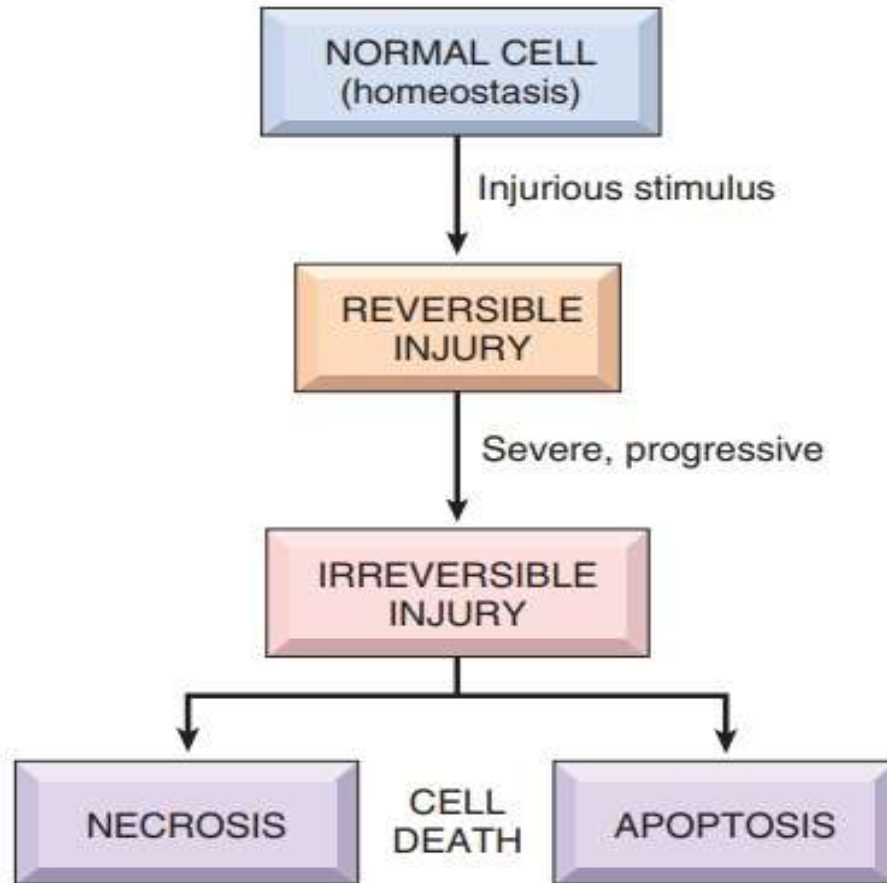


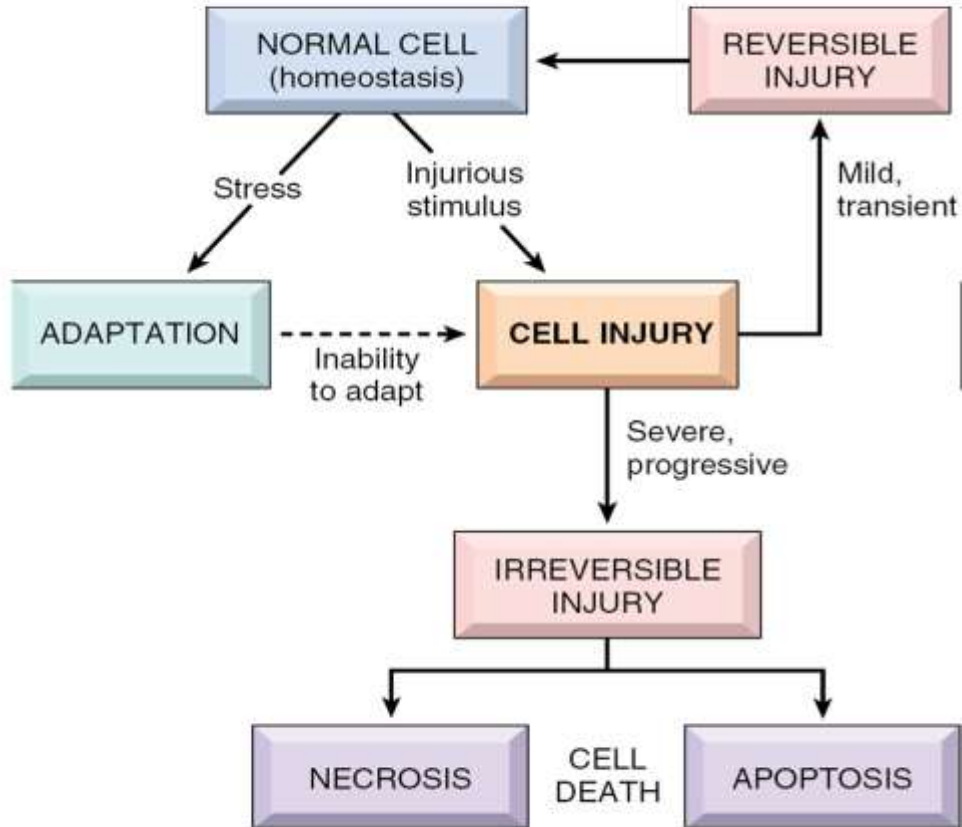
Cell Injury and Necrosis-3

Apoptosis

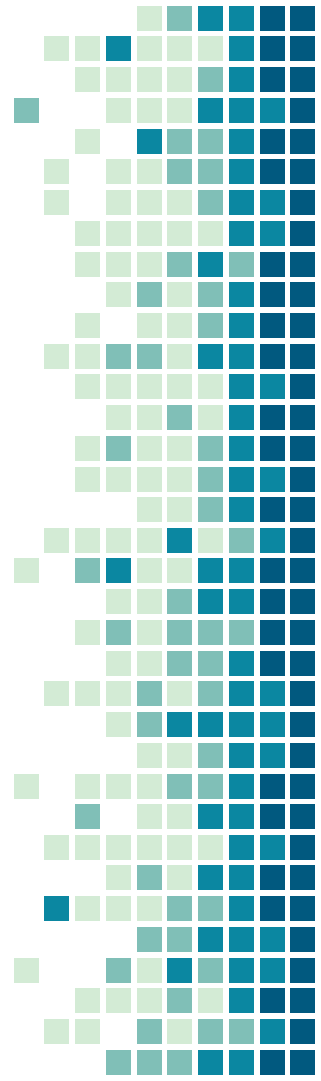
Ghadeer Hayel, M.D.
Assistant Professor of Pathology
