

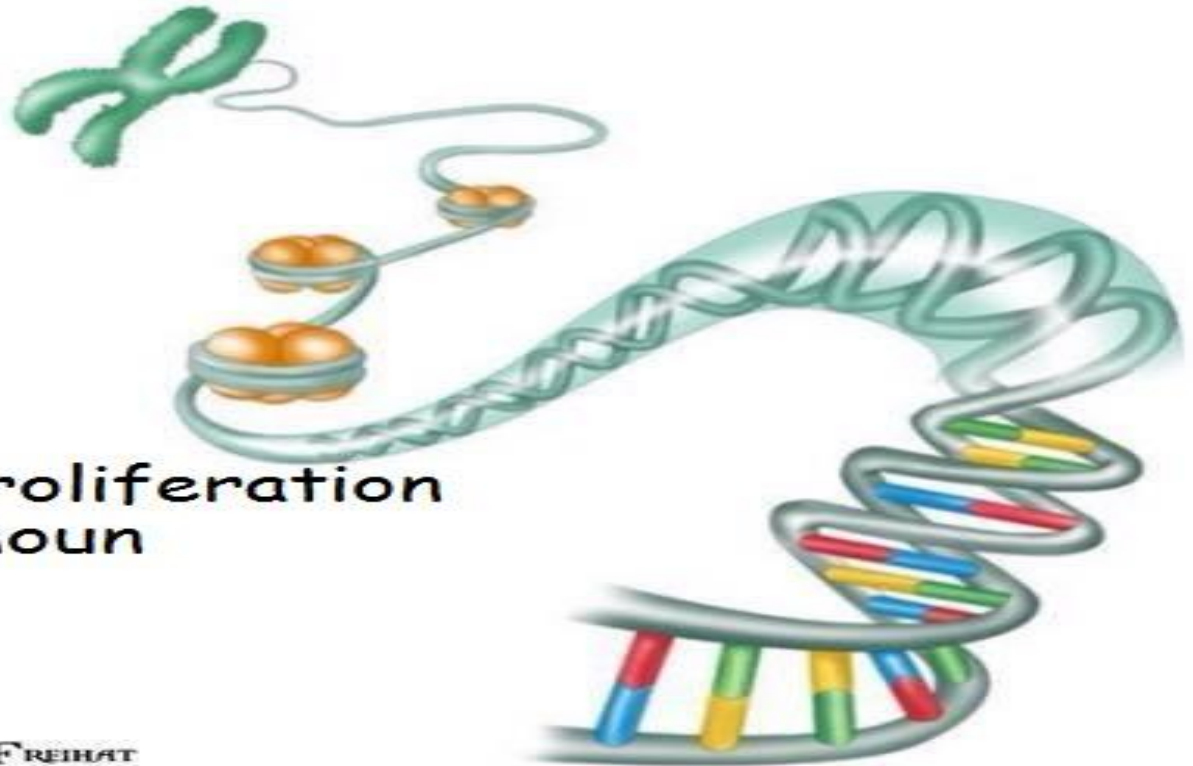


UNIVERSITY OF JORDAN
FACULTY OF MEDICINE
BATCH 2013-2019



GENETICS & MOLECULAR BIOLOGY

☒ Slides ☐ Sheet ☐ Handout ☐ other.....



Number #11

Title: Cell proliferation

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Done By:

Date:

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DESIGNED BY NADEEN AL-FREIHAT



Lecture 11: Cell proliferation, differentiation, and death

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Second year, Second semester, 2014-2014

