Cell Injury and Necrosis-3

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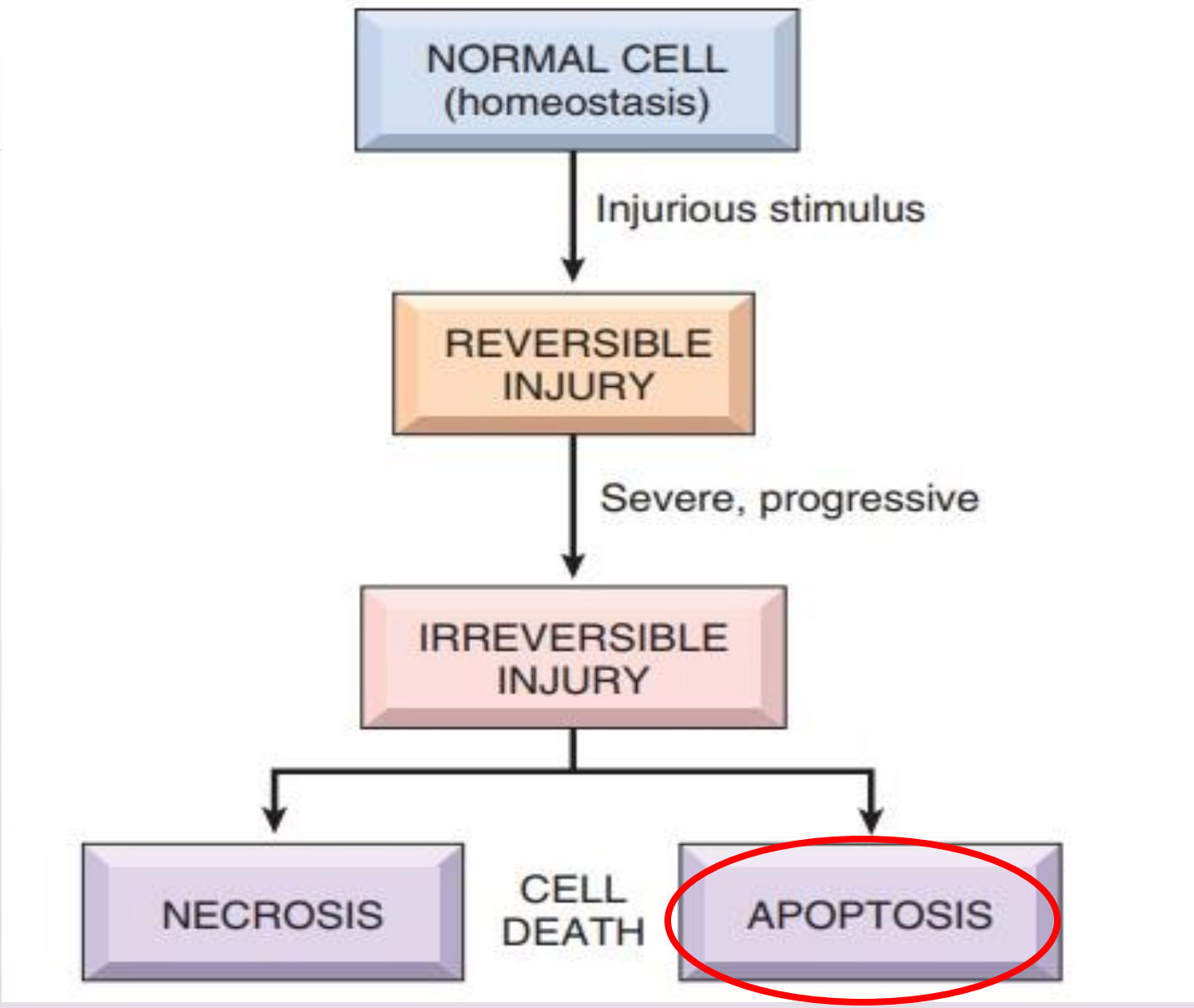