Consultant Hematopathologist
10/13/2024





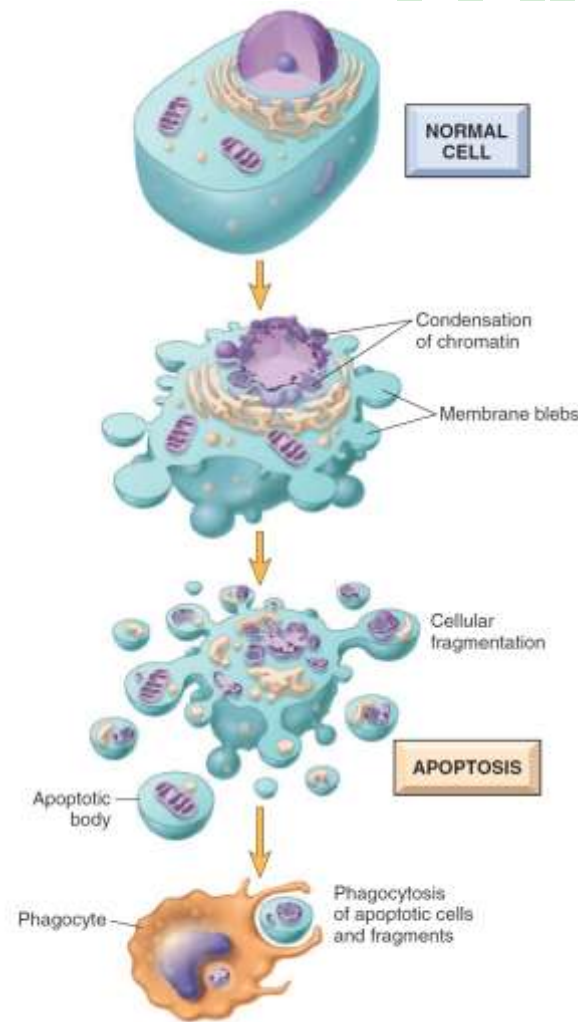


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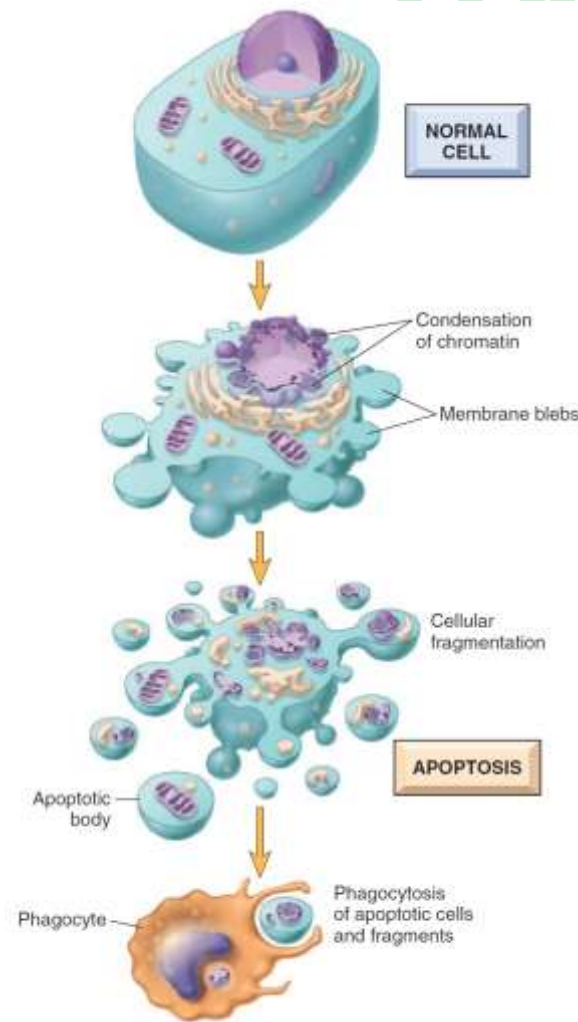
Apoptosis

