Lecture 10: Cell renewal and death

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School of Medicine
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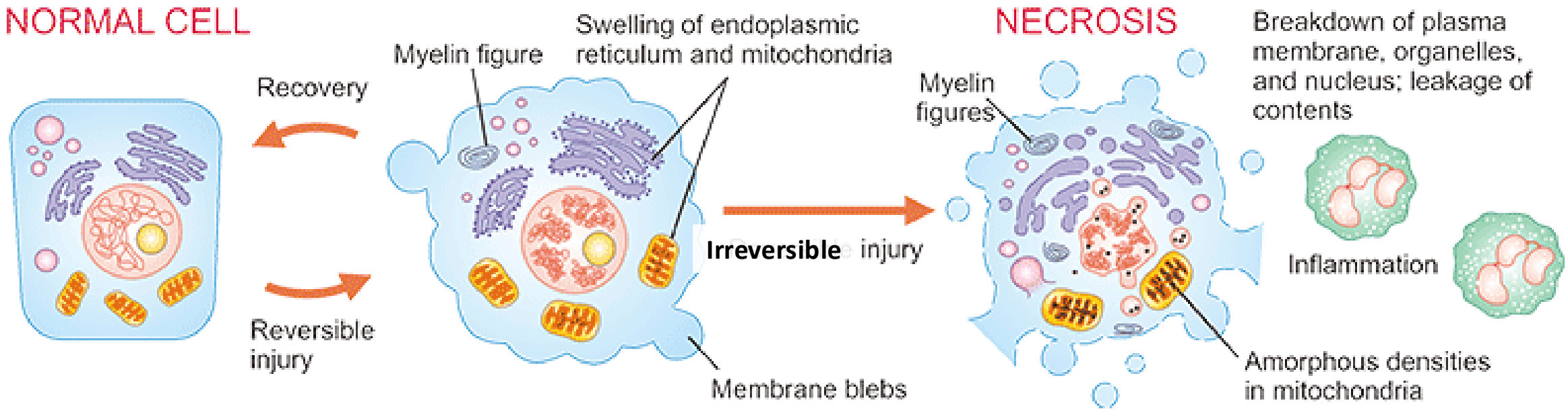
Programmed cell death

- Cell death occurs due to a harsh injury or by a programmed process called apoptosis, which can be a natural biological reason, due to a signal, or a result of a physical damage to the cell or DNA.
  - Renewal of >100 x 10^9 blood cells a day
  - Elimination of nerve cells with a faulty connection
  - Elimination of damaged cells with DNA damage or viral infection
- Programmed cell death is a normal physiological form of cell death with a distinct process known as apoptosis (“leaves falling down”).

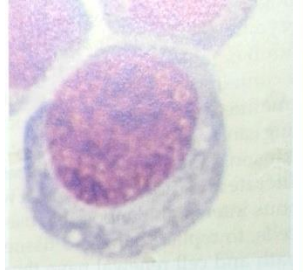
Necrosis

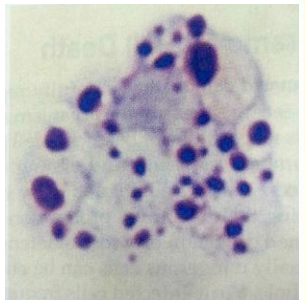
- The accidental death of cells that results from an acute (harsh) injury.
- Cell necrosis results in membrane damage, enlargement of cells, release of intracellular contents, and inflammation.

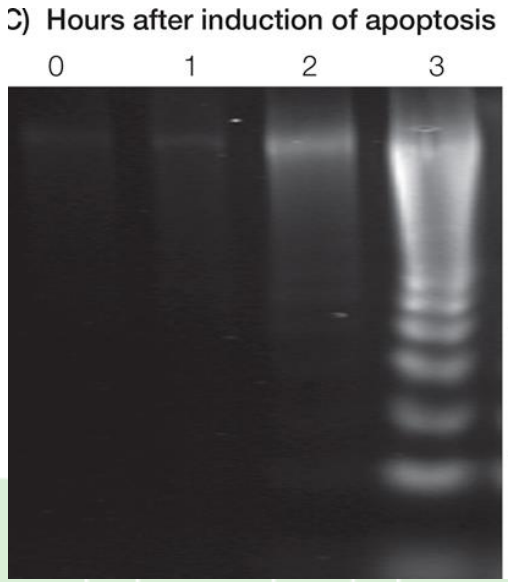


Apoptosis

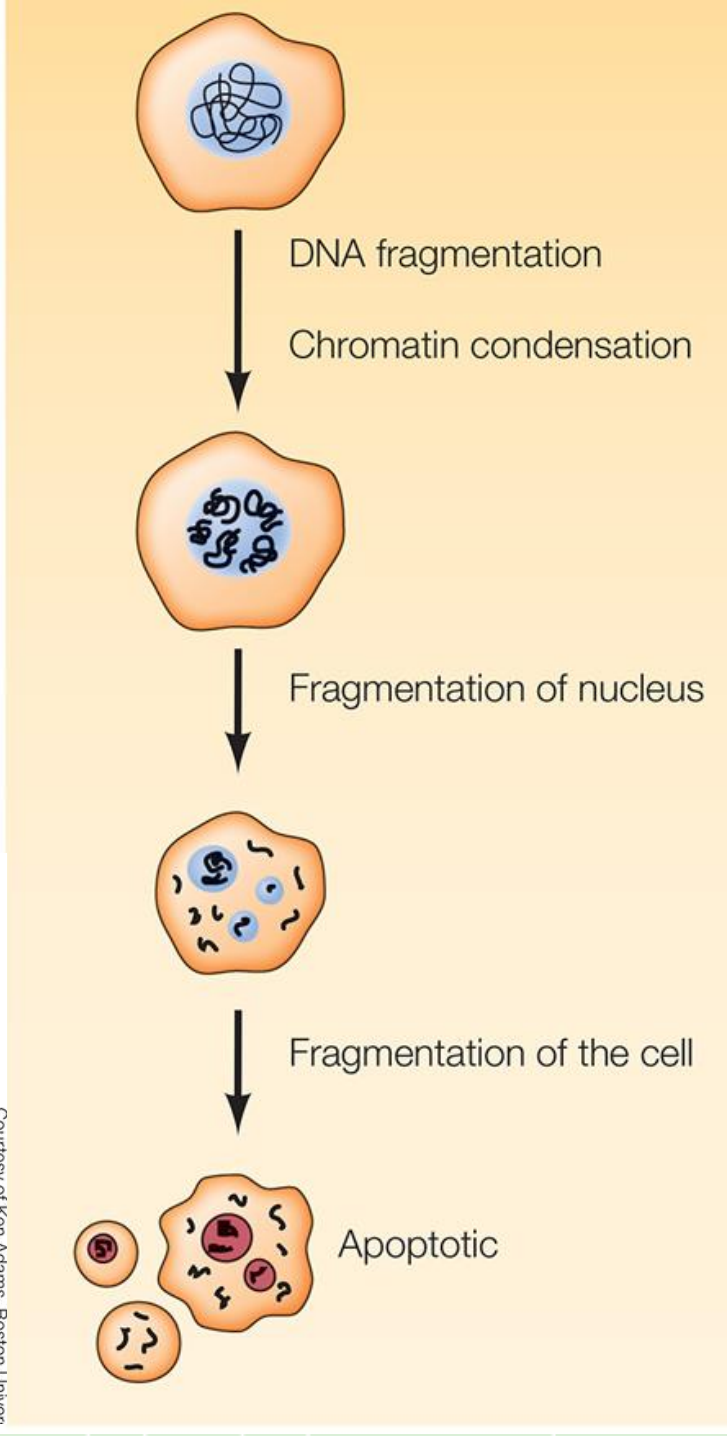
- Fragmentation of chromosomal DNA
- Chromatin condensation
- Nuclear fragmentation
- Cell shrinkage
- Cell fragmentation (apoptotic bodies)
- Phagocytosis by macrophages and neighboring cells (“eat me” signal)



