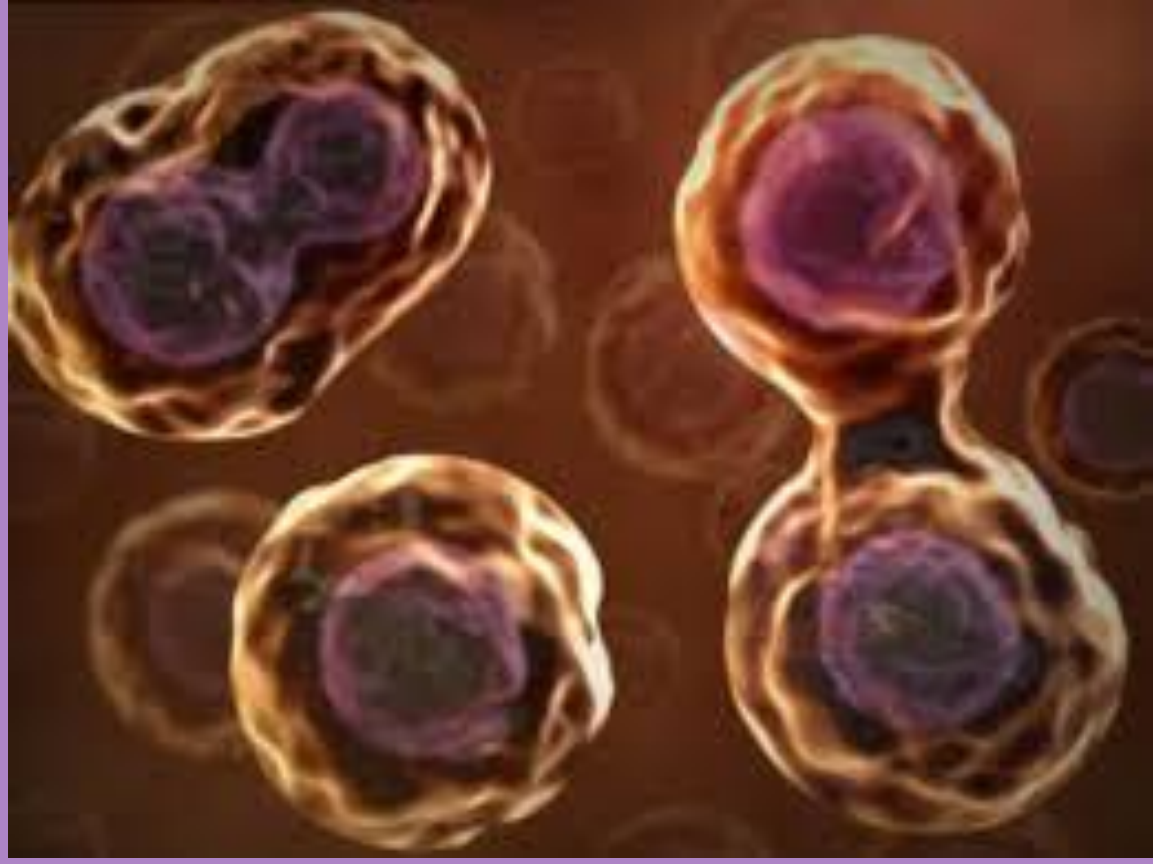
Lecture 11:

Cell cycle, proliferation, differentiation, and death



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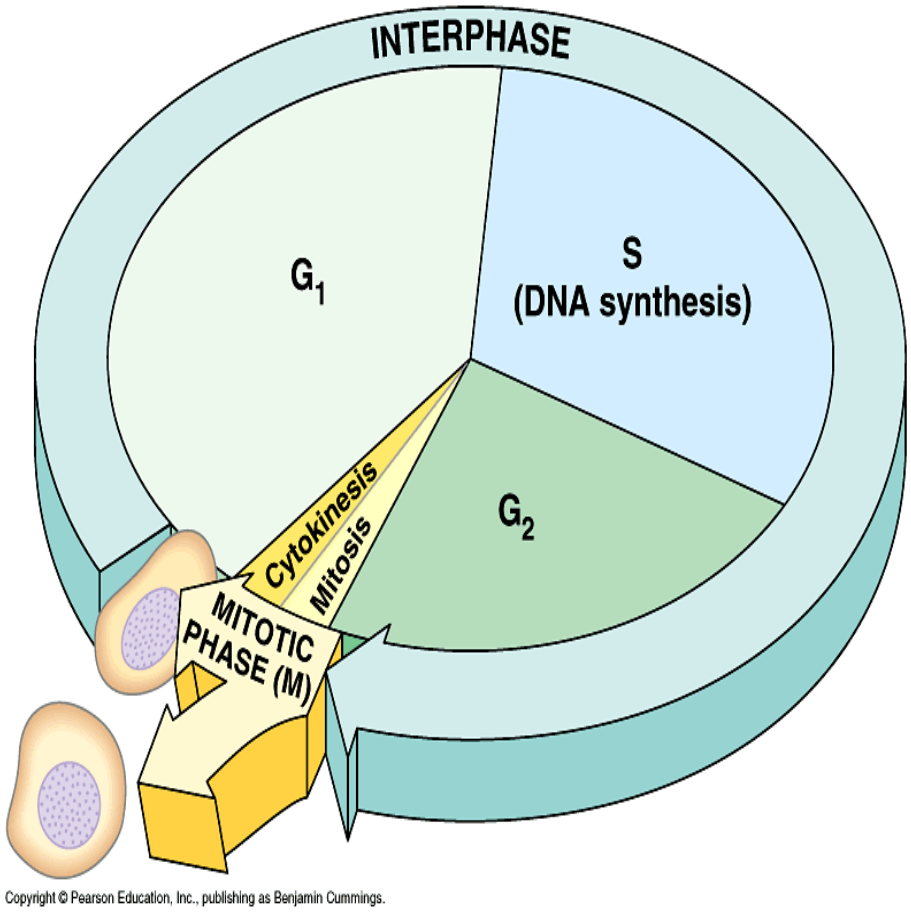
Principles of Genetics and Molecular Biology

The cell cycle

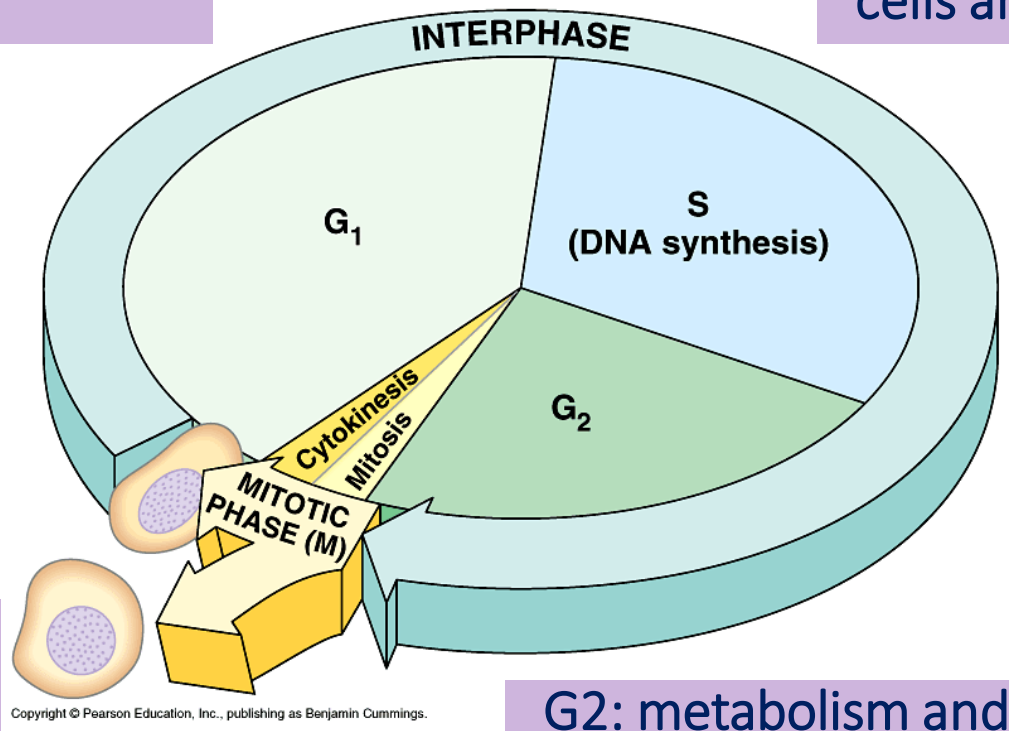


- A typical eukaryotic cell cycle divides ~every 24 hours.
- Mitosis and cytokinesis = ~1 hour
- Interphase: cell growth and DNA replication occur in an orderly manner in preparation for cell division.
- Zygote: no G1 or G2, but rapid S and M phases
- Some cells (nerve cells) enter a quiescent stage (G_0 phase)

Phases of cell cycle

G1: increased metabolism and cell growth; cells are dipoloid (2n)