- + Apoptosis - suicide - programmed 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 pathologic and physiologic
- + **Doesn't elicit** inflammation.



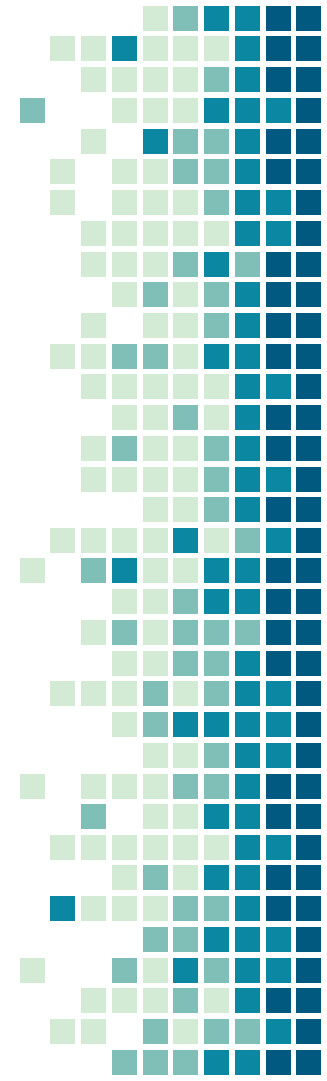
Apoptosis does not elicit inflammation:

- + 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.

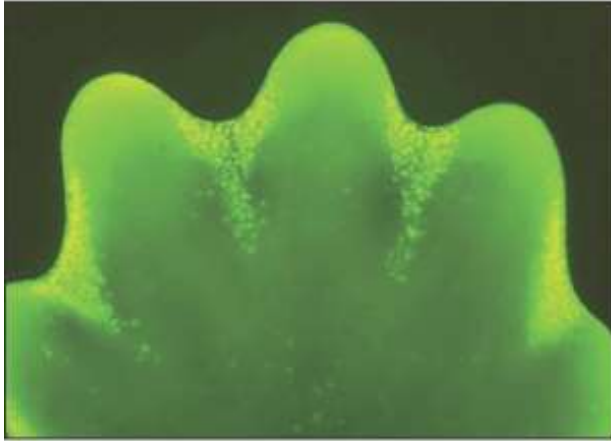


Physiologic Apoptosis:

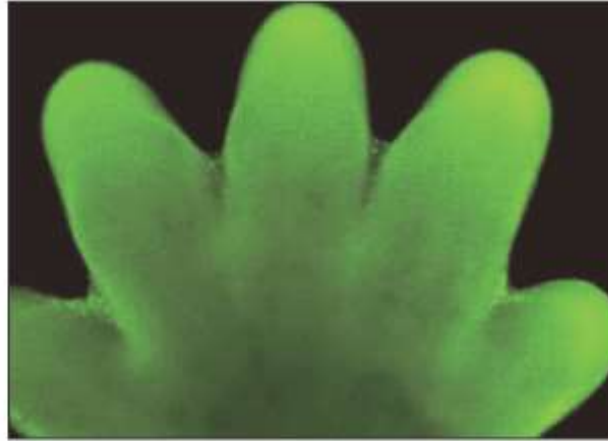
Condition	Mechanism of Apoptosis
During embryogenesis	Loss of growth factor signaling(presumed mechanism)
Turnover of proliferative tissues (e.g., intestinal epithelium, lymphocytes in bone marrow, and thymus)	Loss of growth factor signaling(presumed mechanism)
Involution of hormonedependent tissues (e.g., endometrium)	Decreased hormone levels leadto 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



During embryogenesis (implantation, organogenesis, developmental involution, separation of digits in limb development)



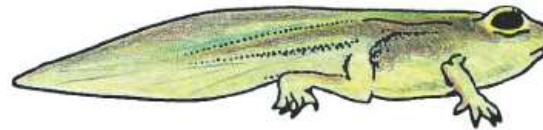
A)



(B)

1 mm

in adult multicellular organisms
cell death is a regular occurrence.
In humans EACH HOUR!!