NORMAL CELL
(homeostasis)
Injurious stimulus
REVERSIBLE
INJURY
Severe, progressive
IRREVERSIBLE
INJURY
NECROSIS
CELL
DEATH
APOPTOSIS

Apoptosis

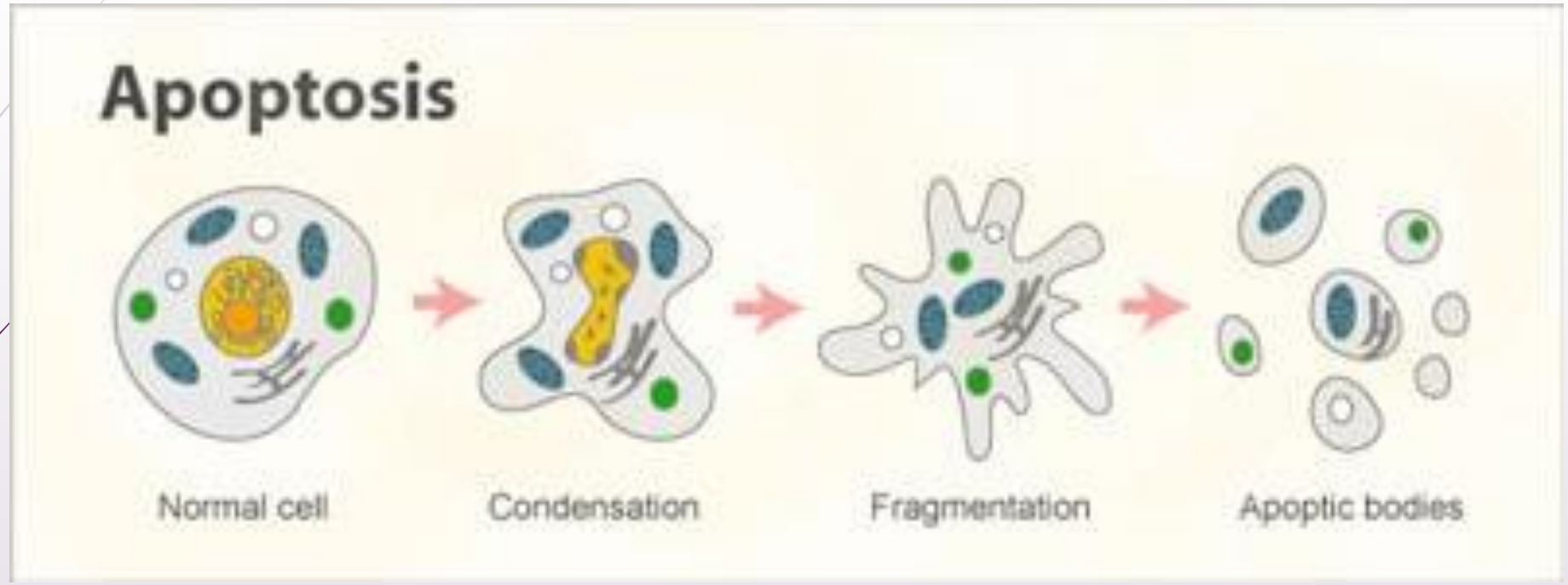
- The process of programmed cell death.
- Characterized by distinct morphological characteristics and energy-dependent biochemical mechanisms which include mainly:
- activated enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins.
- Can be pathologic and physiologic

- Physiological apoptosis in mammals is a type of programmed cell death, an important element in the developmental features ensuring tissue homeostasis and proper disposal of cells that are no longer needed, such as :