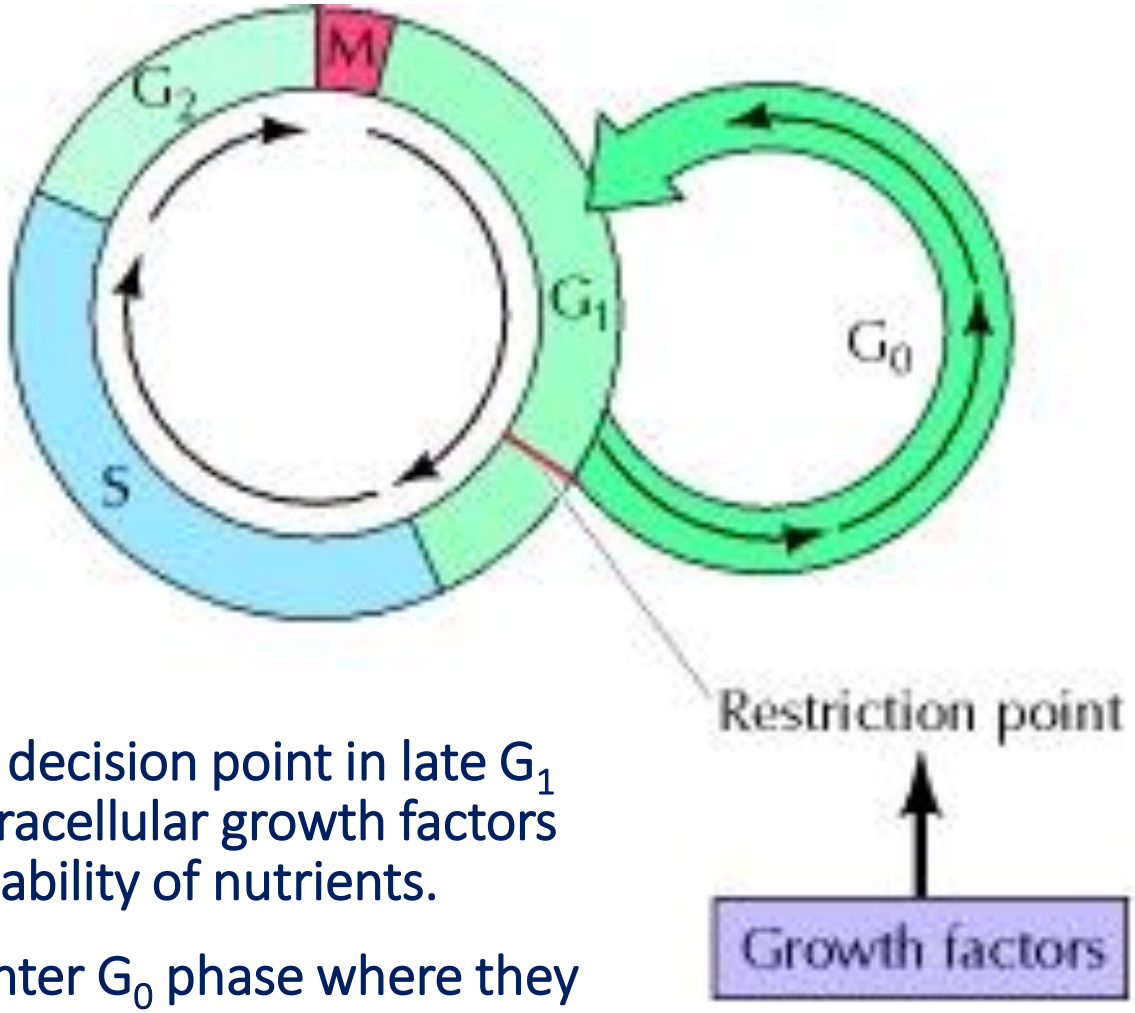
S: DNA replication; cells are 2-4n



M: chromosomal segregation, nuclear and cell division (4n)