Principles of Genetics and Molecular Biology

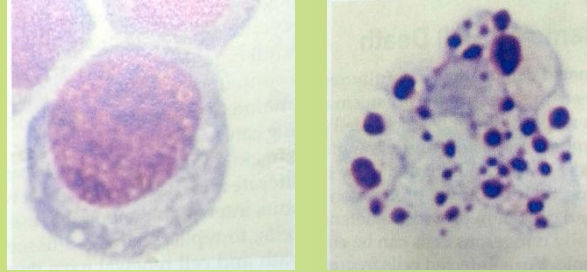
Programmed cell death



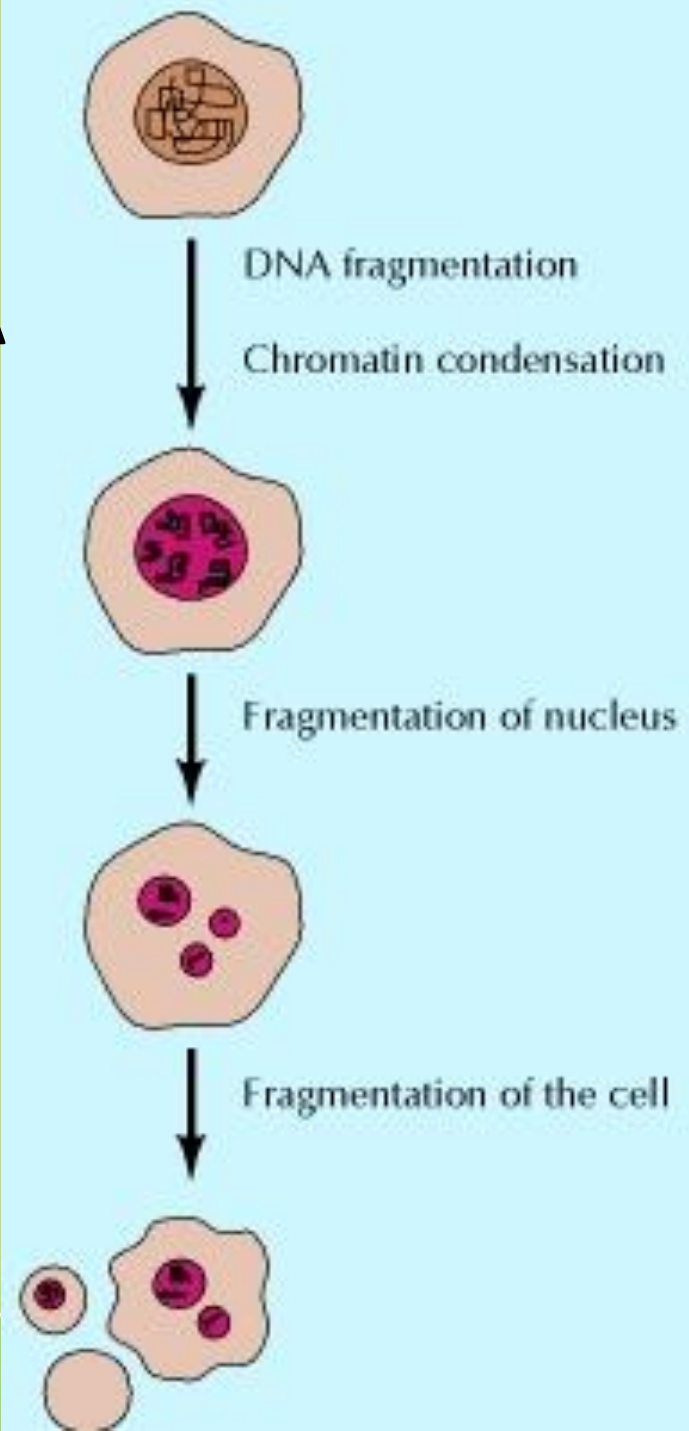
- It is a normal physiological form of cell death with a distinct process known as **apoptosis**.
- It plays a key role both in the maintenance of adult tissues and in embryonic development.
 - Renewal of 5×10^{11} blood cells a day
 - elimination of nerve cells with faulty connection
 - Elimination of damaged and potentially dangerous cells
 - Cells with DNA damage
 - Virus-infected cells

Intrinsic pathway: simulated by DNA damage
Extrinsic pathway: stimulated by signals from other cells

Apoptosis



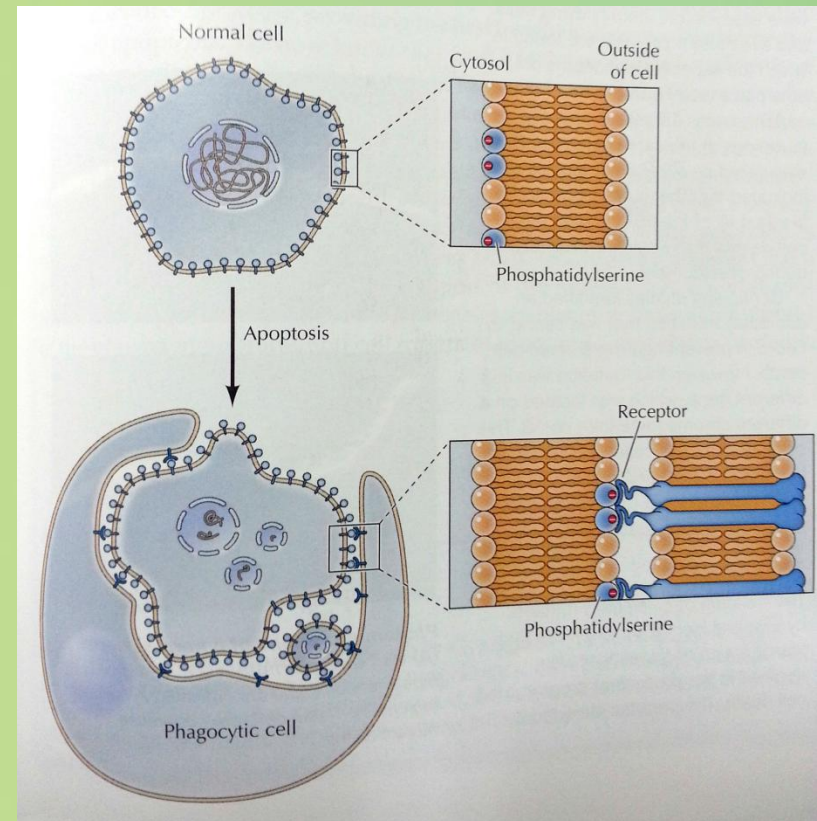
- Fragmentation of chromosomal DNA
- Chromatin condensation
- Breaking up nucleus into small pieces.
- Cell shrinkage
- Cell fragmentation (**apoptotic bodies**)
- Phagocytosis by macrophages and neighboring cells
- In contrast, cell necrosis results in membrane damage, enlargement of cells, release of intracellular contents, and causing inflammation.



