ **when stimulated** → dimerize
→ insert into mitochondrial membrane → form channels
→ cytochrome c escapes into cytosol

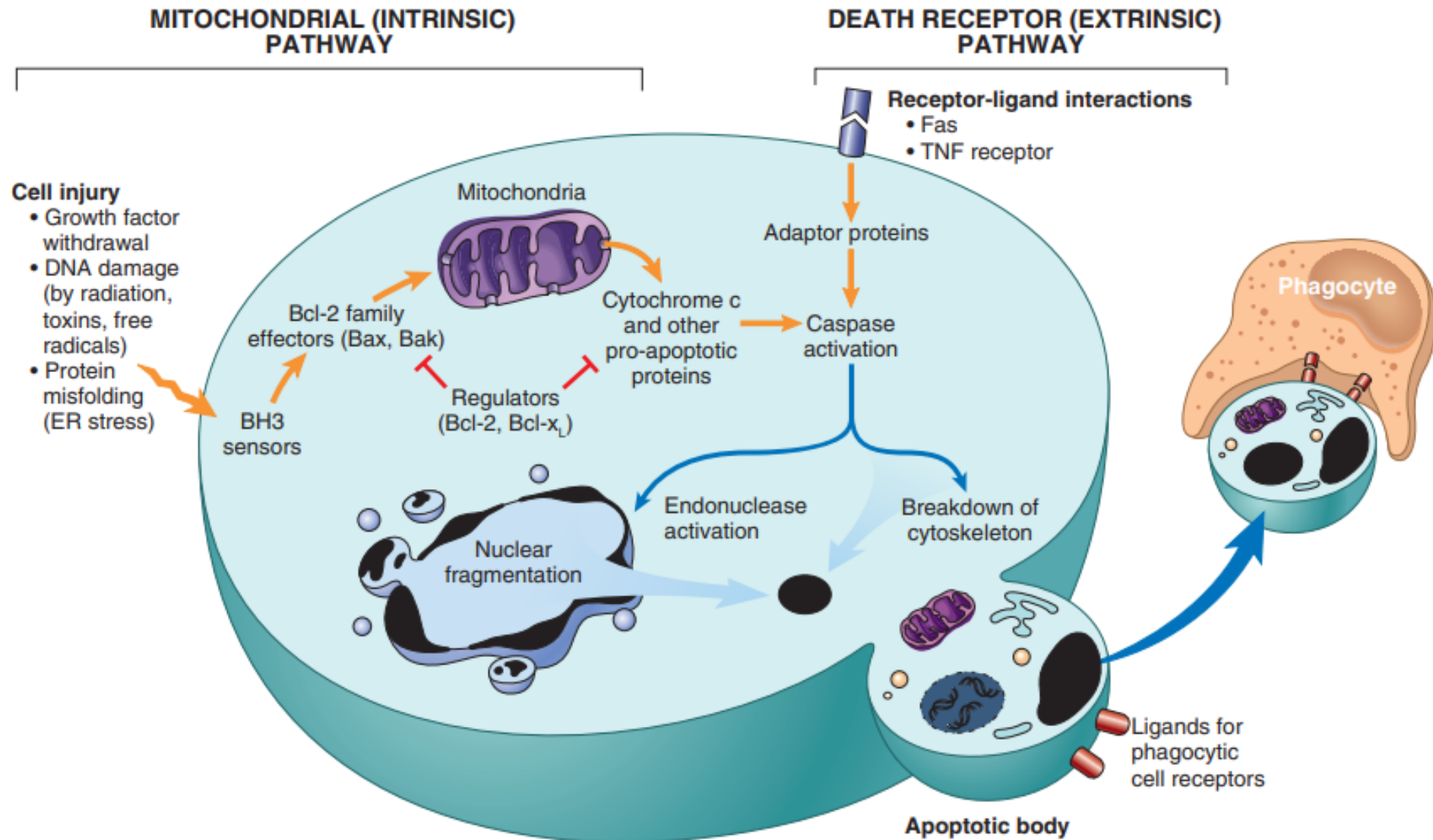


+ **Antiapoptotic** members are **BCL-2 & BCL-xL**

+ produced in response to **growth factors & survival signals**.