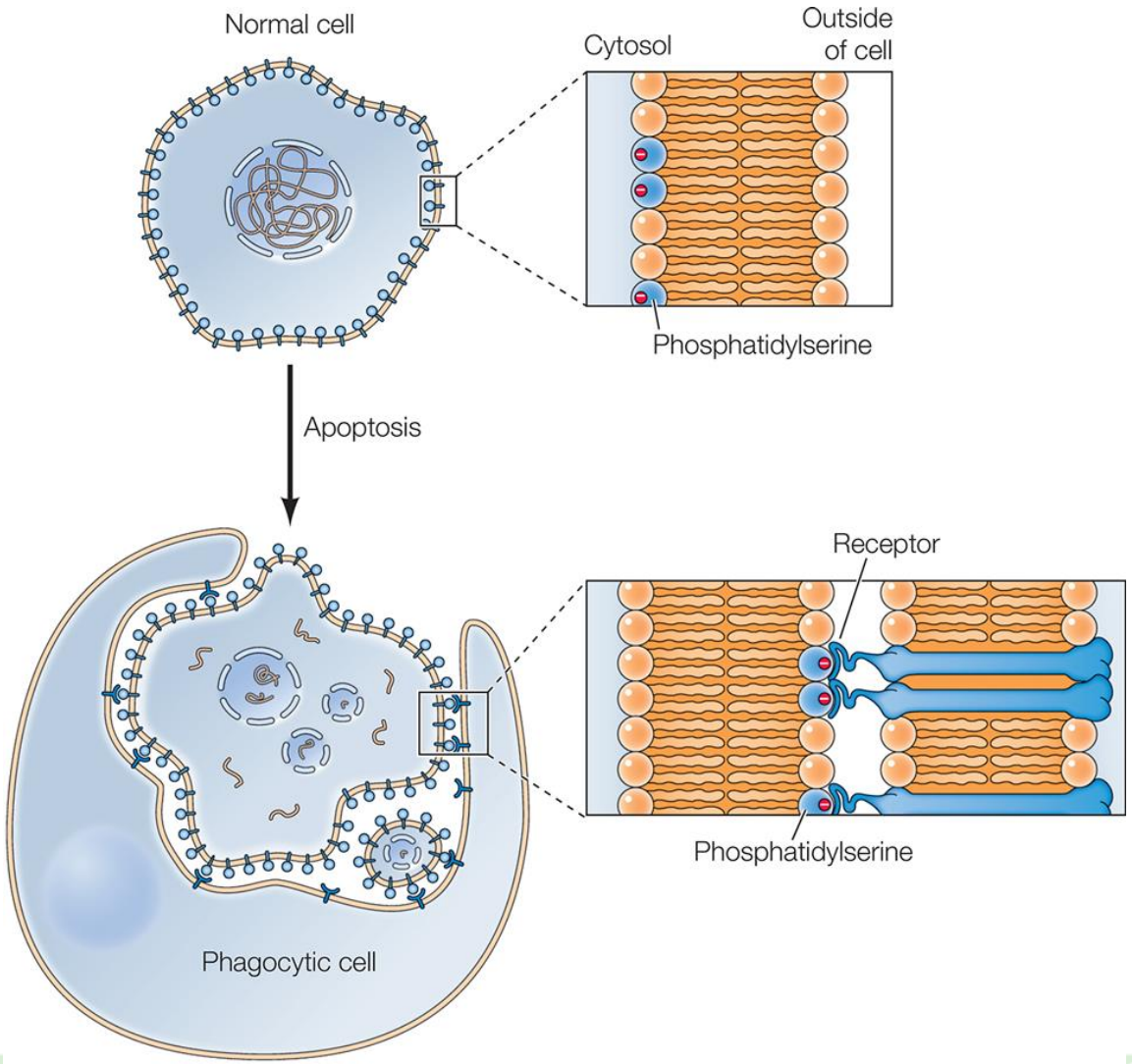




Courtesy of Ken Adams, Boston Univer



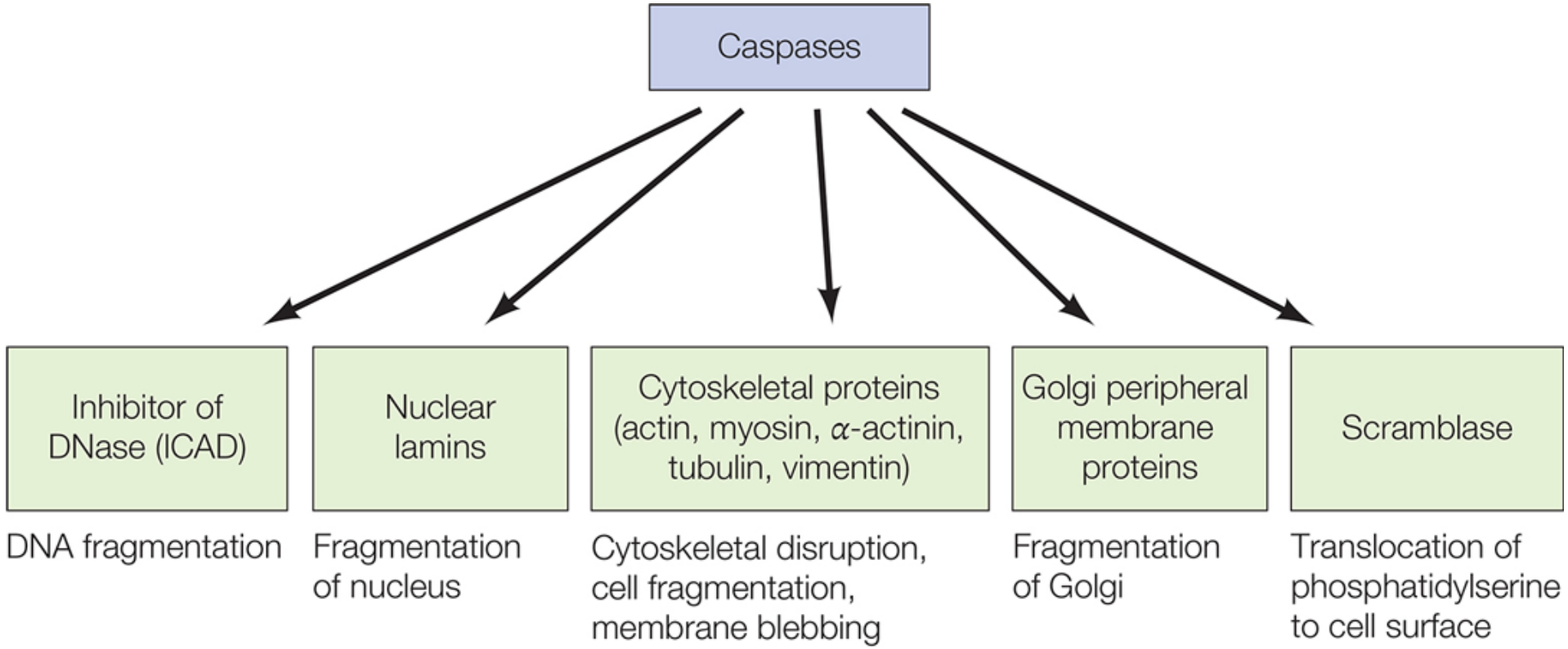
Role of phosphatidylserine



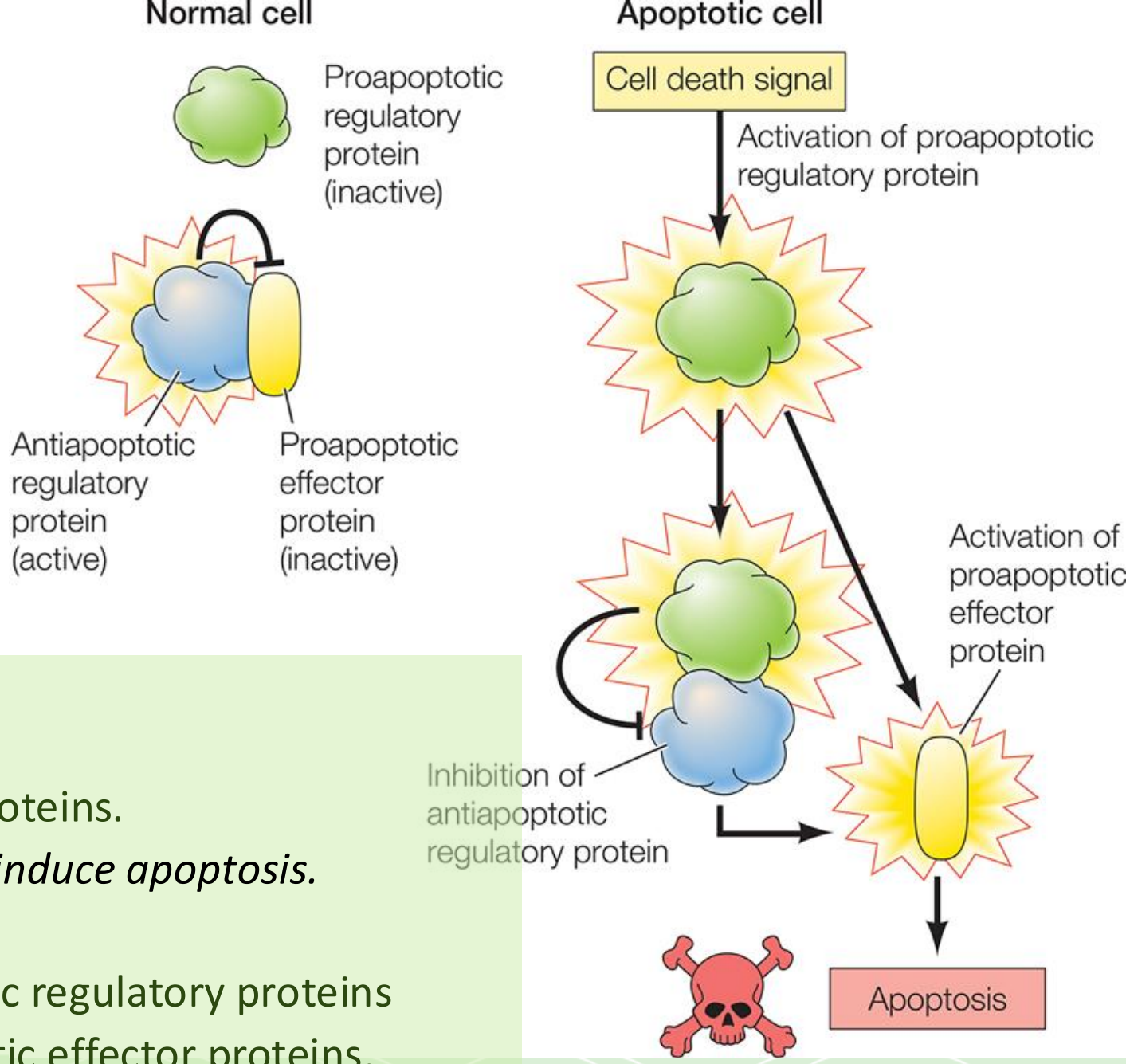
- Normally, PS is expressed on the inner leaflet of cells.
- During the initiation of apoptosis, PS is flipped to the outer leaflet.
- It is then recognized by receptor on the membrane surface of phagocytic cells.

Caspases: the culprits of apoptotic actions

- The caspases are the ultimate effectors or executioners of apoptosis cleaving more than 100 different target proteins (know specific examples).