Developing mouse paw,
a. Embryonic day 12.5



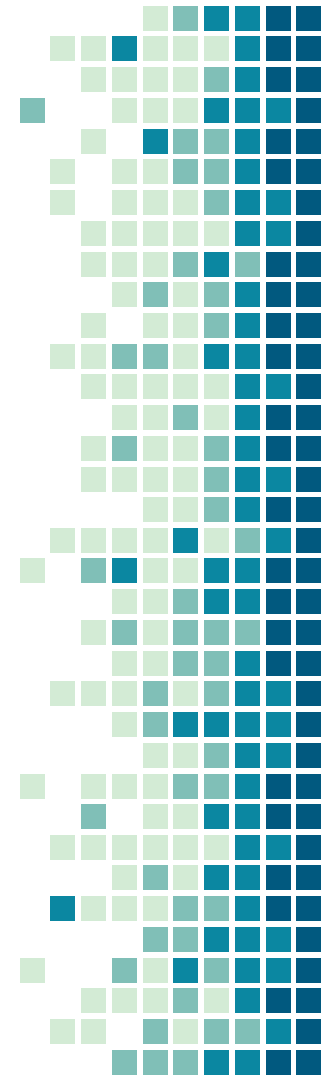
b. Embryonic day 13.5



c



d



Pathologic Apoptosis:

Condition	Mechanism of Apoptosis
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.



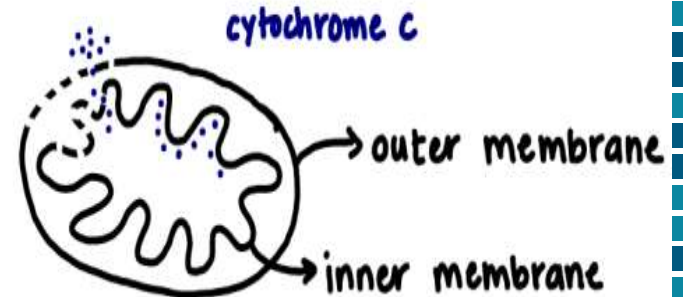
Mechanisms of Apoptosis

- ❖ 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



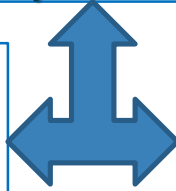
Intrinsic pathway; mitochondrial pathway

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**



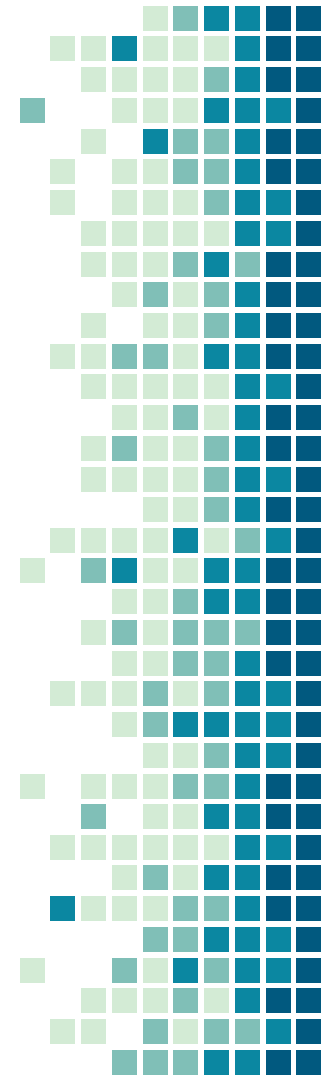
+ **Antiapoptotic** members are **BCL-2 & BCL-xL**

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

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

Intrinsic pathway; mitochondrial pathway

- **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

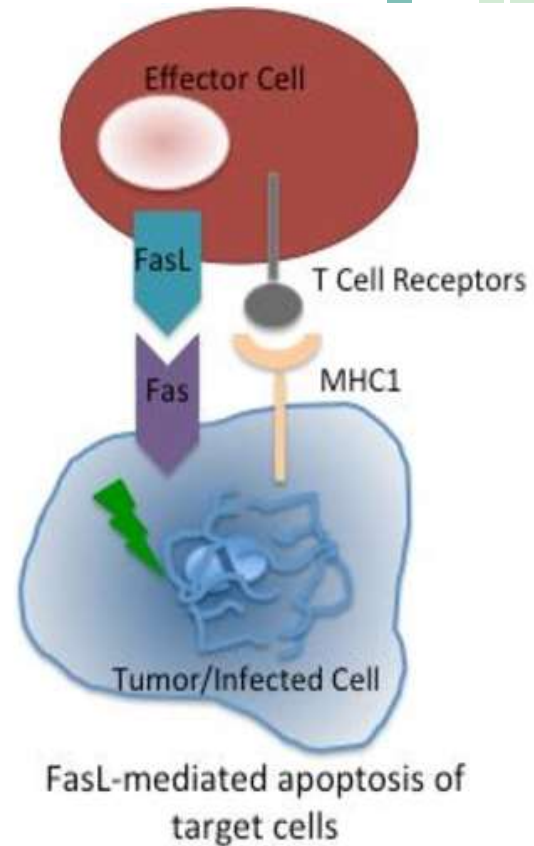
+ **Tumor necrosis factor (TNF)** receptor family.