+ maintain the **integrity of mitochondrial membranes** → holding proapoptotic in check.

⚡ Intrinsic pathway; mitochondrial pathway



⚡ Intrinsic pathway; mitochondrial pathway



- BH3 protein: a group of sensors (called BH3 proteins because they contain the third domain seen in Bcl-family)
- Activated when:
 1. Cells are deprived of growth factors & survival signals.
 2. Cells are exposed to agents that damage DNA.
 3. Cells accumulate unacceptable amounts of misfolded proteins.
- They shift the life-sustaining balance in favor of pro-apoptotic Bak and Bax.

⚡ Extrinsic pathway; death receptor pathway



- **Tumor Necrosis Factor (TNF) Receptor Family:**

- **Prototypic Death Receptors:**

- A. Type I TNF receptor

- B. Fas (CD95)

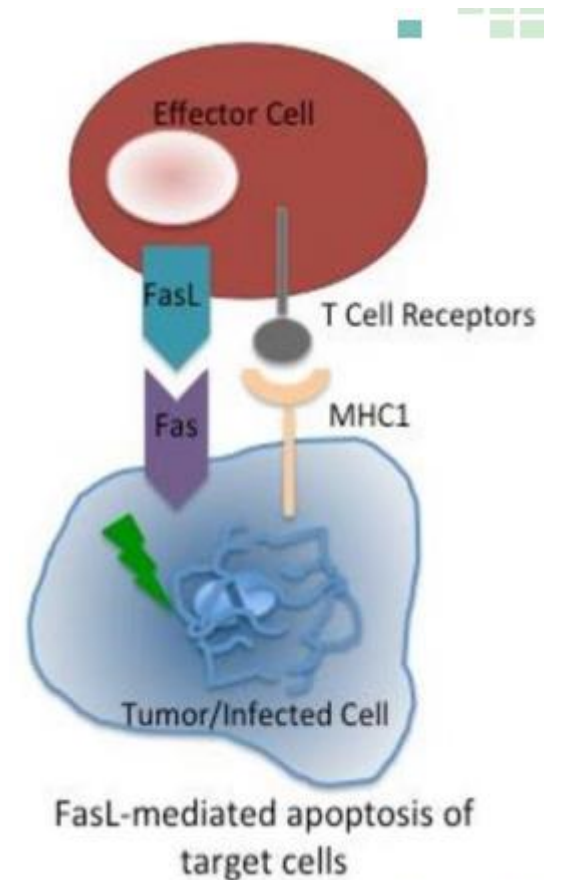
- **Structural Features:**

- Contain cytoplasmic regions known as “death domains”.