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

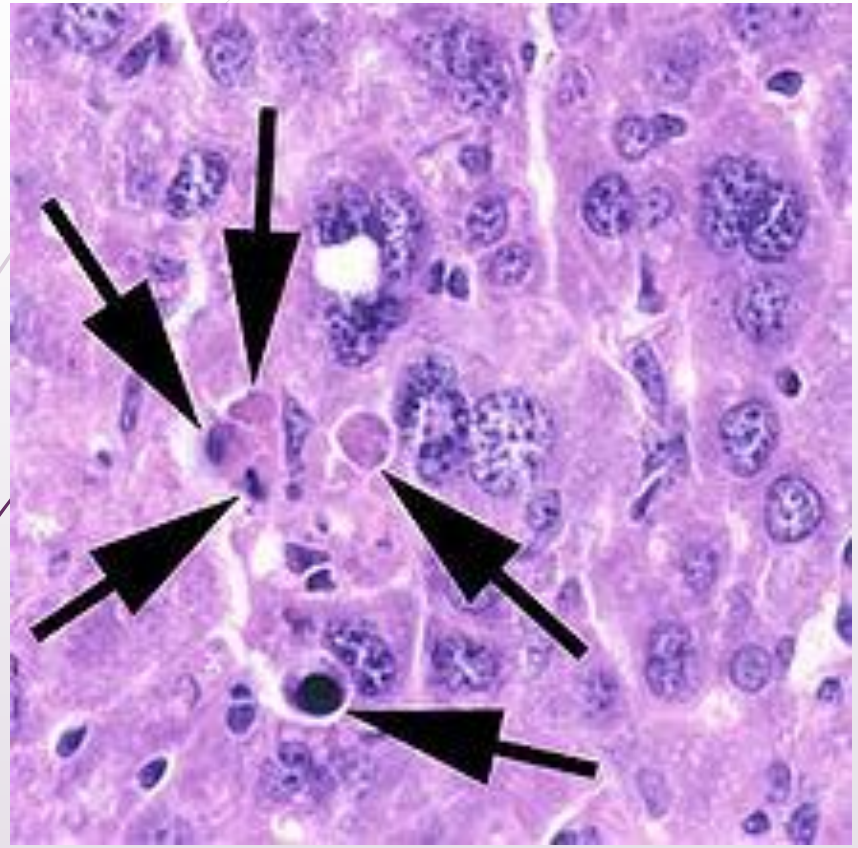
Pathological

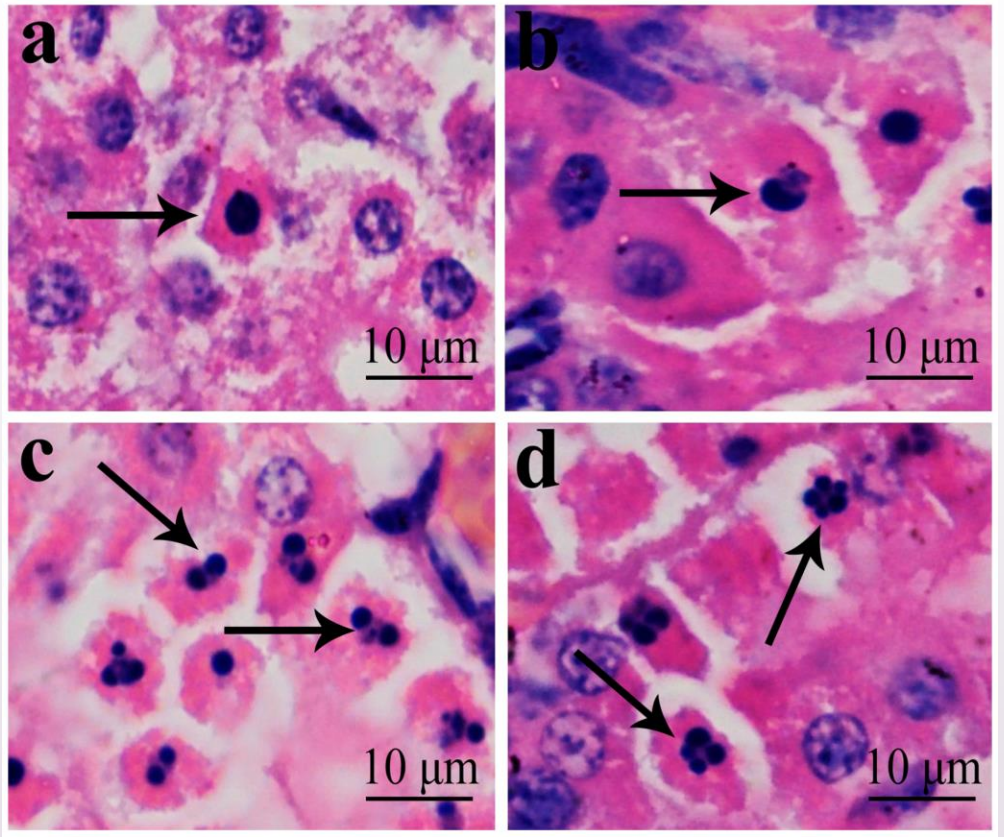
Pathologic	
DNA damage	Activation of proapoptotic proteins by BH3-only sensors
Accumulation of misfolded proteins	Activation of proapoptotic proteins by BH3-only sensors, possibly direct activation of caspases
Infections, especially certain viral infections	Activation of the mitochondrial pathway by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