+ The prototypic death receptors are the **type I TNF** receptor & **Fas (CD95)**.

+ contain a cytoplasmic regions → **“death domain”**

+ **Fas ligand (FasL)** : membrane protein expressed on **activated T lymphocytes**.

+ **T cells** recognize fas expressing target , fas molecules are **cross linked** by **fasL** to activate **caspase 8**

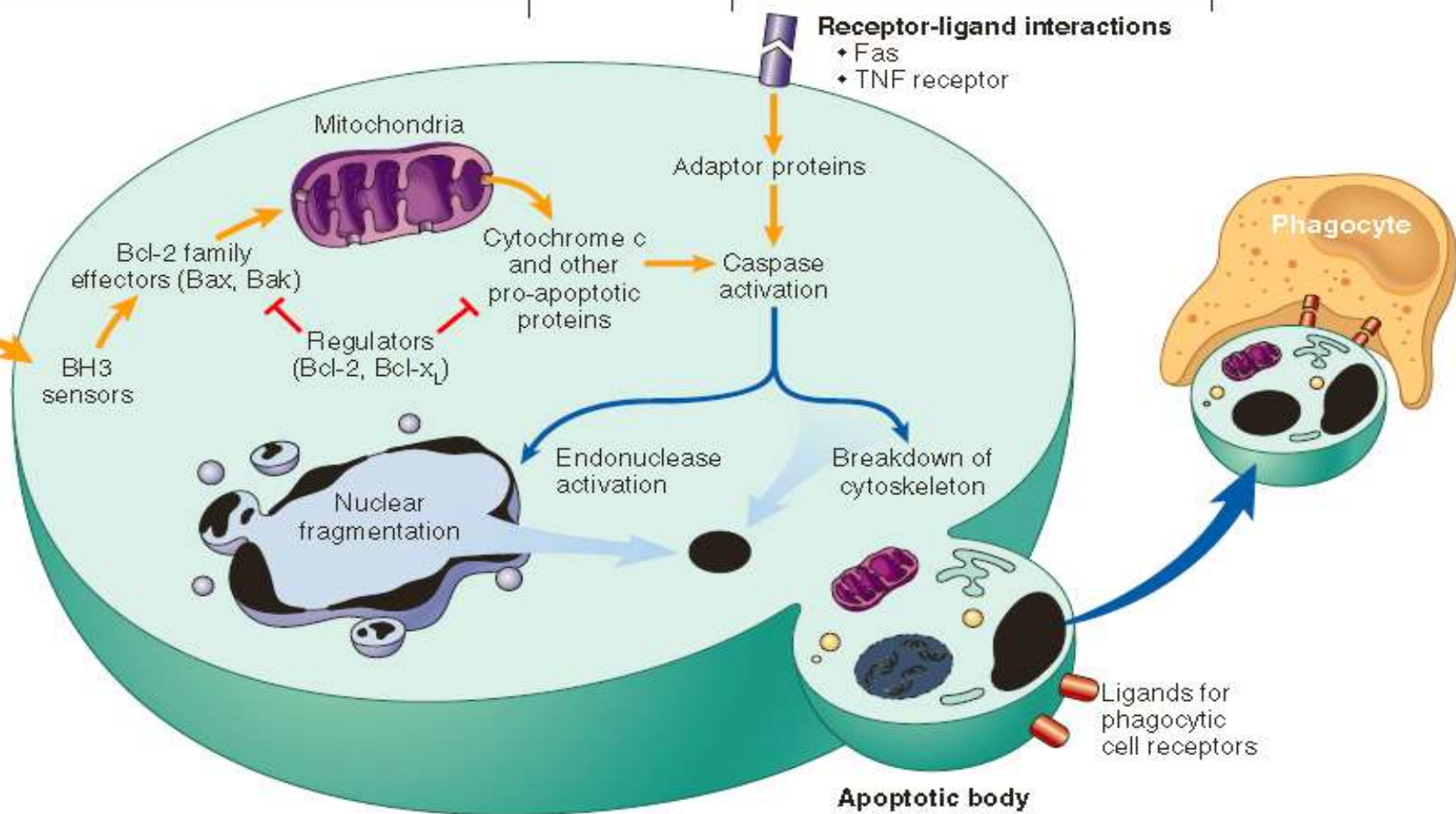