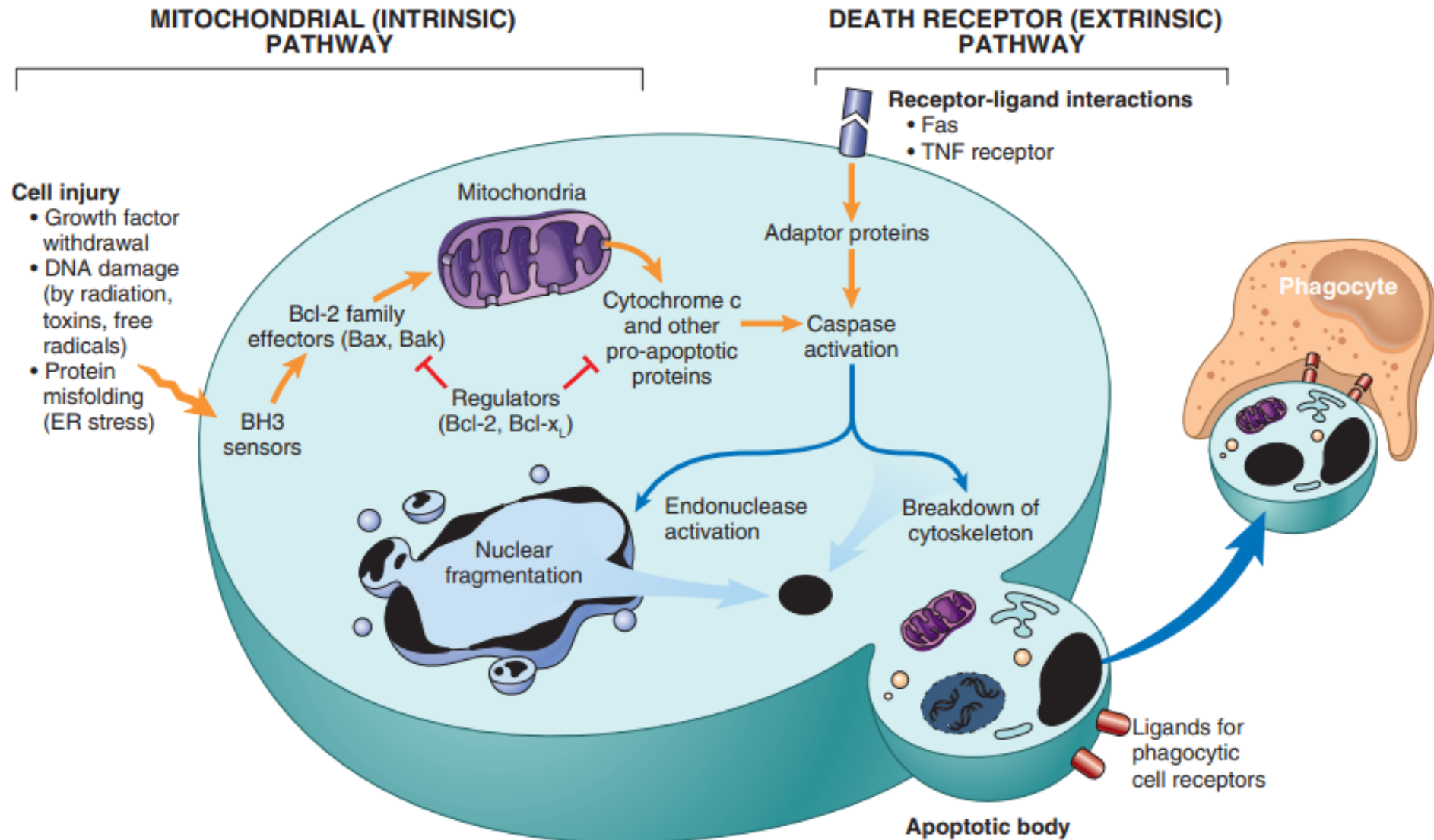
- **Fas Ligand (FasL):** A membrane protein expressed on activated T lymphocytes.

- **Mechanism of Action:**

1. T cells recognize target cells expressing Fas.
2. Fas molecules on the target cells are cross-linked by FasL.
3. This cross-linking activates **caspase-8**, initiating apoptosis.