The regulators

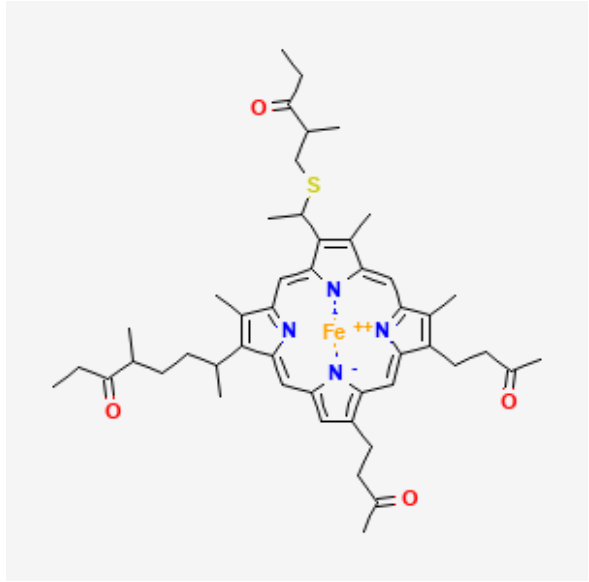


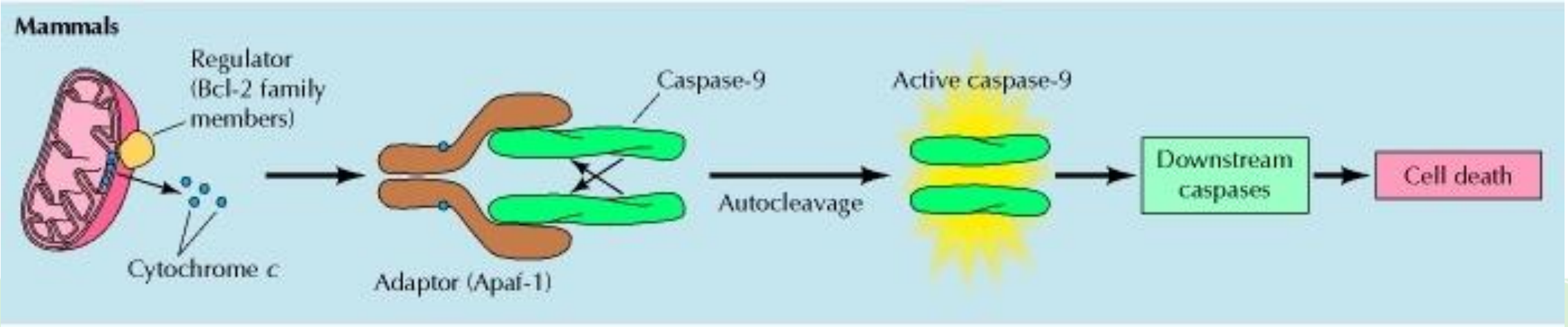
The Bcl-2 family

- The antiapoptotic regulatory proteins
  - They inhibit the proapoptotic effector proteins.
- The proapoptotic effector proteins *directly induce apoptosis.*
- The proapoptotic regulatory proteins
  - They bind to and inhibit the antiapoptotic regulatory proteins
  - They allow the release of the proapoptotic effector proteins.

The molecular activation of apoptosis

- Activation of the apoptotic pathway involves stimulation of the proapoptotic effector proteins that oligomerize to form pores in the mitochondrial outer membrane.
- The pores allow the release of cytochrome c from the intermembrane space.
- Cytosolic cytochrome c forms the **apoptosome complex** with caspase 9 and Apaf-1.
- Caspase 9 activates caspase 3 (a downstream effector).





Pathways of apoptosis

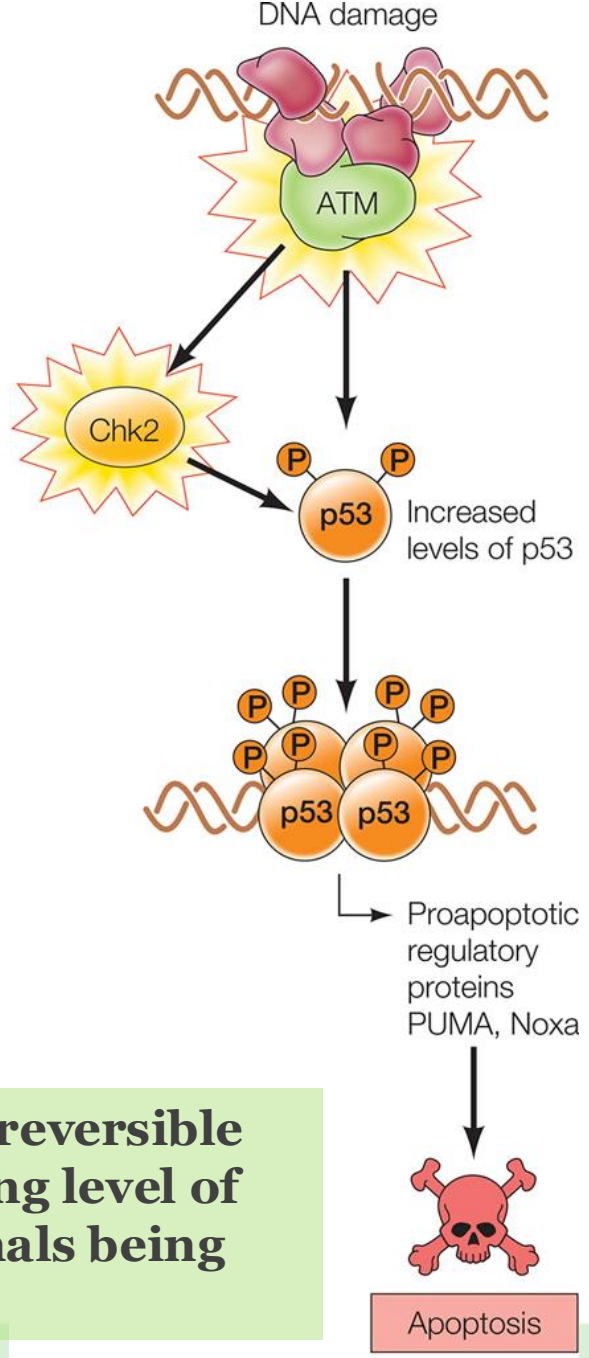
- **Intrinsic pathway** is simulated by DNA damage, viral infection, and cell stress such as growth factor deprivation.
- It involves the regulation of the proapoptotic regulatory members of the Bcl-2 family.

- **Extrinsic pathway** is stimulated by ligands or by receptors of other cells such as immune cells.

They differ in the involvement of Bcl-2 family proteins and in the identity of the caspase that initiates cell death