Apoptosis
Normal cell
Condensation
Fragmentation
Apoptic bodies

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.

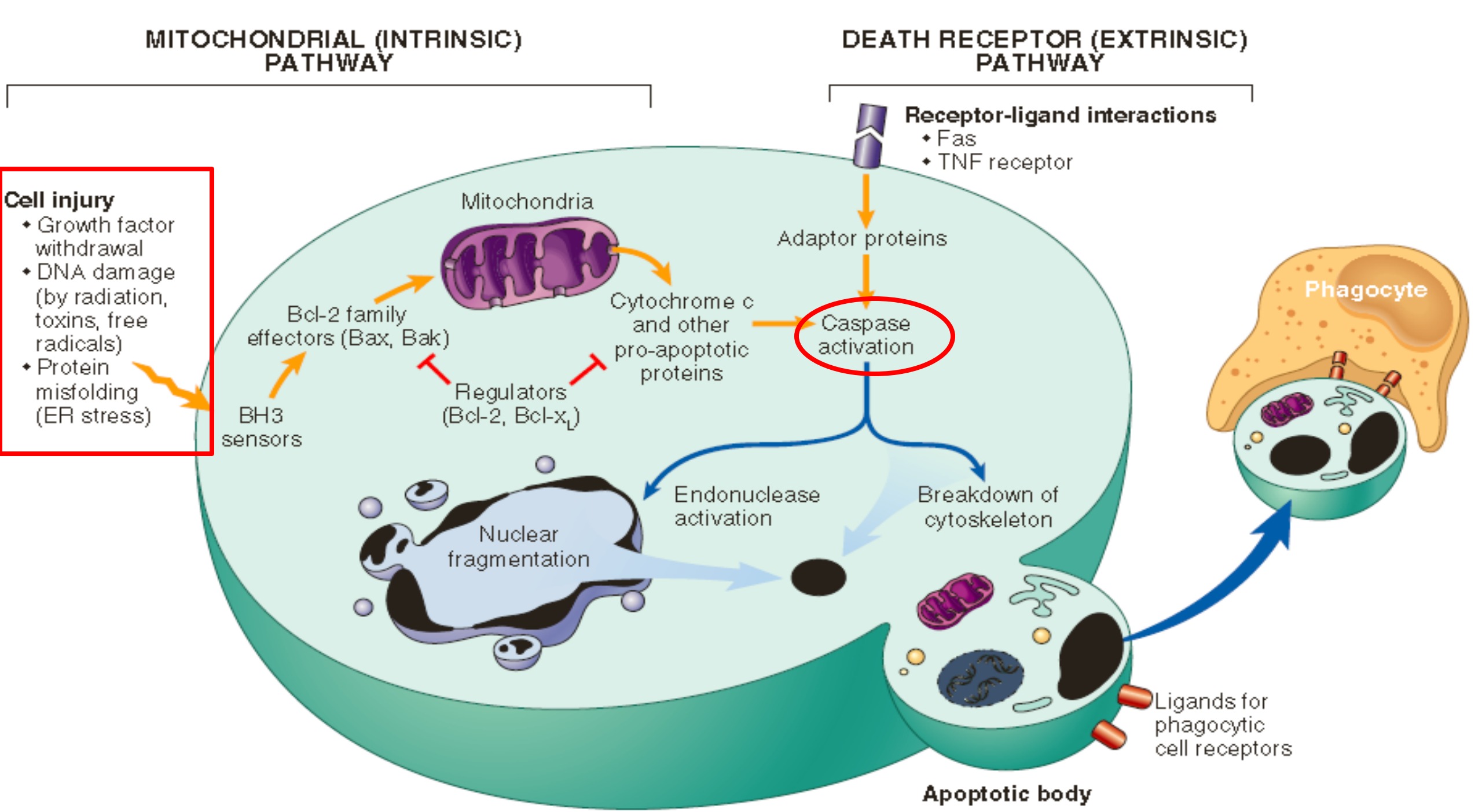



a
10 μm
b
10 μm
c
10 μm
d
10 μm

Mechanisms

- **Phases:**
- **Initiation .**
- **execution.**
- **clearing of dead cells.**

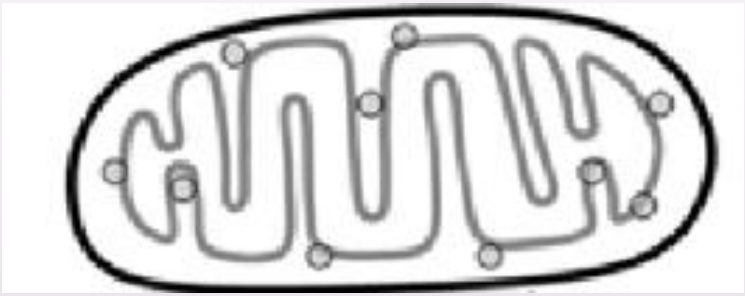
- **Pathways:**
- **Intrinsic**
- **Extrinsic**


MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor-ligand interactions
• Fas
• TNF receptor
Cell injury
• Growth factor withdrawal
• DNA damage (by radiation, toxins, free radicals)
• Protein misfolding (ER stress)
Mitochondria
Adaptor proteins
Bcl-2 family effectors (Bax, Bak)
Cytochrome c and other pro-apoptotic proteins
Caspase activation
Regulators (Bcl-2, Bcl-xL)
BH3 sensors
Endonuclease activation
Breakdown of cytoskeleton
Nuclear fragmentation
Phagocyte
Ligands for phagocytic cell receptors
Apoptotic body

Mitochondrial (intrinsic) pathway:

- **In the mitochondria , the status of cytochrome c production is under control of balance between proapoptotic and Antiapoptotic.**