⚡ Intrinsic pathway; mitochondrial pathway



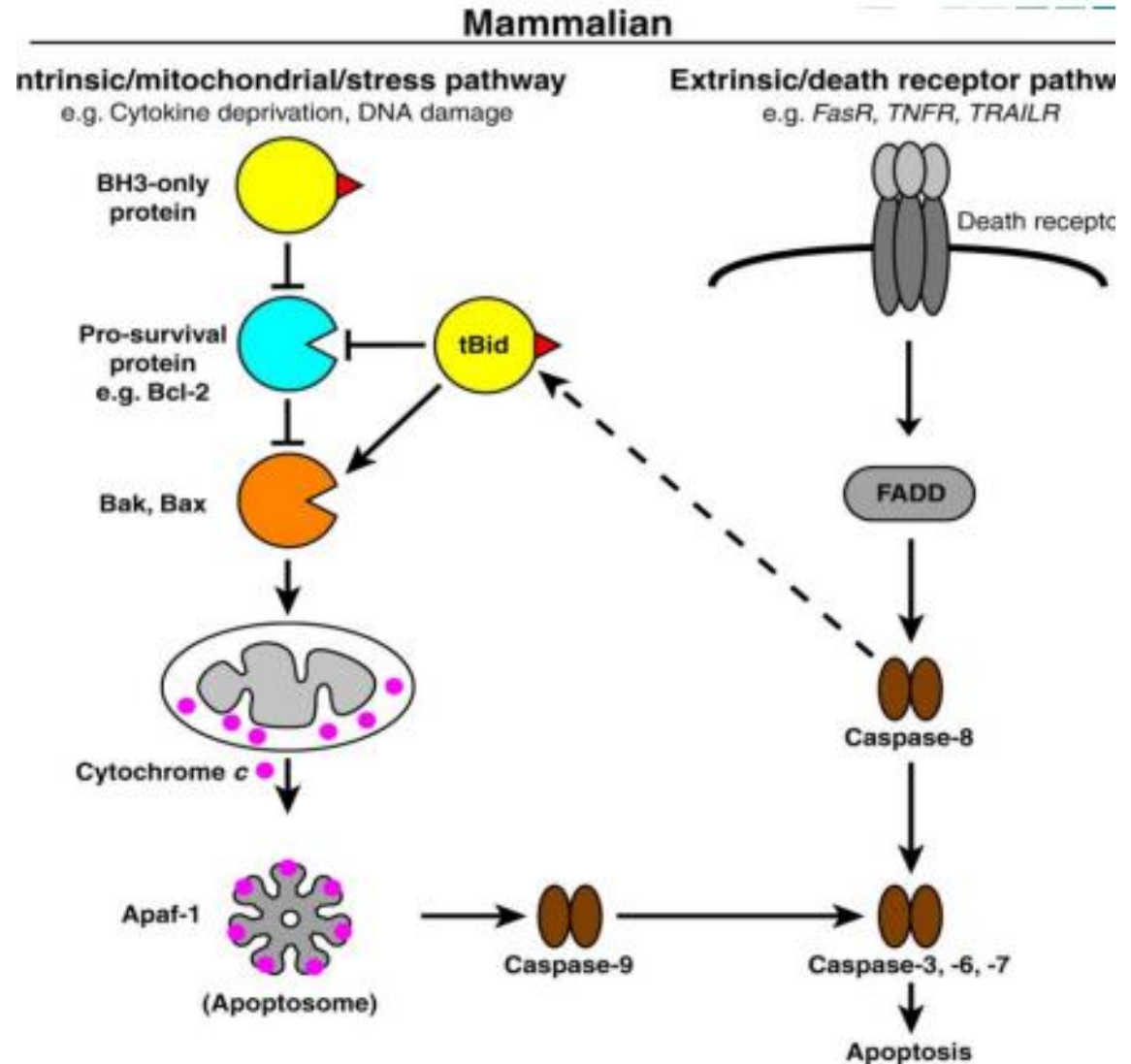
Extrinsic pathway; death receptor pathway



- In Either pathway:**

- After caspase-9 or caspase-8 is activated → it cleaves & thereby activates additional caspases → that cleave numerous targets → activate enzymes that degrade the cells' proteins & nucleus.

- The end result is the characteristic cellular fragmentation of apoptosis.