Role of phosphatidylserine



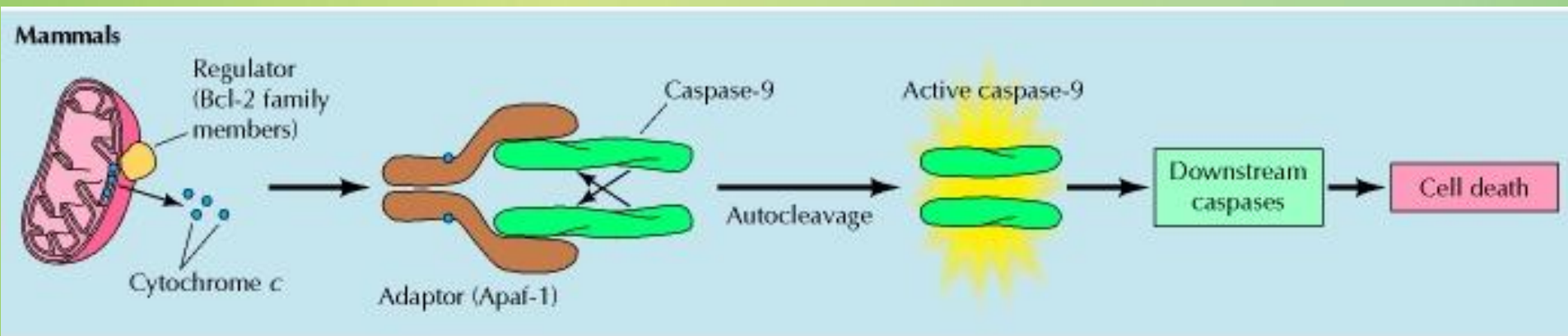
- Normally, PS is expressed on the inner leaflet of cells.
- During the initiation of apoptosis, PS is flipped to the outer leaflet.
- It is then recognized by phagocytic cells.