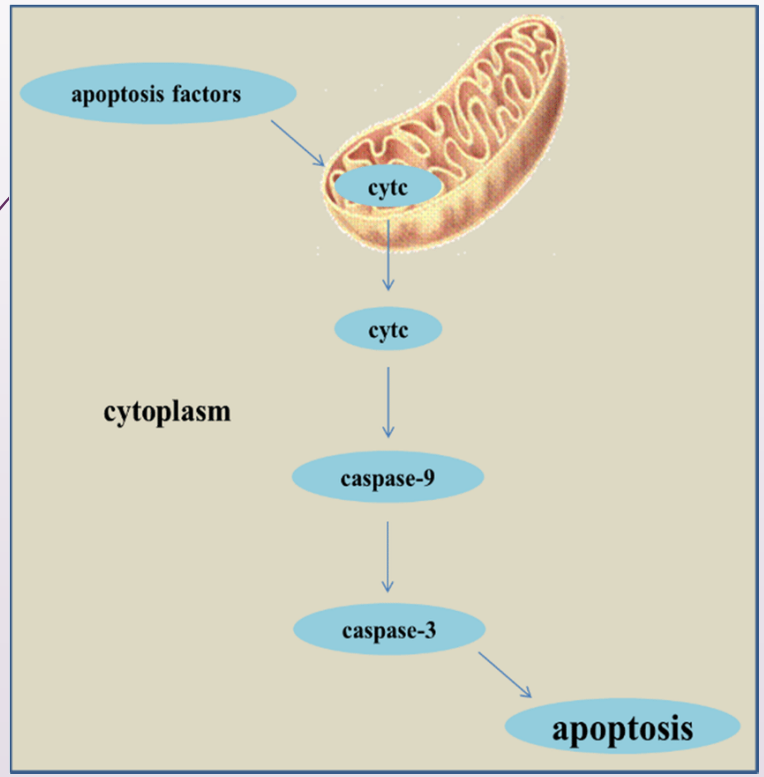
proapoptotic members of the family are **Bax & Bak**



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

Intrinsic pathway cont.

#Undesirable cells → discovered by BH3 sensors → shift of this balance in favor of pro-apoptotic Bak and Bax



Increased mitochondrial permeability

cytochrome c leaks

triggering **caspase 9**

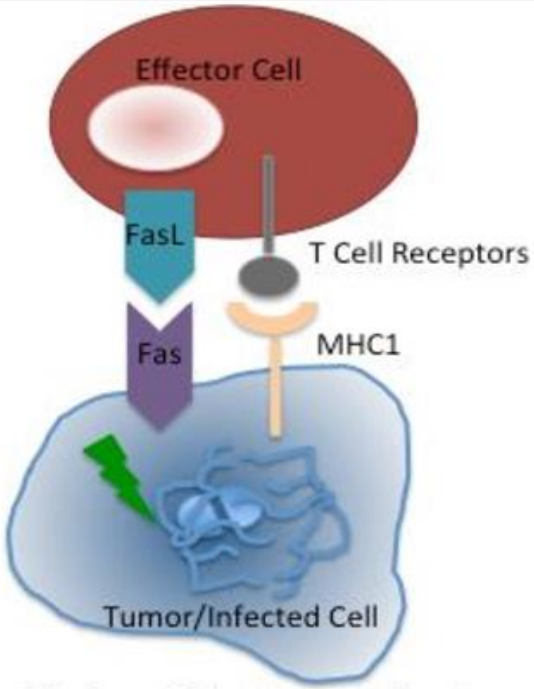
Extrinsic pathway; death receptor pathway

- The primary cells that induce the extrinsic pathway of apoptosis are NK and CTL lymphocytes. NK cells are lymphocytes, yet are part of the innate immune system, whereas CTLs are T lymphocytes of the adaptive immune system.

- NK cells and CTLs are designed to eradicate either infected or altered cells that are potentially tumorigenic.