MITOCHONDRIAL (INTRINSIC) PATHWAY

DEATH RECEPTOR (EXTRINSIC) PATHWAY

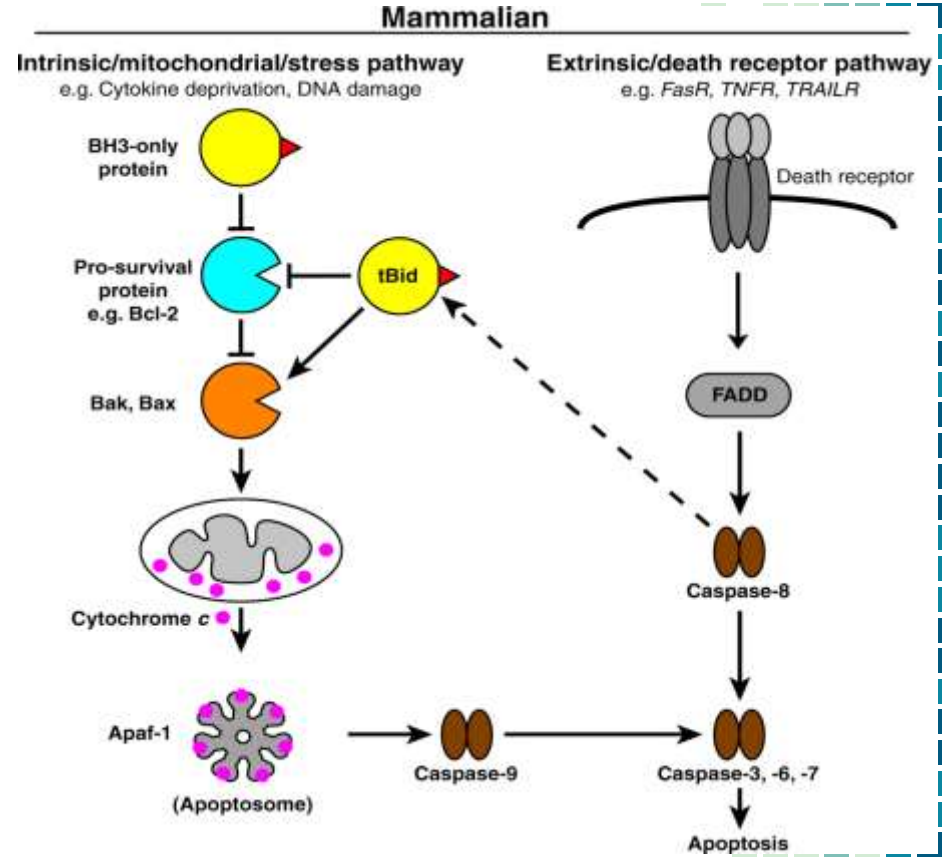
Cell injury

- Growth factor withdrawal
- DNA damage (by radiation, toxins, free radicals)
- Protein misfolding (ER stress)



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.



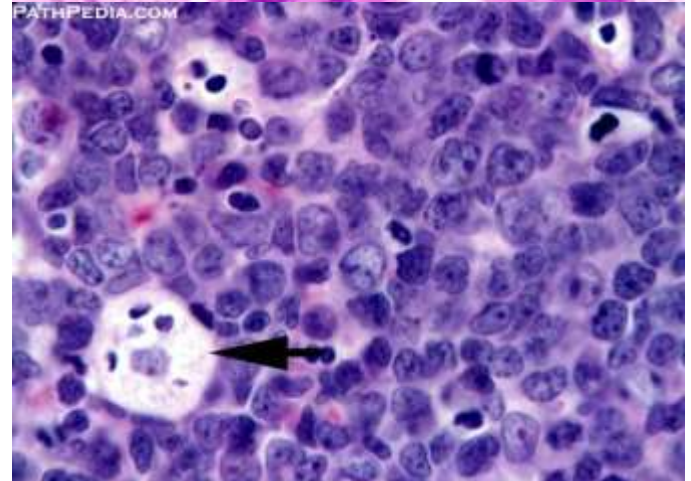
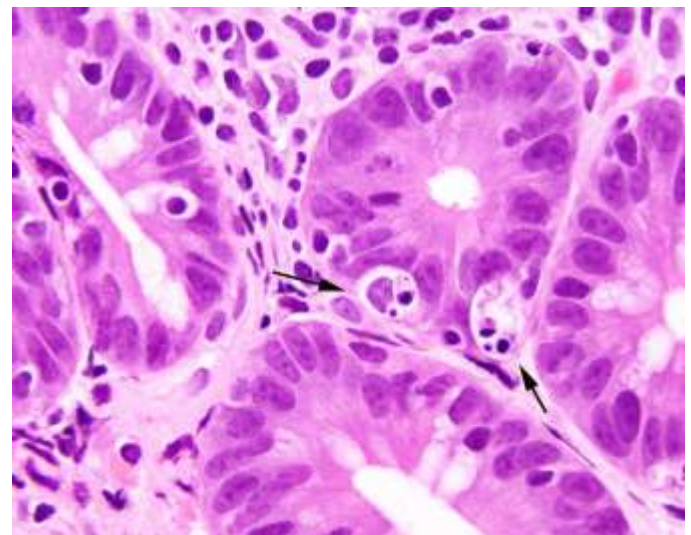
Clearance of apoptotic cells.