G2: metabolism and cell growth; cells are 4n

Regulation of cell cycle

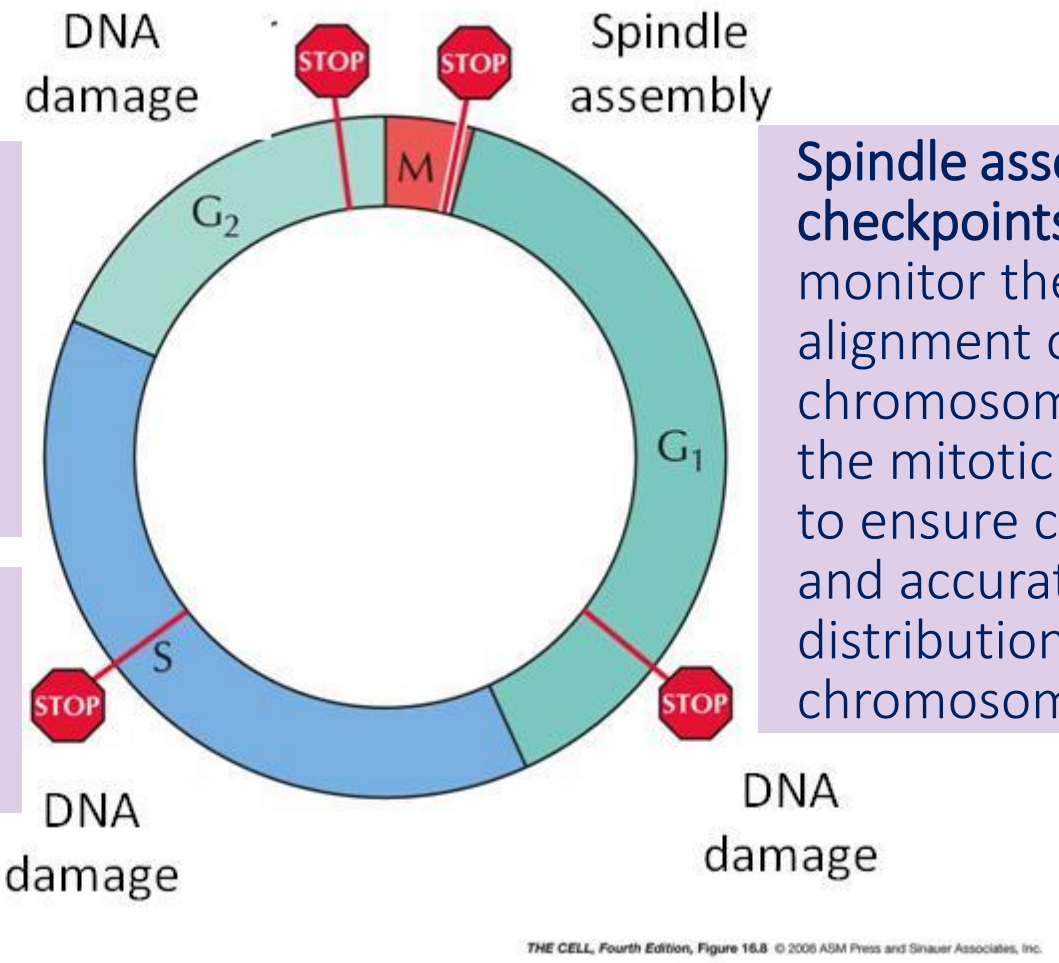


- Restriction point: a decision point in late G_1 regulated by the extracellular growth factors rather than the availability of nutrients.
- If not there, cells enter G_0 phase where they are metabolically active without growth.

Checkpoints

DNA damage checkpoints ensure that incomplete or damaged DNA is not replicated and passed on to daughter cells.

Restricting DNA replication to once per cell cycle by helicase complexes



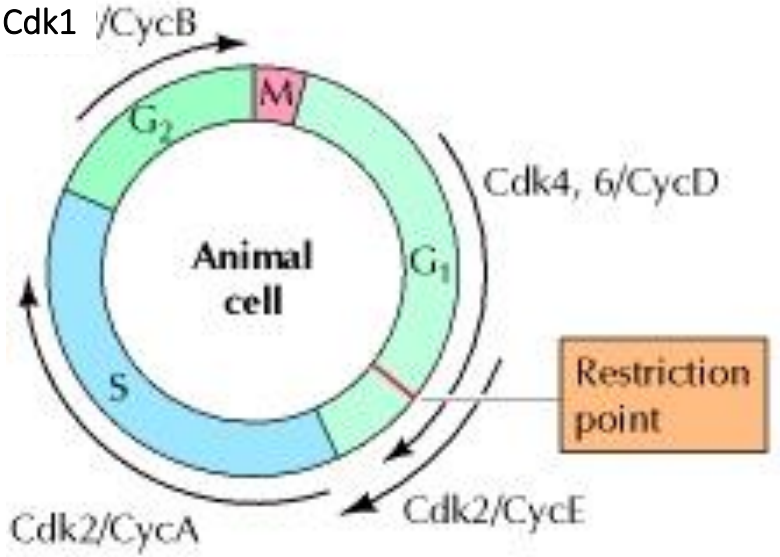
Spindle assembly checkpoints monitor the alignment of chromosomes on the mitotic spindle to ensure complete and accurate distribution of chromosomes.