- T cells recognize fas expressing target ,

fas molecules are cross linked by fasL to activate **caspase 8**

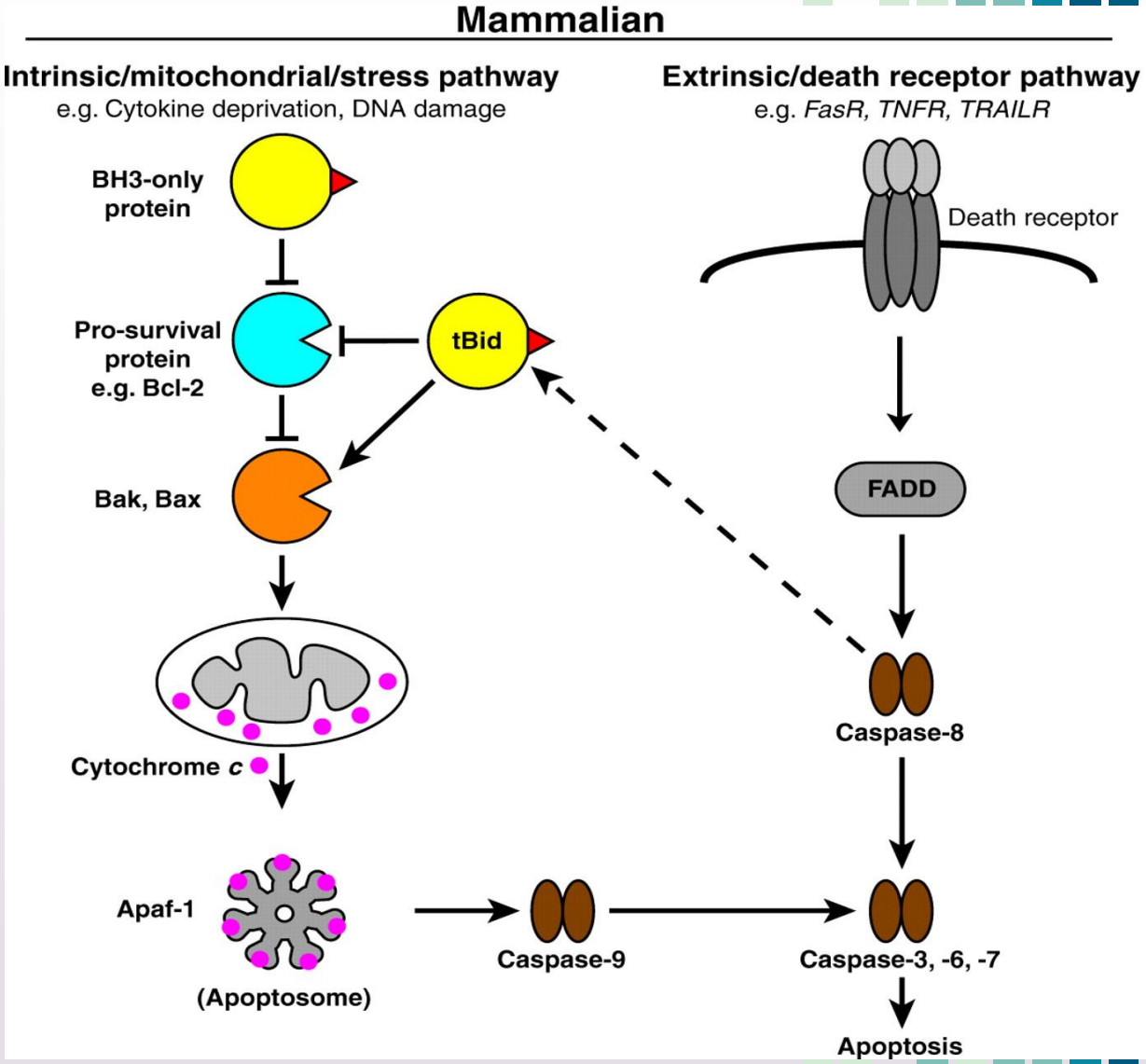


FasL-mediated apoptosis of target cells

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.

- Occur via phagocytes by producing a number of "eat-me" signals:
  - flip 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

	Necrosis *(uncontrolled cell death)*	Apoptosis *(programmed cell suicide)*
Size	Cellular swelling	Cellular shrinkage
	Many cells affected	One cell affected
Uptake	Cell contents ingested by macrophages	Cell contents ingested by neighbouring cells
	Significant inflammation	No inflammatory response
Membrane	Loss of membrane integrity	Membrane blebbing, but integrity maintained
	Cell lysis occurs	Apoptotic bodies form
Organelles	Organelle swelling and lysosomal leakage	Mitochondria release pro-apoptotic proteins
	Random degradation of DNA	Chromatin condensation and non-random DNA degradation