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

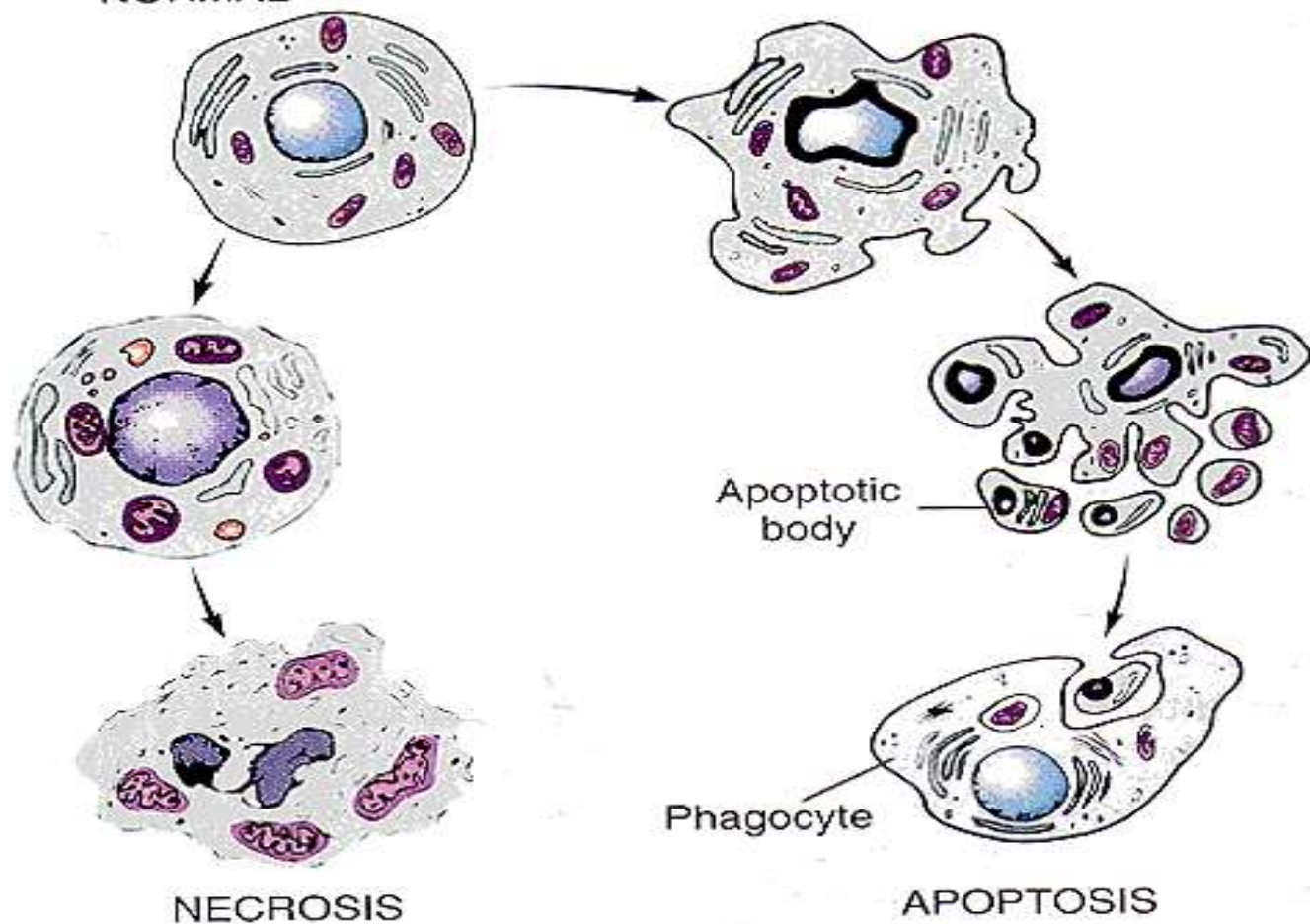


Morphology:

- ❖ Involves single cells or small clusters
- ❖ Cells shrink rapidly, retain **intact plasma membrane**
- ❖ Formation of cytoplasmic buds
- ❖ Fragmentation into **apoptotic bodies**
- ❖ Apoptotic bodies phagocytized rapidly before inflammatory response.