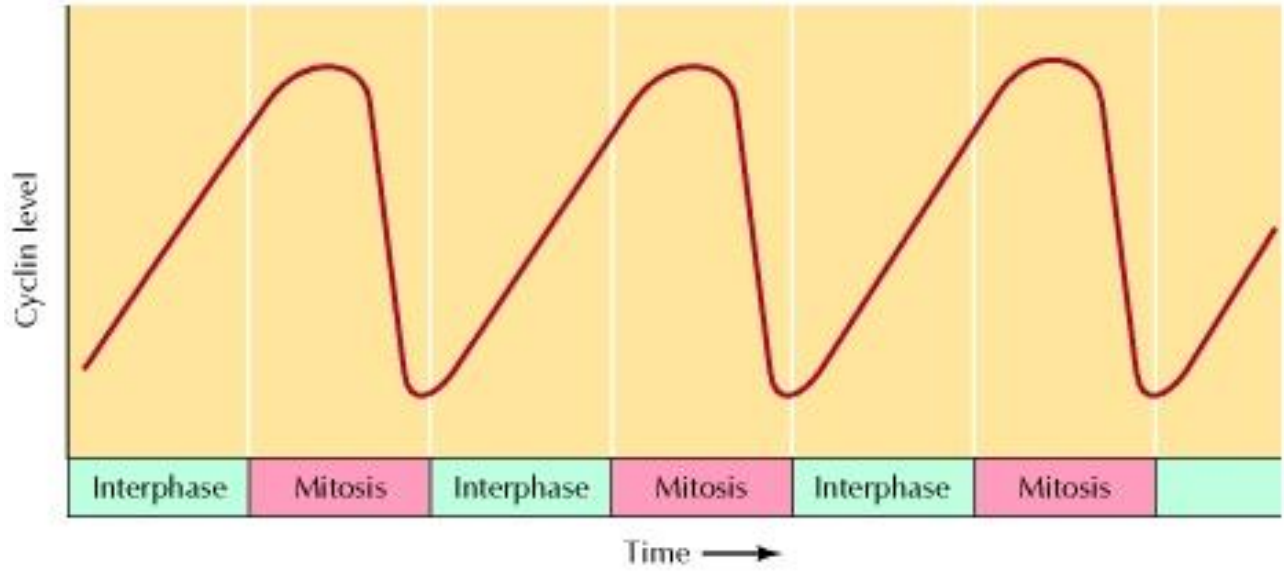
Regulators of cell cycle

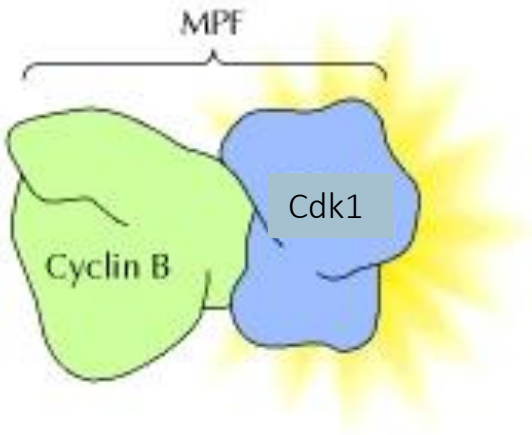
Cyclins are proteins that accumulate throughout the interphase and are rapidly degraded toward the end of mitosis.

Cyclin-dependent kinases (Cdk's): bind to cyclins to activate them.