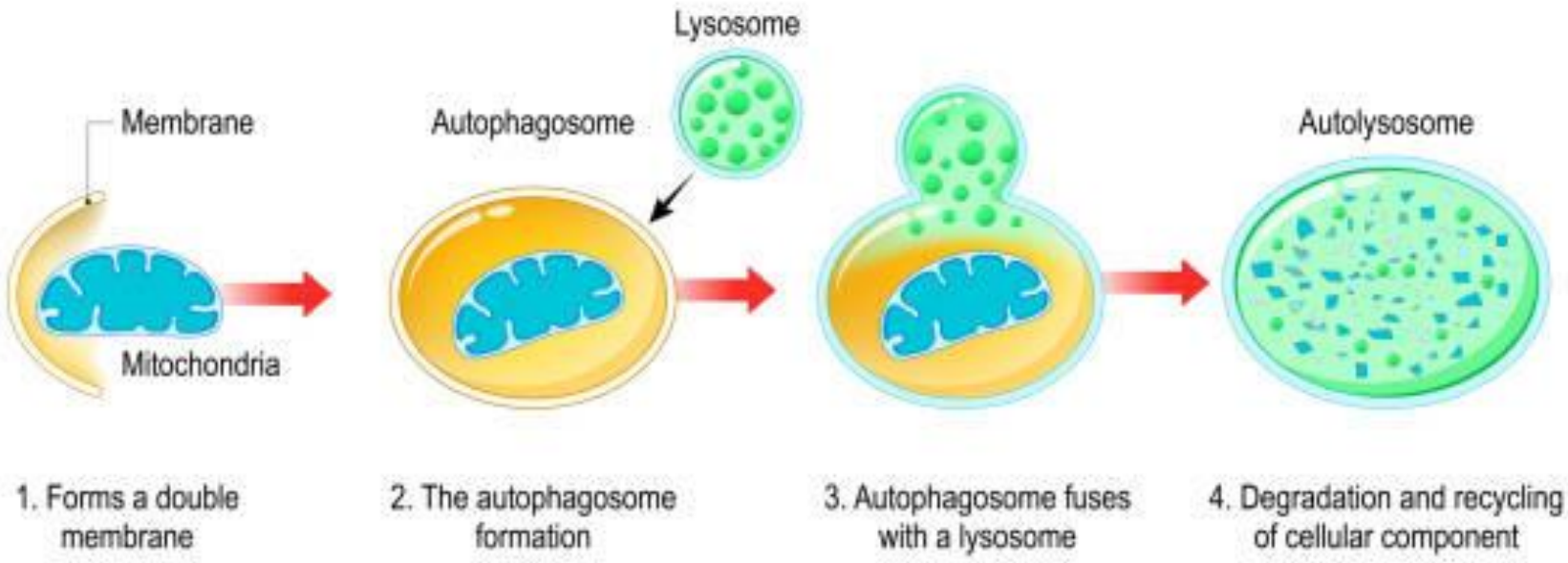
Other Pathways of Cell Death

Autophagy:

autophagy is a self-digesting mechanism responsible for removal of long-lived proteins, damaged organelles, and malformed proteins during biosynthesis by lysosome.

Autophagy is activated in response to diverse stress and physiological conditions. For example, food deprivation, hyperthermia, and hypoxia, which are known as major environmental modulators of ageing,

Autophagy


Lysosome
Membrane
Autophagosome
Autolysosome
Mitochondria
1. Forms a double membrane
2. The autophagosome formation
3. Autophagosome fuses with a lysosome
4. Degradation and recycling of cellular component

Clinical aspect

*** disorders of dysregulated apoptosis**

1. disorders due to too little apoptosis
   - cancer
   - autoimmune disorders
2. disorders due to too much apoptosis
   - neurodegenerative diseases