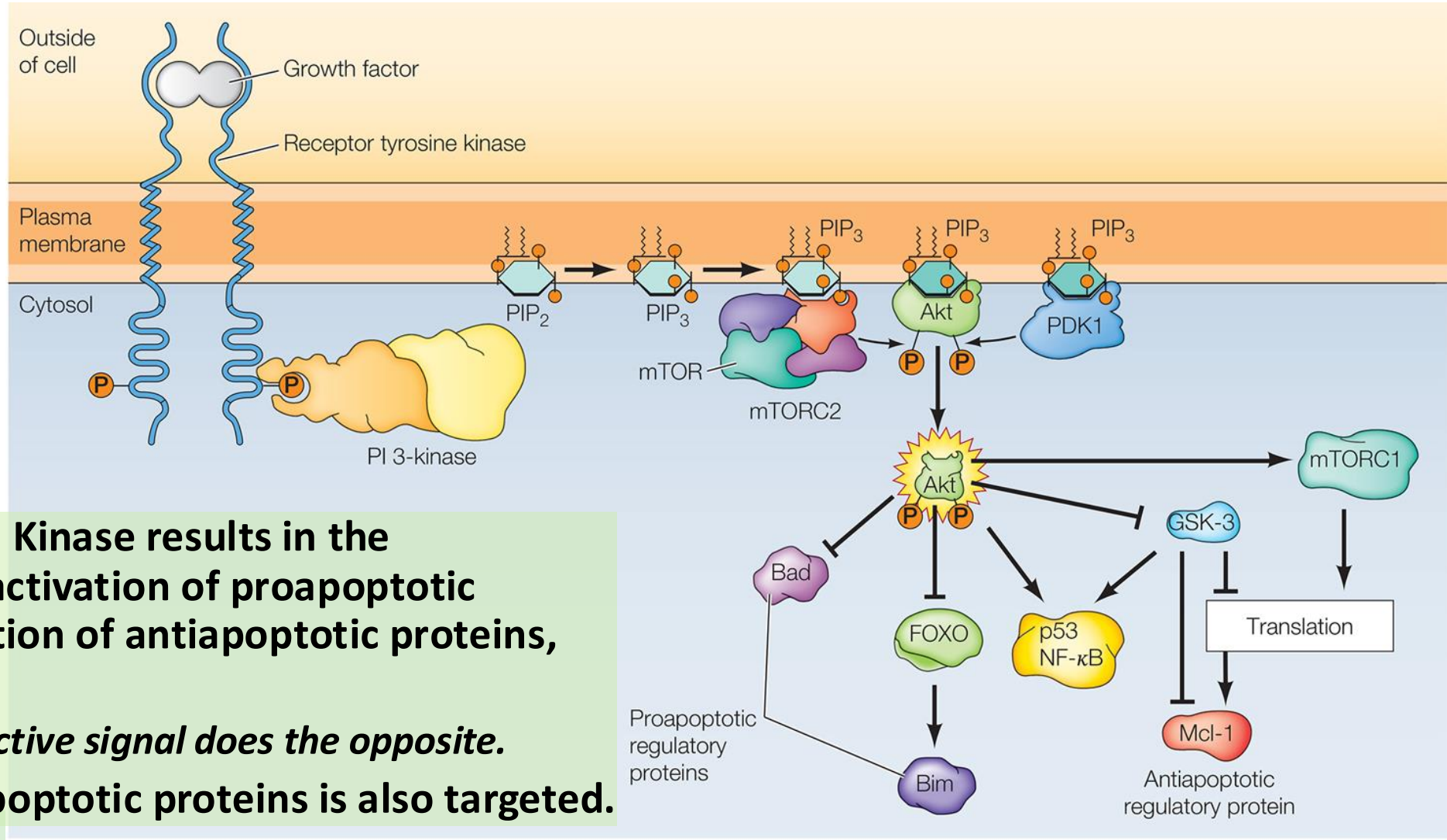
Intrinsic pathway
DNA damage

- DNA damage leads to activation of the ATM and Chk2 protein kinases, which lead to the phosphorylation, stabilization, and increased levels of p53.
- p53 then activates the transcription of genes encoding:
  - (1) proapoptotic regulatory proteins that drive cell death by releasing cytochrome c
  - 2) p21, which inhibits Cdk2/cyclin E complexes.



Note: Whether DNA damage in a given cell leads to apoptosis or reversible cell cycle arrest depends on the extent of damage and the resulting level of p53 induction, as well as on the influence of other life/death signals being received by the cell.

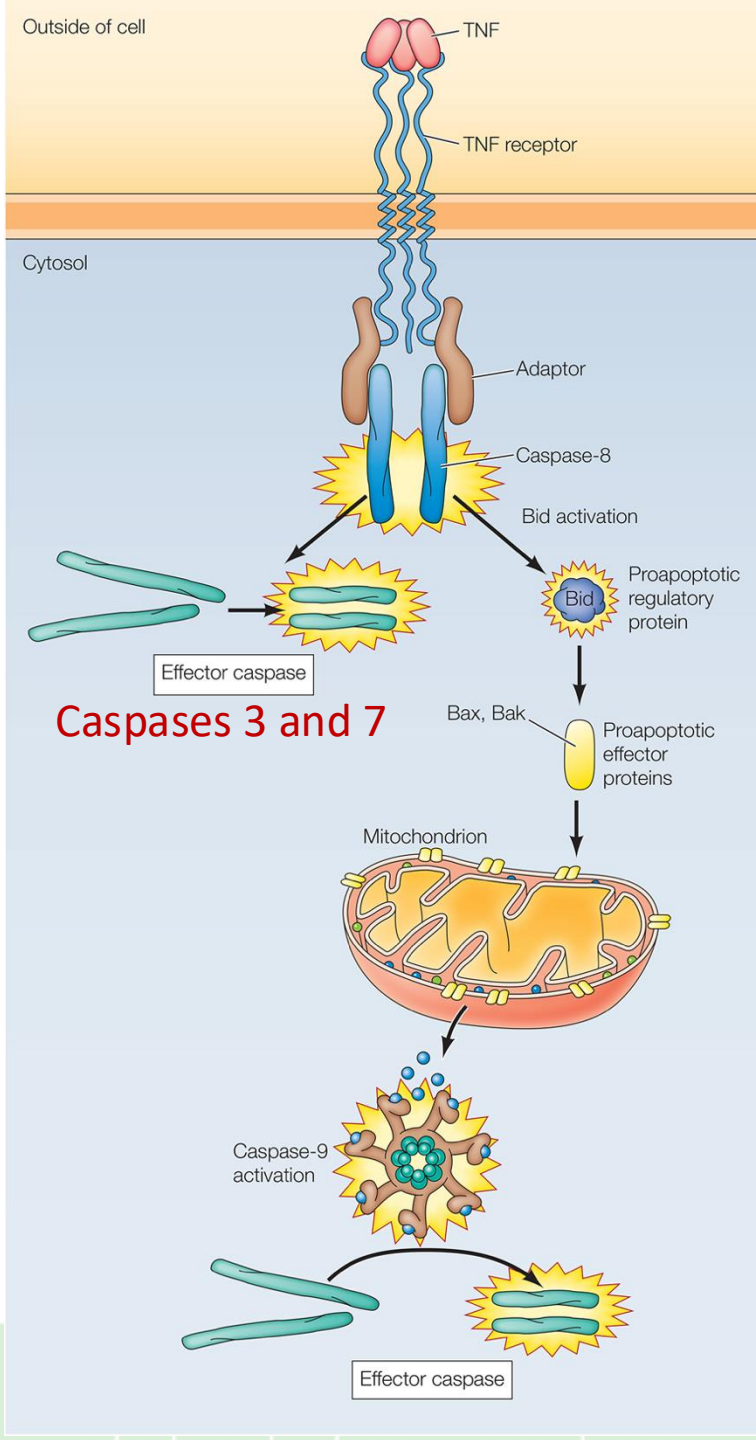
Intrinsic pathway
Growth factors



- **Activation of Akt by PI-3 Kinase results in the phosphorylation and inactivation of proapoptotic proteins, and the activation of antiapoptotic proteins, inducing cell survival.**
  - ***The absence of an active signal does the opposite.***
- **The expression of antiapoptotic proteins is also targeted.**