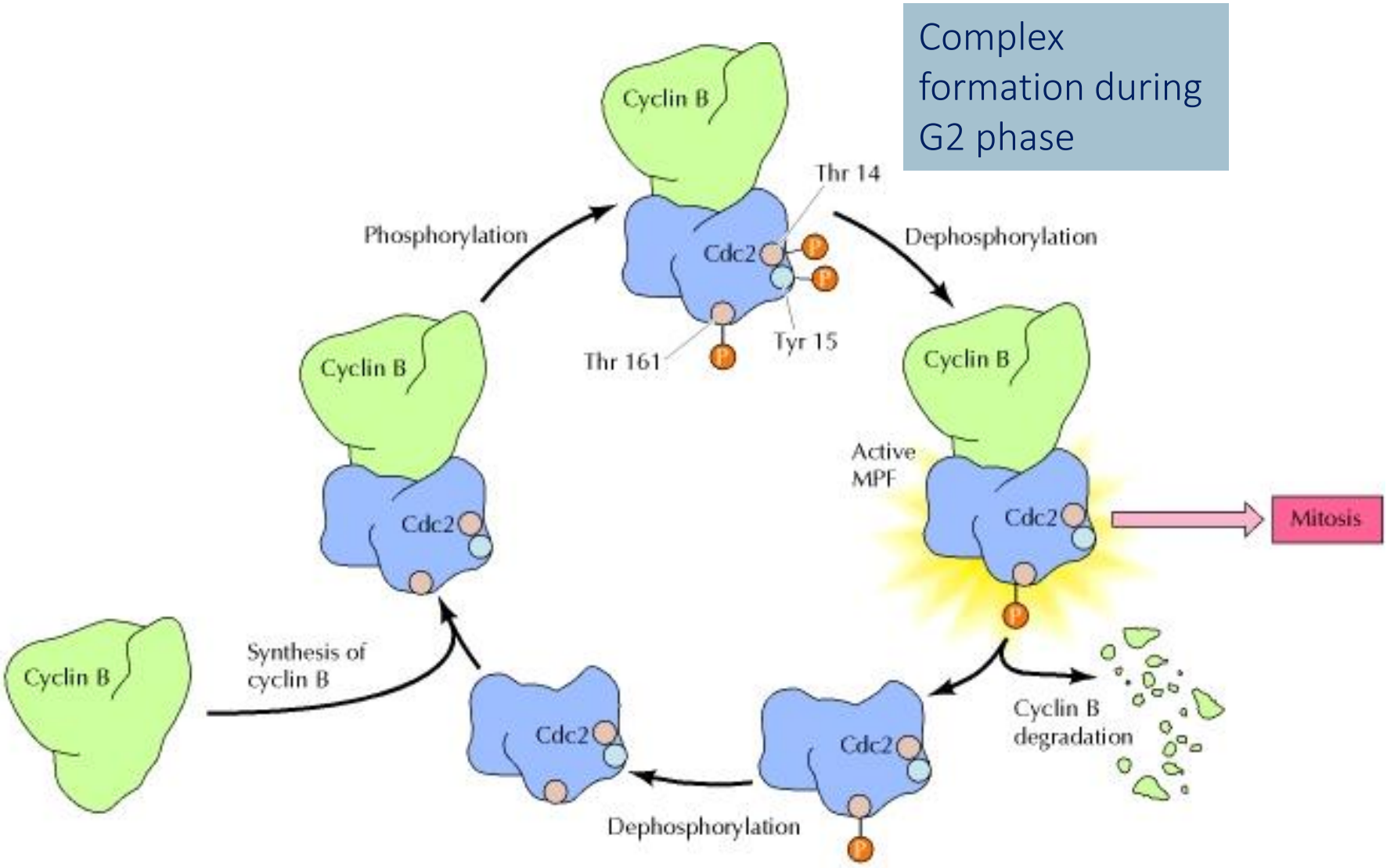
Cdk inhibitors: inhibit Cdk activity



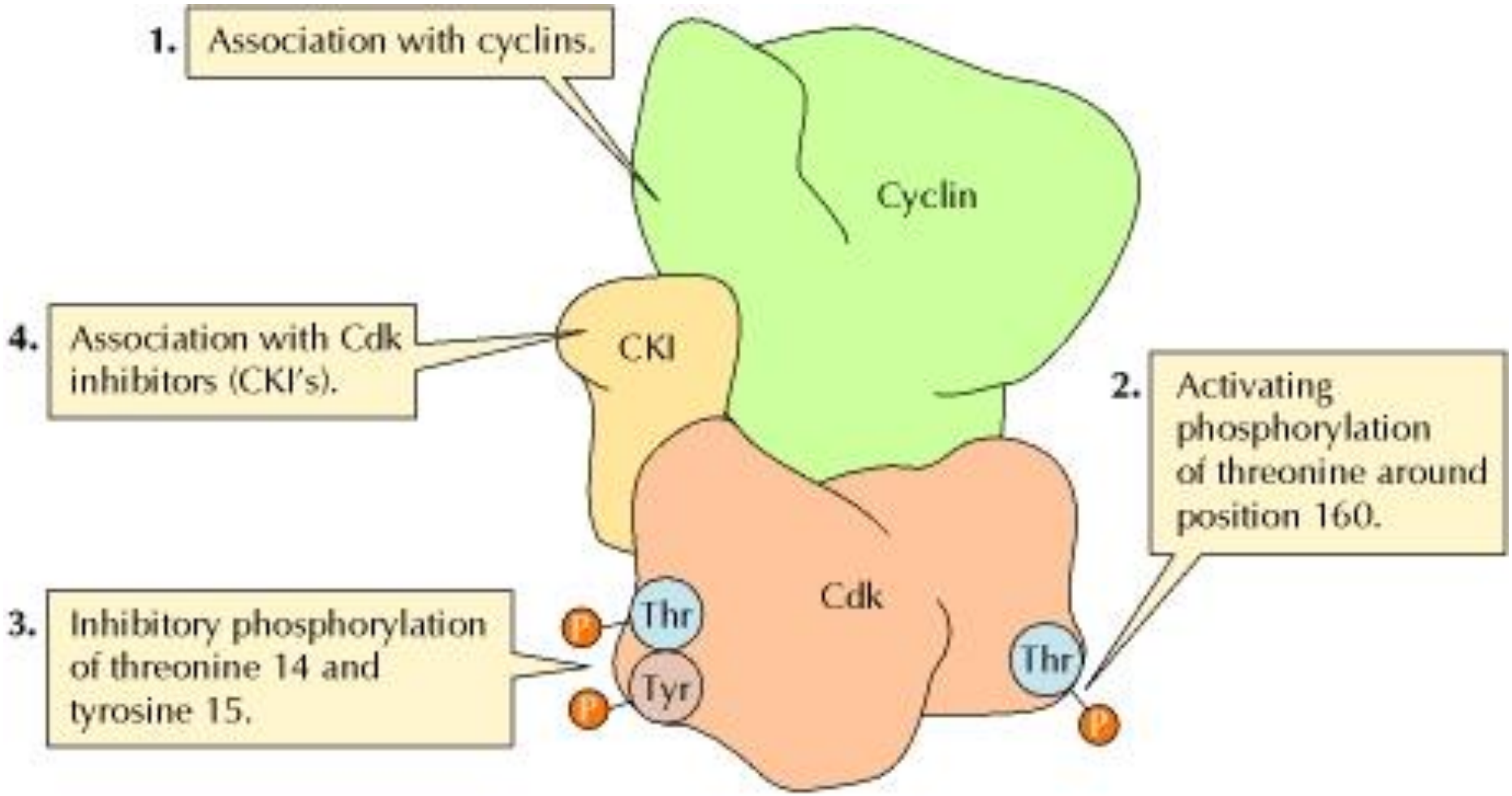




Regulation of cell cycle progression



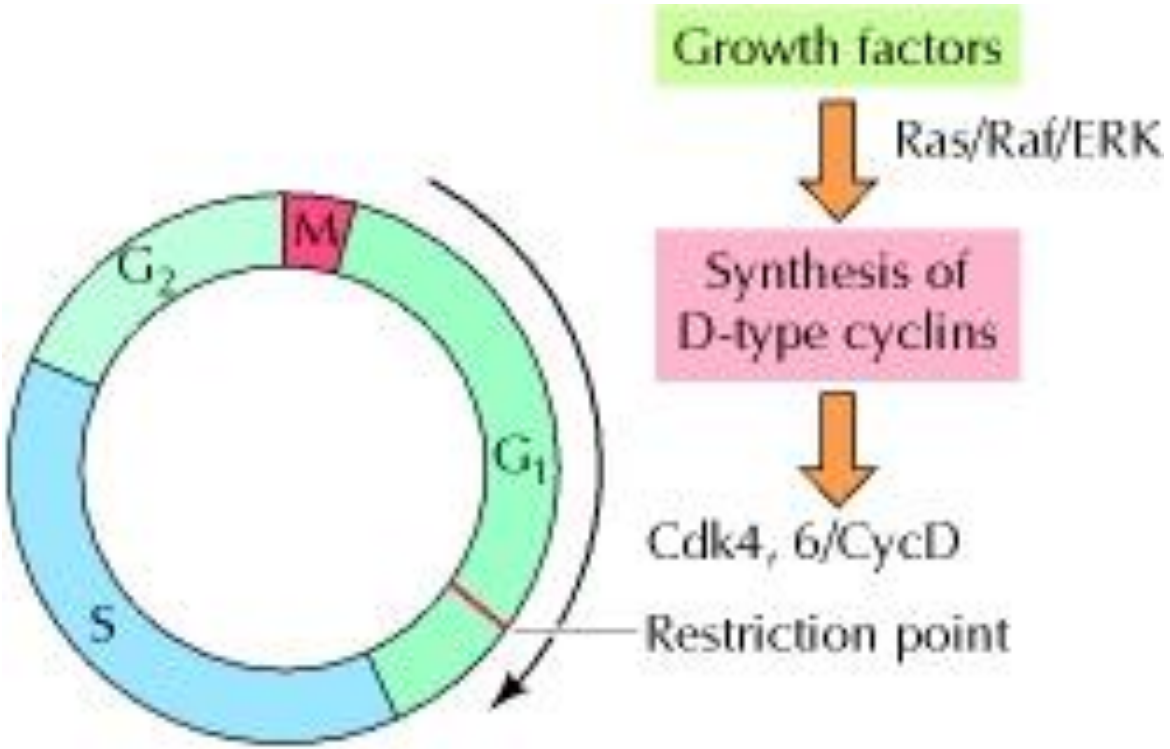
Mechanisms of Cdk regulation



Cells signaling and cell cycle

Growth factors regulate cell cycle progression through the G_1 restriction point by inducing synthesis of D-type cyclins via the Ras/Raf/ERK signaling pathway.