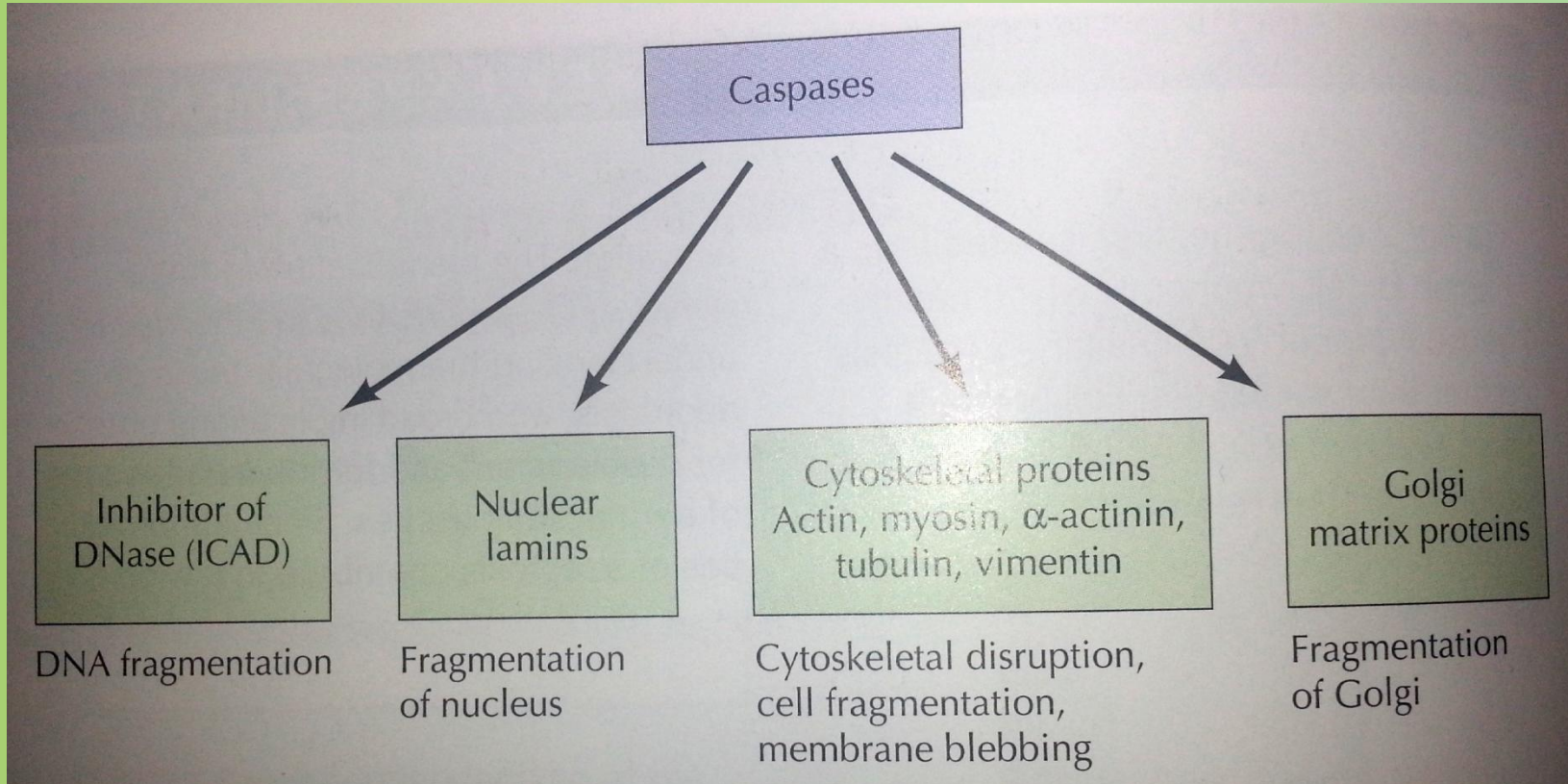
The molecular activation of apoptosis



- Release of cytochrome *c* from mitochondria thus signals the activation of caspase-9, which then activates downstream caspases to induce apoptosis.
- Regulators of the Bcl-2 family act at the mitochondria to control release of cytochrome *c*, which is required for the binding of caspase-9 to the adaptor Apaf-1



What do caspases do?



Bcl-2 family



- There are three classes of Bcl-2 according to their domains and apoptotic effect:
 - Anti-apoptotic proteins contain four specific domains
 - Proapoptotic proteins:
 - Multi-domain
 - BH3-only domain