Extrinsic pathway
The tumor necrosis factor (TNF) signaling

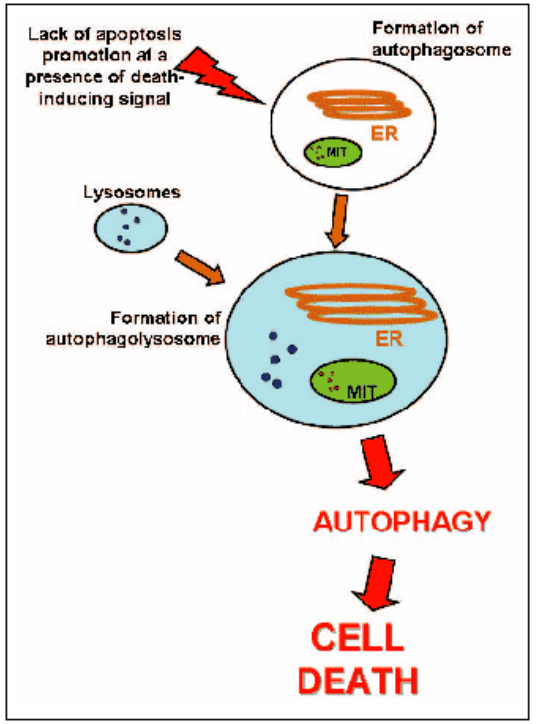
- TNF binds to TNF receptors such as Fas, inducing apoptosis in a variety of cell types, like:
  - Apoptosis induced by activation of Fas is responsible for killing target cells of the immune system, such as cancer cells or virus-infected cells.
- Receptor activation leads to the activation of caspase 8 (an initiator protein), which either activates:
  - Proapoptotic effector molecules (caspases 3 and 7)
  - Proapoptotic proteins that, ultimately, activate caspase 9 (for signal amplification purposes).

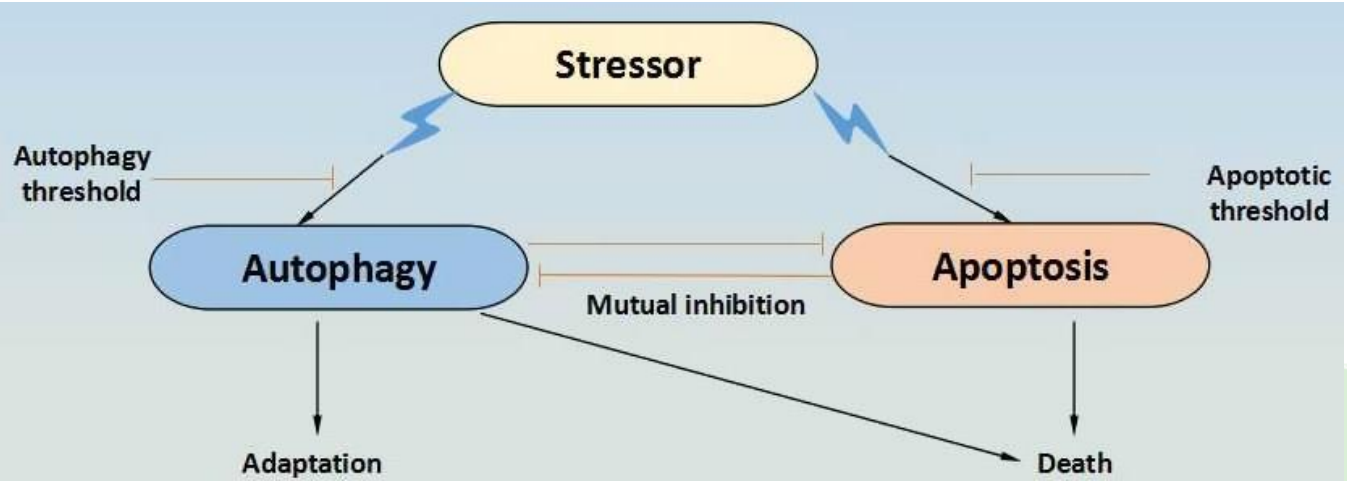


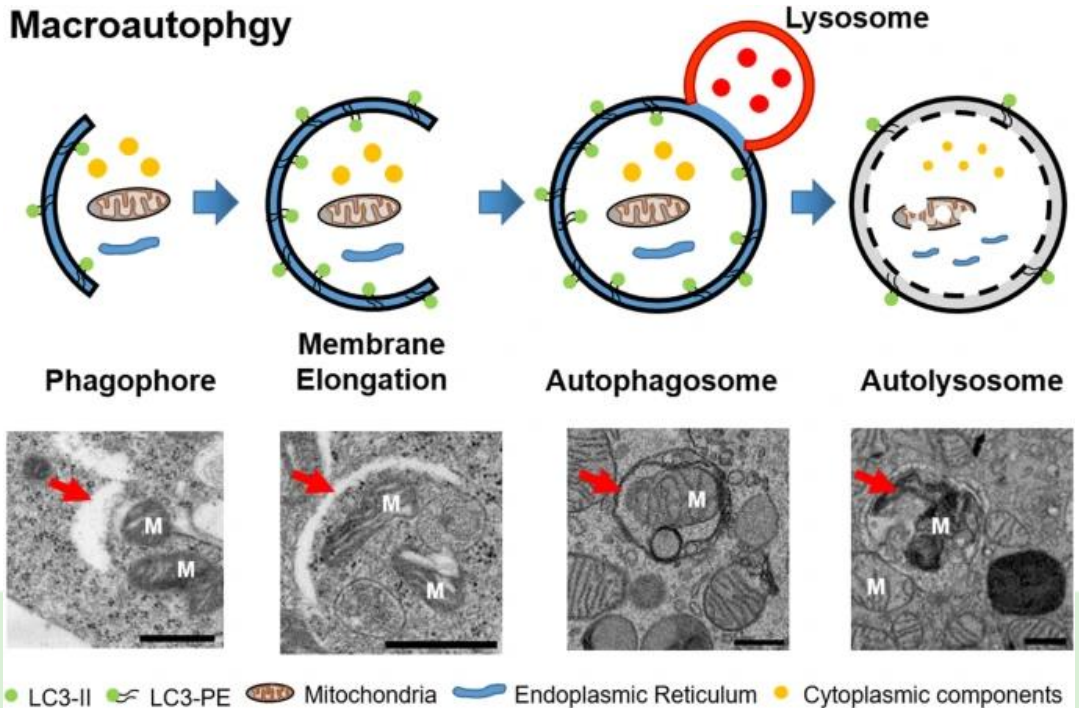
Autophagy (cell self-eating)

An alternative mechanism of apoptosis

- Autophagy is caspase-independent and is mediated by mTOR signaling.
- The dying cell has accumulating lysosomes.
- Autophagy and apoptosis inhibit each other.