NORMAL



NECROSIS

APOPTOSIS

Necrosis Vs Apoptosis

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

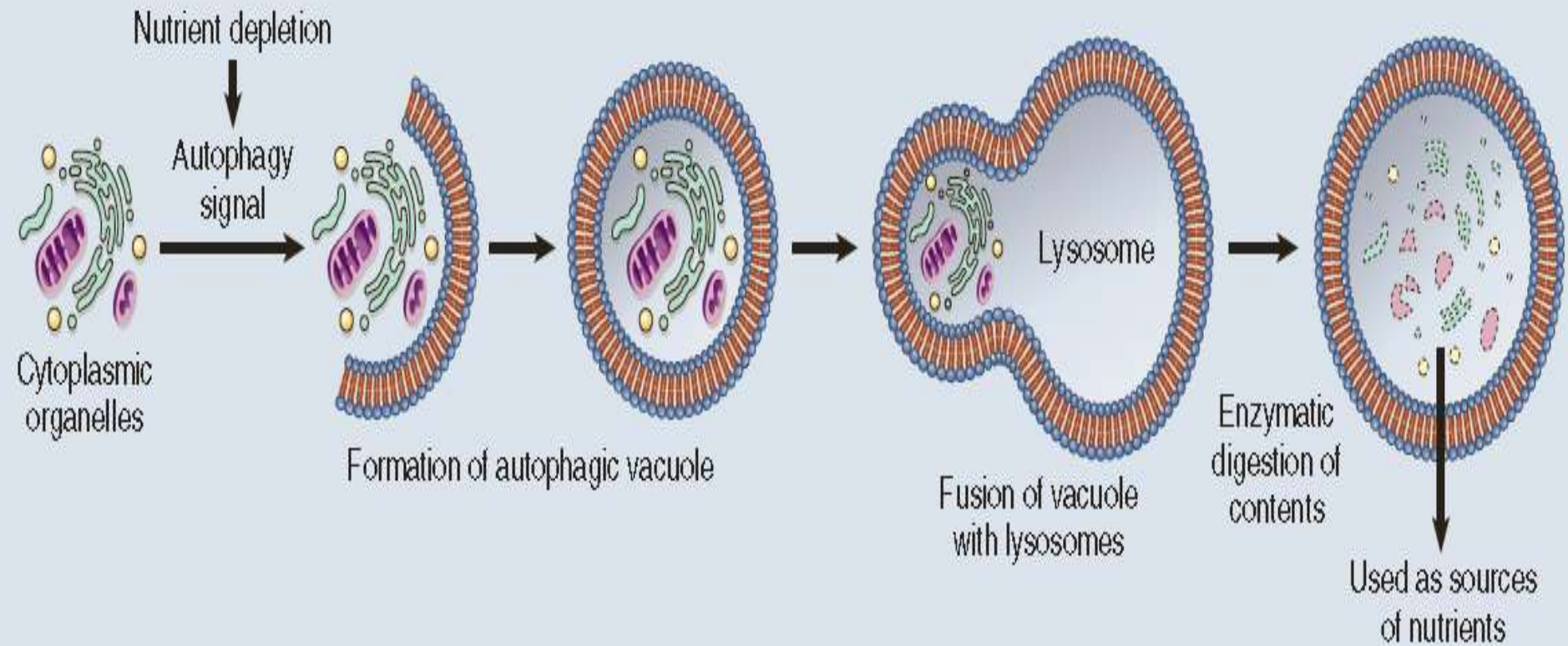
- Features of **both** necrosis and apoptosis.
- initiated by engagement of TNF receptors → receptor interacting protein (RIP) kinases are activated → initiating dissolution of the cell like necrosis

Pyroptosis

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

Autophagy

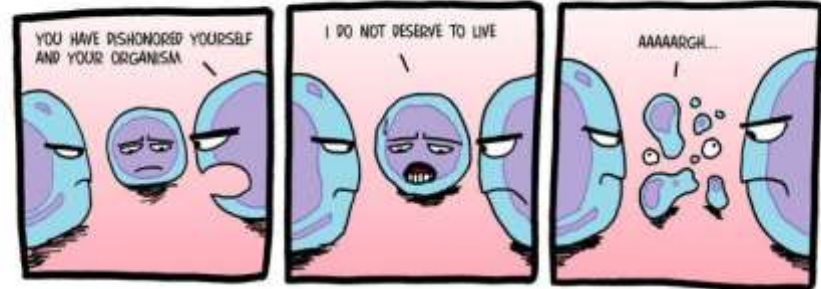
- (“self-eating”)
- refers to lysosomal digestion of the cell’s own components.
- Nutrient deprivation
- Survival pathway





THANKS!

Any questions?



APOPTOSIS
cellular
harakiri

Uchi