Anti-apoptotic
Bcl-2 proteins



Multi-domain
pro-apoptotic
effectors

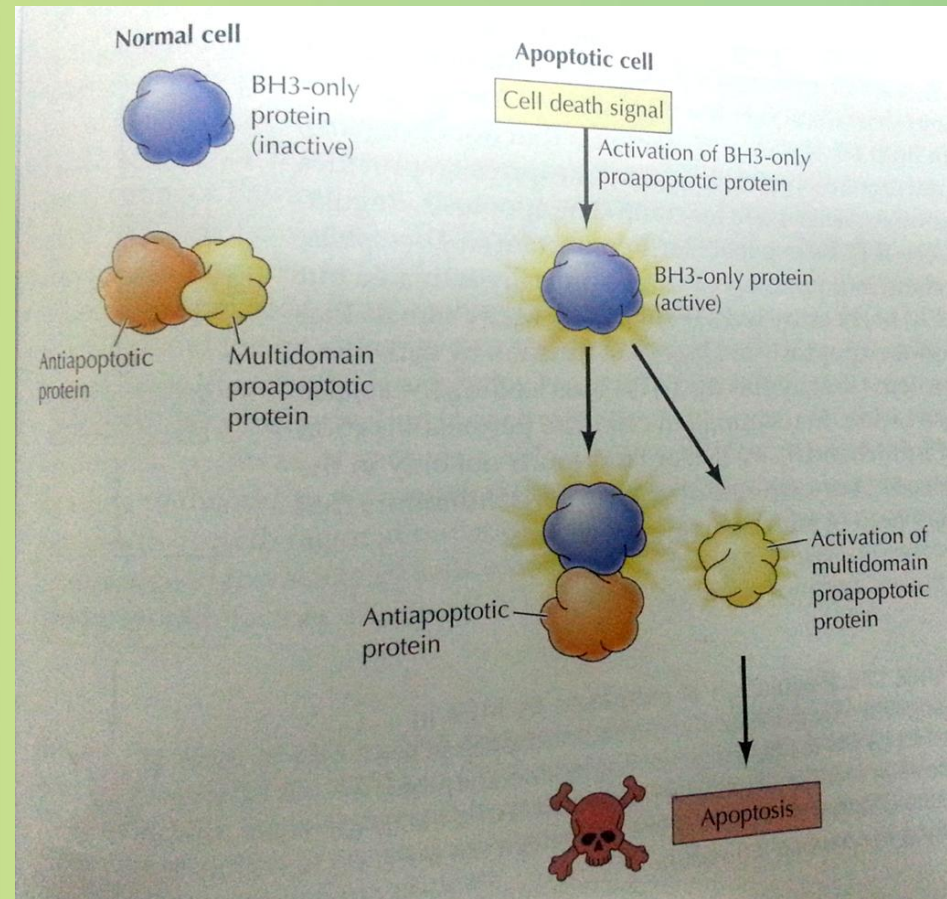


Pro-apoptotic
BH3-only

How is apoptosis activated upstream?



- Normally, BH3-only protein is inactive and the multi-domain proapoptotic protein is inactivated by the anti-apoptotic protein.
- Death signals inactivate the anti-apoptotic protein and release the multi-domain proapoptotic protein.



How is cytochrome c released from mitochondria?

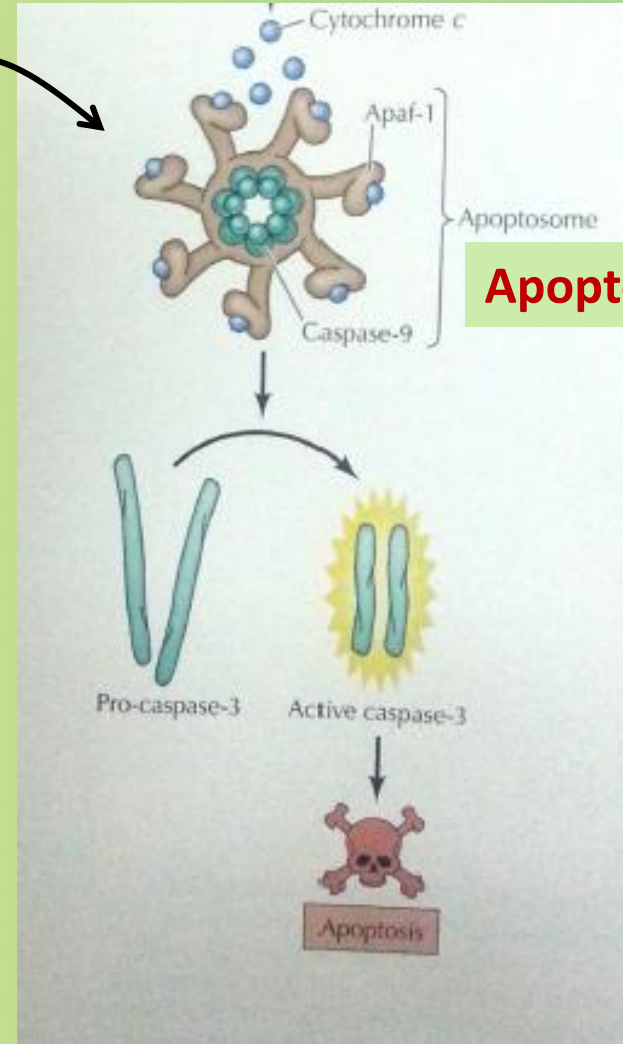
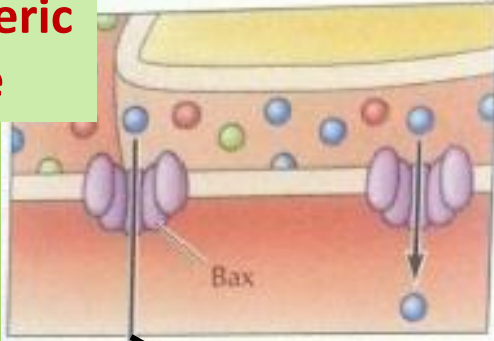
Proapoptotic multidomain