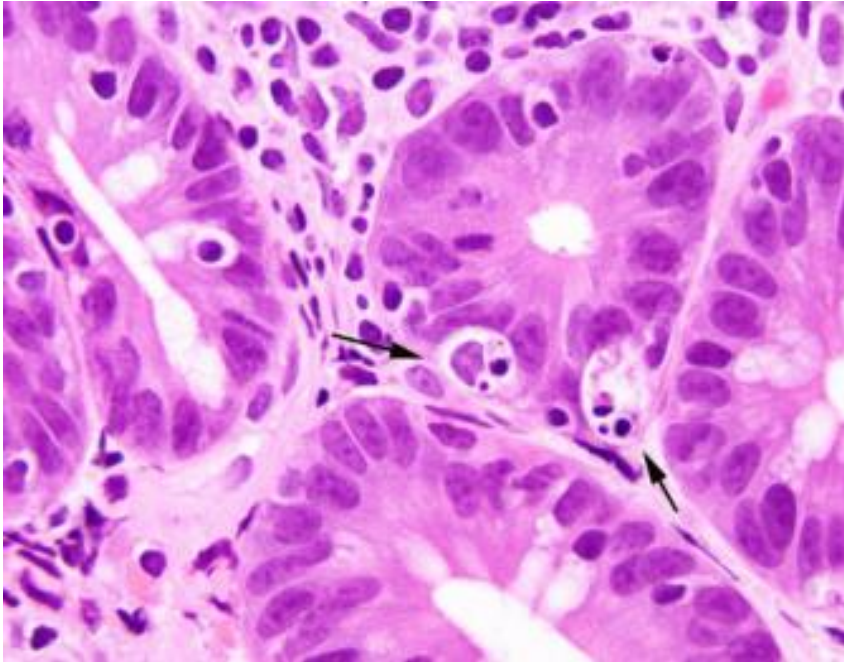
~ Clearance of apoptotic cells

- Entice phagocytes by producing a number of “eat-me” signals:
 1. “Flips” phospholipid to the outer leaflet, expose phosphatidylserine.
 2. Secrete soluble factors that recruit phagocytes.
- ✓ Happens before the cells undergo membrane damage and release their contents...
So no inflammation!

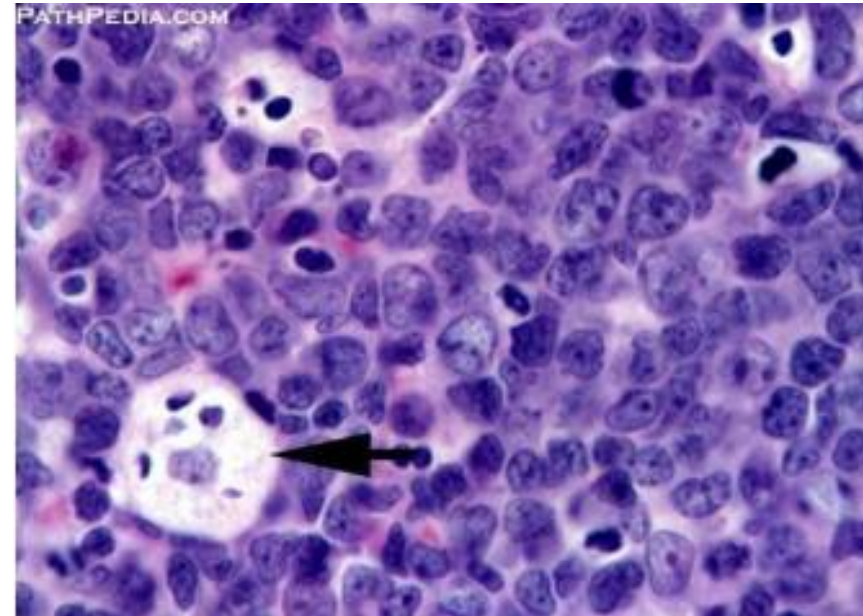
~ Morphology:



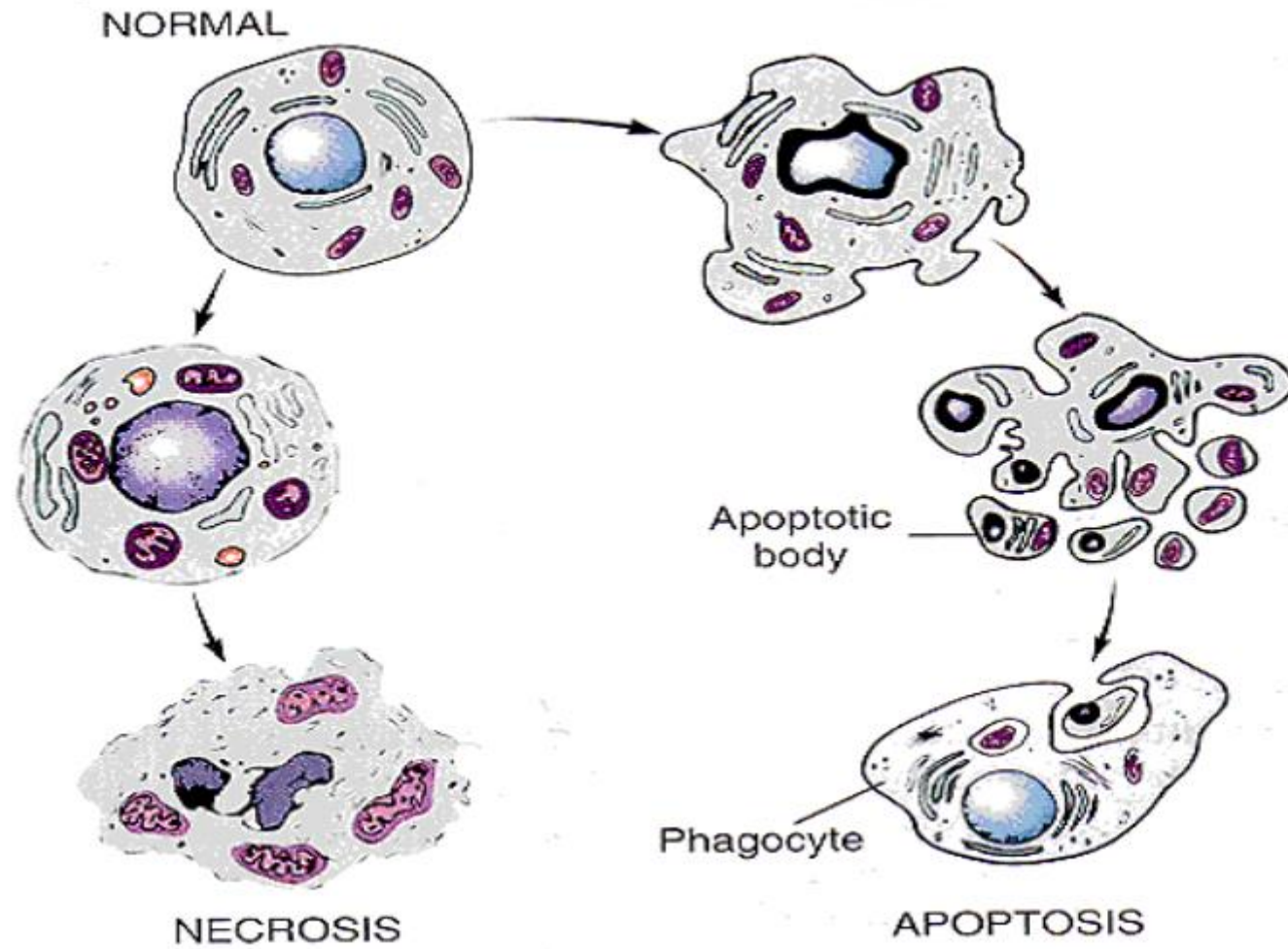
1. Involves single cells or small clusters
2. Cells shrink rapidly, retain intact plasma membrane
3. Formation of cytoplasmic buds
4. Fragmentation into apoptotic bodies
5. Apoptotic bodies phagocytized rapidly before inflammatory response



- Intestinal epithelial cells



- Lymph node → Macrophage





Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-sized 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 (culmination of irreversible cell injury)	Often physiologic means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA and protein damage



Other Pathways of Cell Death:

Necroptosis

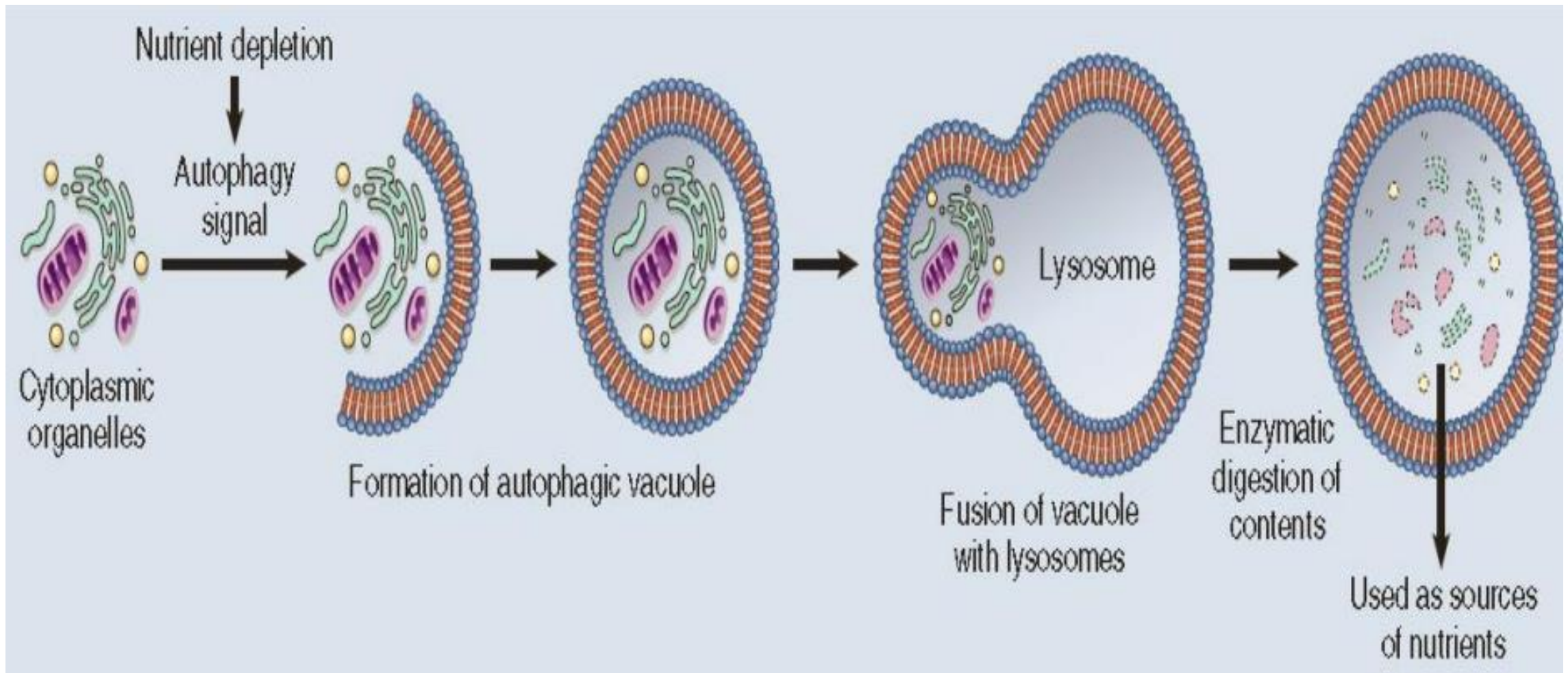
- Features of **both** necrosis and apoptosis.
- initiated by engagement of TNF receptors → receptor interacting protein (RIP) kinases are activated → initiating dissolution of the cell like necrosis

Pyroptosis

- activation of a cytosolic danger-sensing protein complex called the **inflammasome**.
- Greek, *pyro* = fire
- Used by infectious microbes
- Fever + inflammation + apoptosis

Autophagy

- (“self-eating”)
- refers to lysosomal digestion of the cell’s own components.
- Nutrient deprivation
- Survival pathway





«Education is the passport to the future, for tomorrow
belongs to those who prepare for it today»

- Maclom X-