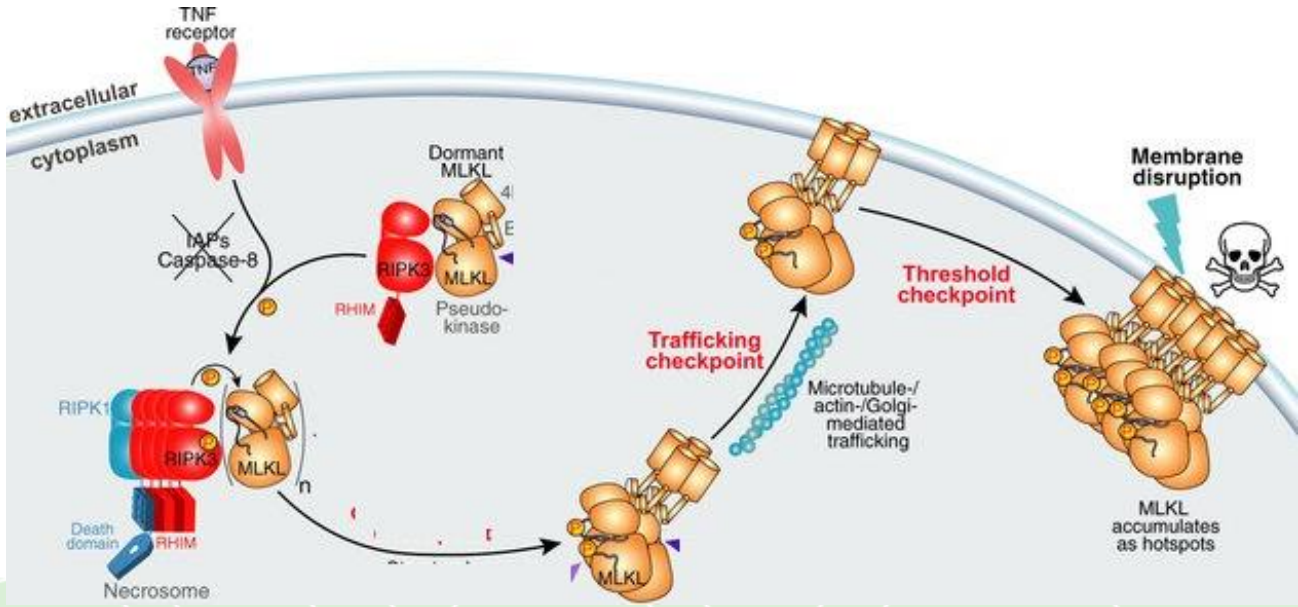






Necroptosis

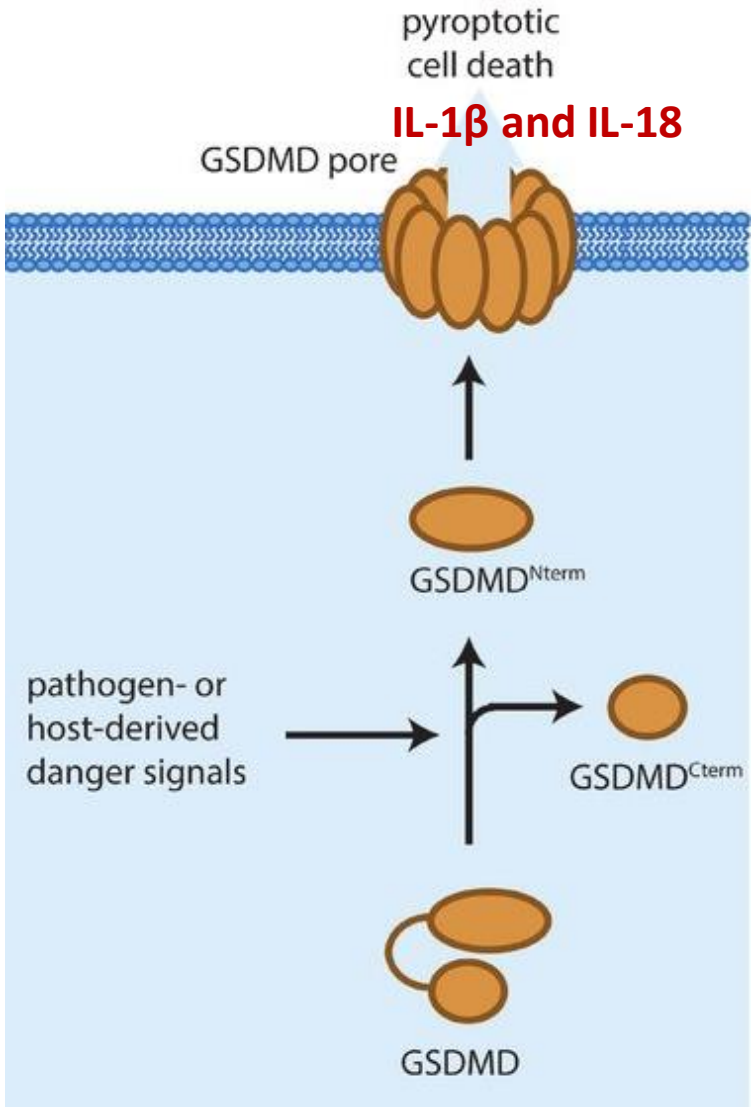
- Necroptosis (like necrosis, but not necrosis) results in the extracellular release of intracellular substances triggering an immune response.
- Unlike necrosis, necroptosis is:
  - triggered by specific stimuli such as bacterial infection, DNA damage, or TNF signaling
  - executed by a specific molecular mechanism
- The protein MLKL assembles into an oligomeric pore in the plasma membrane allowing for a rapid flux of ions into and out of the cell, causing cell swelling and rupture.
- The immune response facilitates the attack.