Death signal

Bax



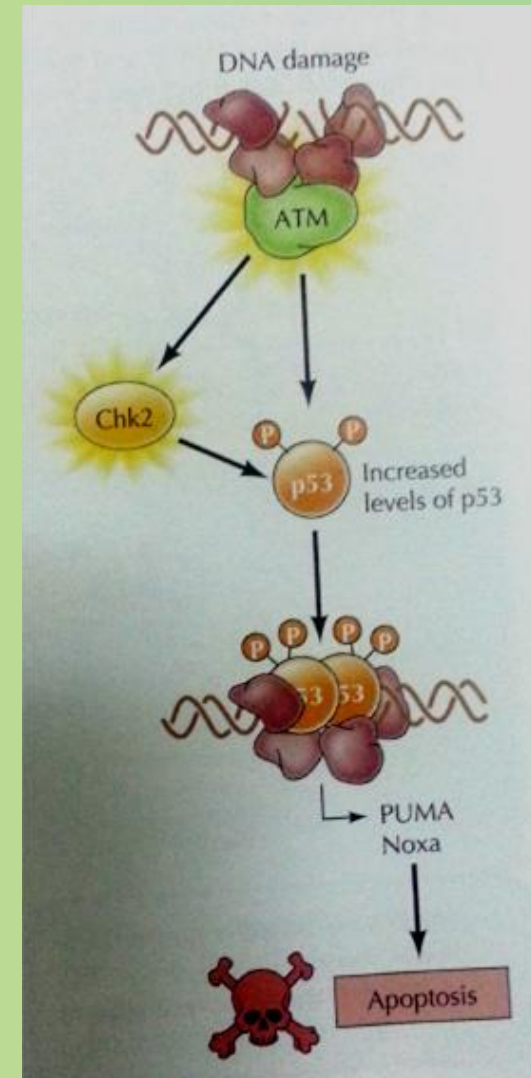
Oligomeric pore



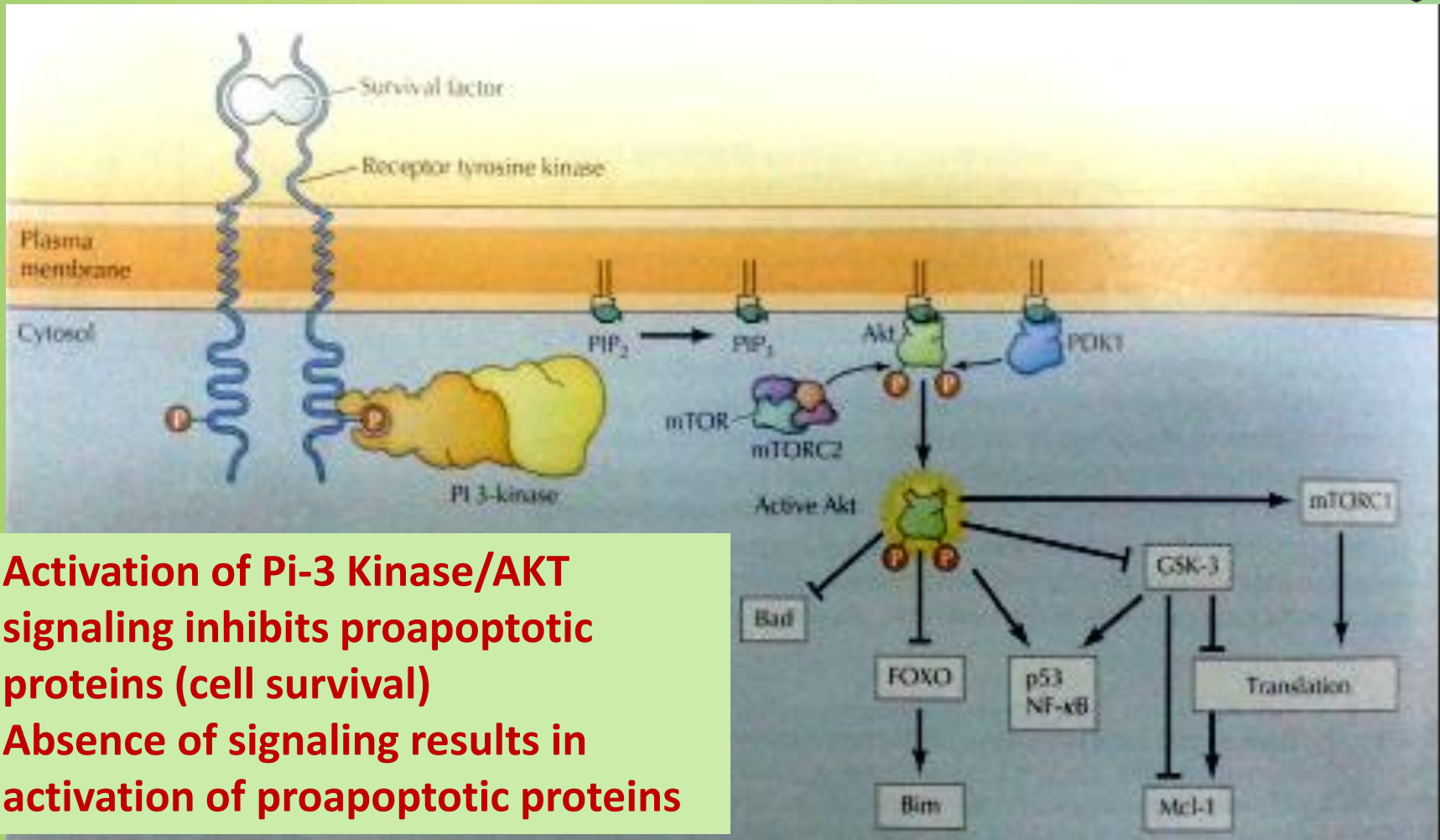
Apoptosome

Internal pathway

- Stimulation of p53 phosphorylation by ATM/Chk2 signaling results in induced expression of BH3-only proteins.