Pyroptosis

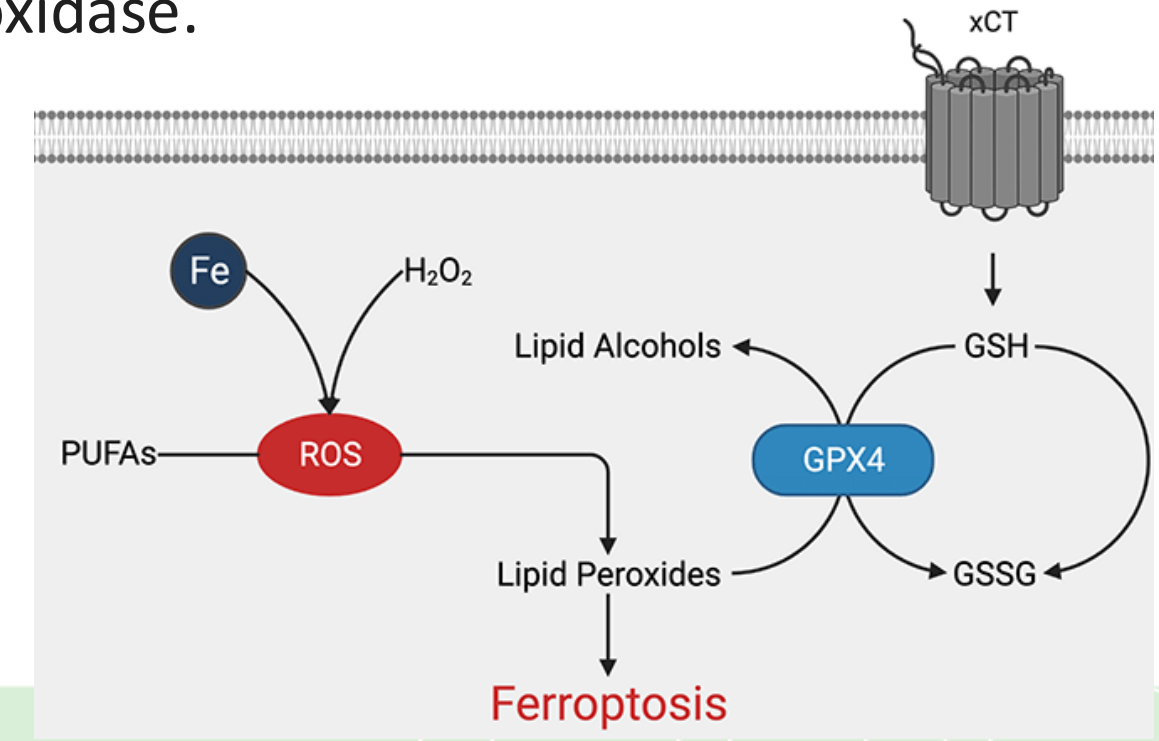
pyro (fire/fever) and ptosis (to-sis, falling)

- Pyroptosis is a form of cell death that is triggered by proinflammatory signals and associated with inflammation.
- It is seen primarily in inflammatory cells such as macrophages.
- It is induced by specific stimuli such as microbial infection, executed by specific pyroptotic machinery, and involves activation and oligomerization of a protein—**gasdermin**—into a pore complex at the plasma membrane.
- A feature of pyroptosis is the activation and release of pro-inflammatory cytokines IL-1β and IL-18 through the gasdermin pore, which triggers an active immune response.

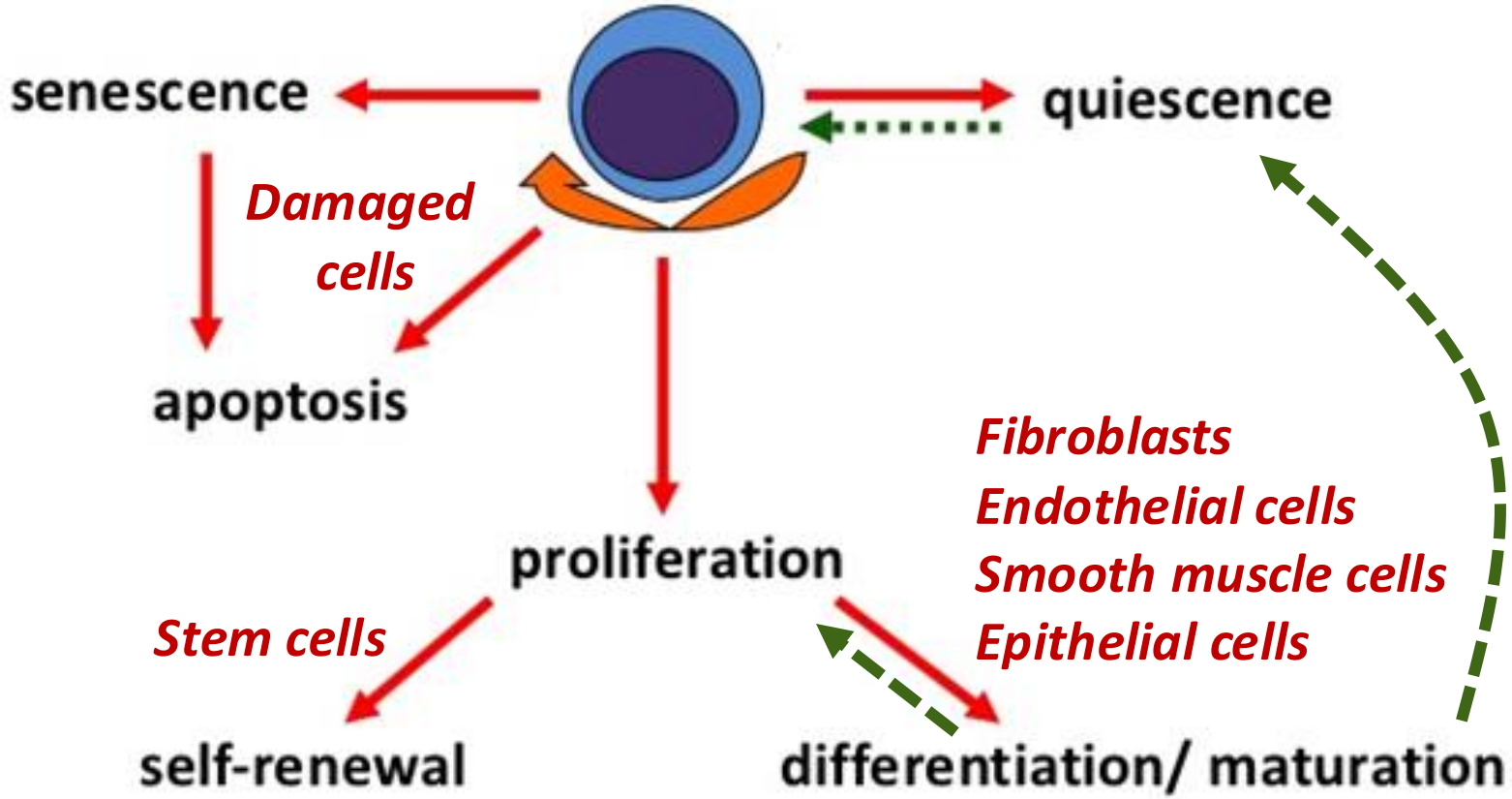


Ferroptosis

- Ferroptosis is an iron-dependent and oxidative damage-induced cell death that results from iron accumulation and lipid peroxidation, and loss of selective permeability of the plasma membrane.
- It involves depletion in the protective antioxidant enzymes, particularly glutathione peroxidase.



Cell fate


senescence
quiescence
Damaged cells
apoptosis
proliferation
Fibroblasts
Endothelial cells
Smooth muscle cells
Epithelial cells
Stem cells
self-renewal
differentiation/ maturation