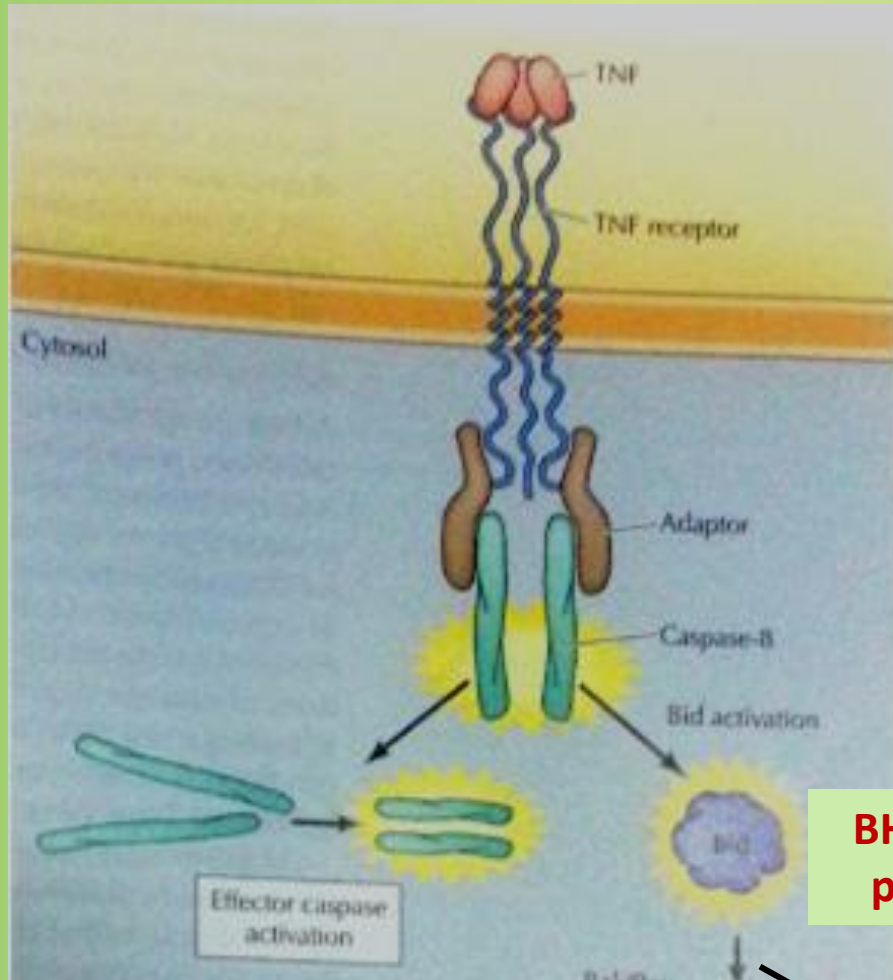


External signaling (1): pro-survival

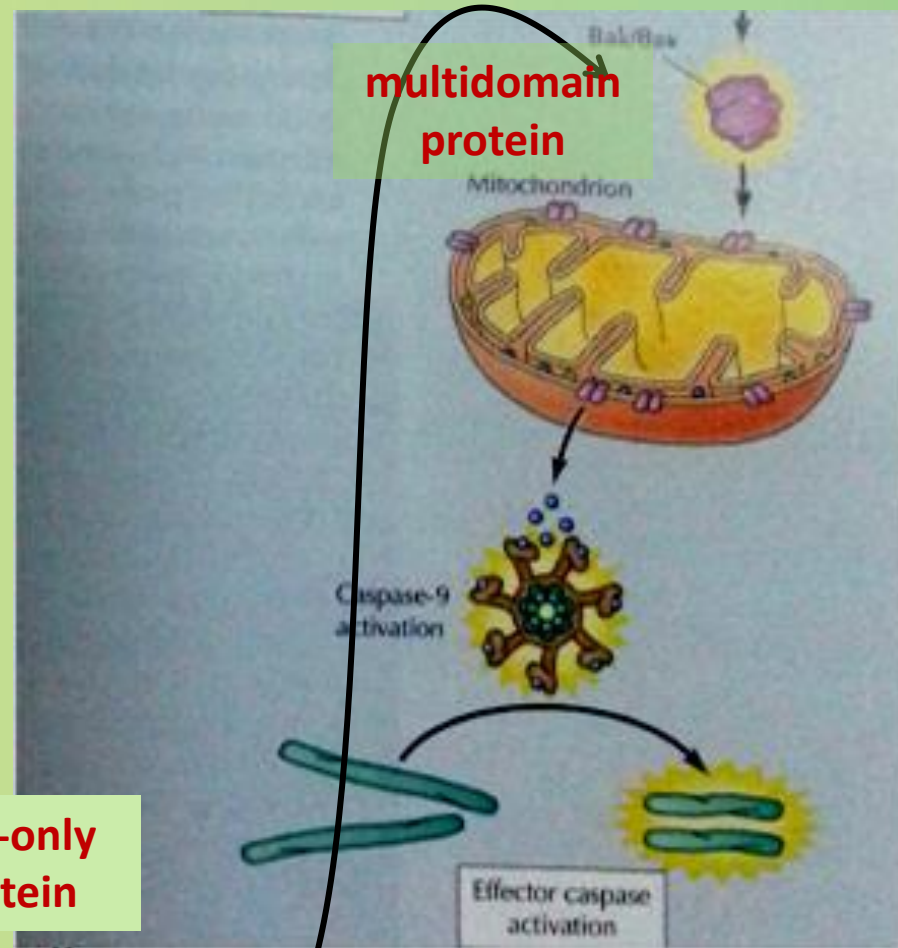


- Activation of Pi-3 Kinase/AKT signaling inhibits proapoptotic proteins (cell survival)
- Absence of signaling results in activation of proapoptotic proteins

External signaling (2): pro-death



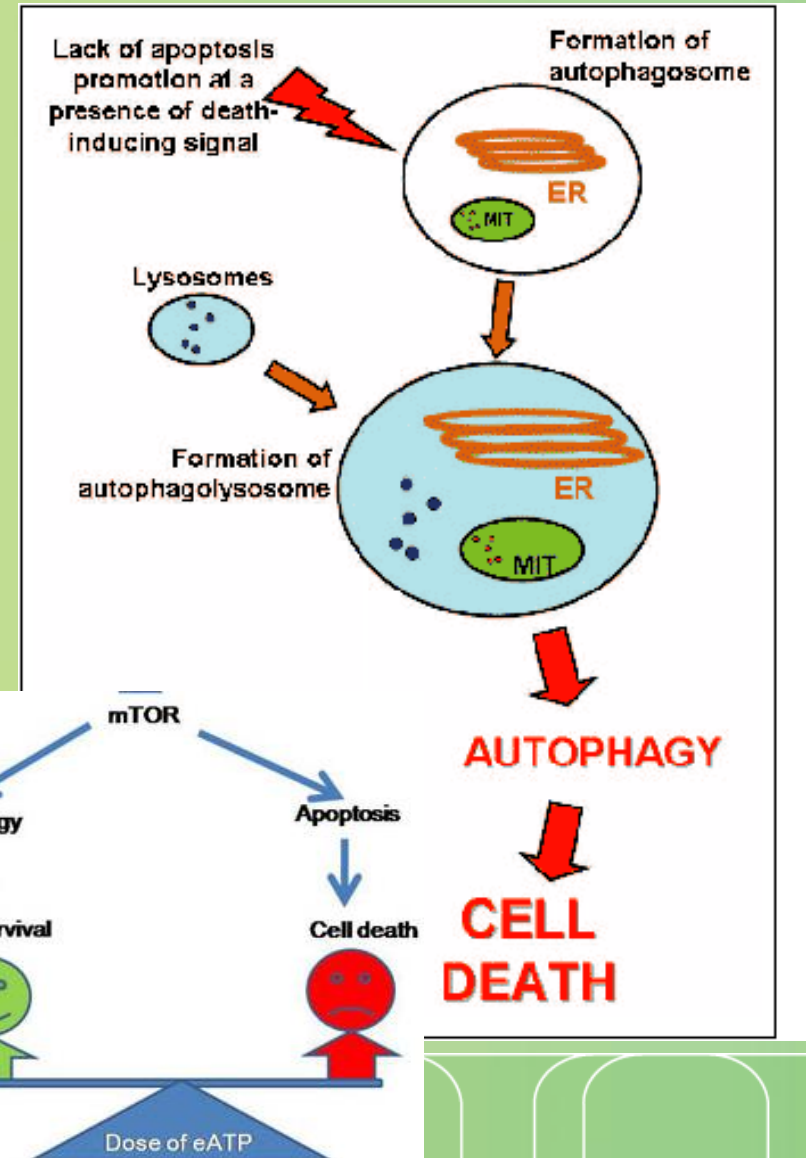
BH3-only protein



multidomain protein

Autophagy

- Apoptosis can be caspase-independent, but mediated by autophagy through mTOR signaling.
- The dying cell does not go through the same morphological features, but accumulate lysosomes.
- Advantages:
 - When cells lack molecular machinery of apoptosis
 - It provides cells with an opportunity to repair the damage prior to death



Cell fate