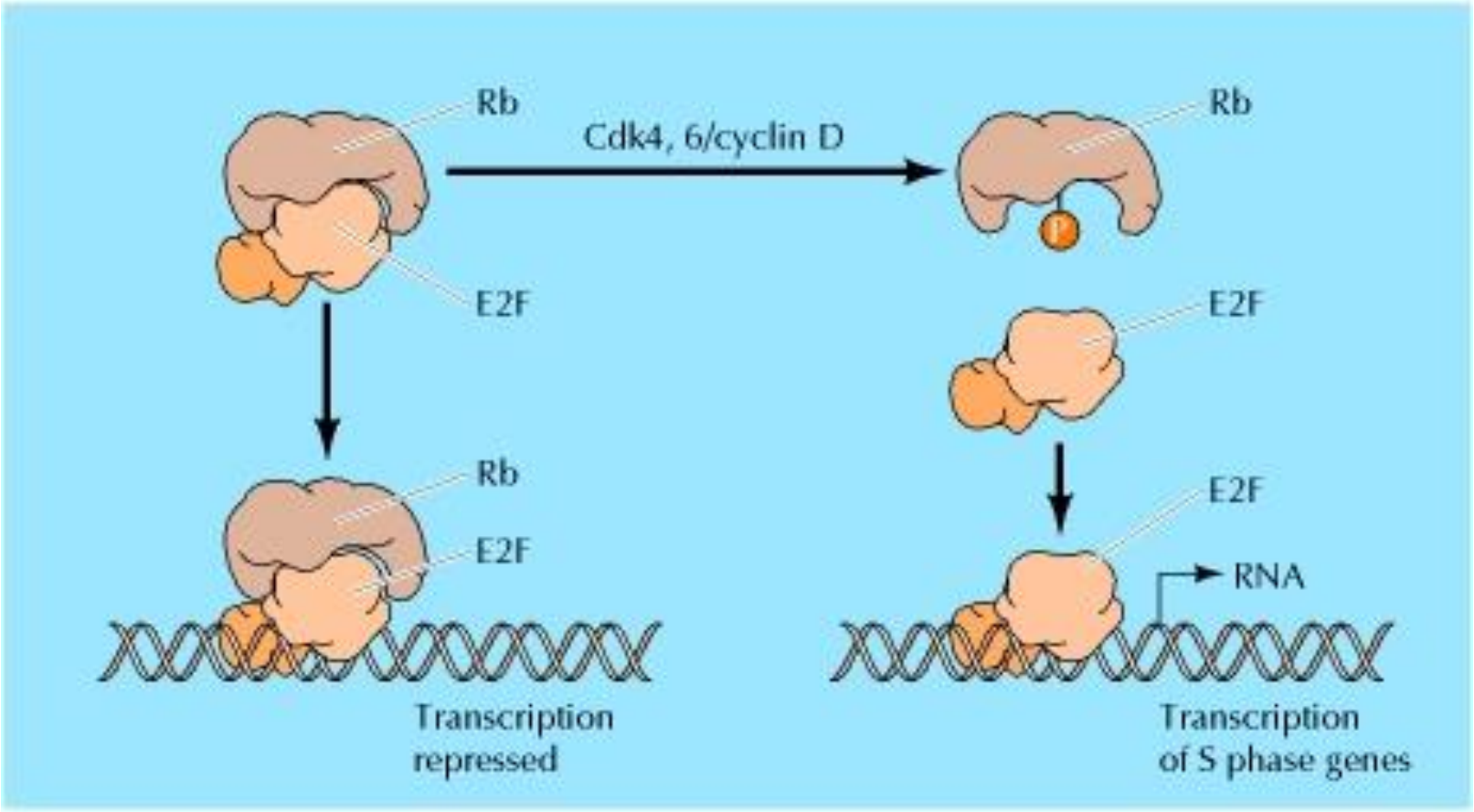
Defects in cyclin D regulation lead to the loss of growth regulation that is characteristic of cancer cells.



Retinoblastoma

When **unphosphorylated**, **Rb** binds to **E2F** proteins and **represses** transcription of E2F-regulated genes.

E2F is freed when **Rb** is **phosphorylated** by **Cdk4**, **6/cyclin D stimulating** cell cycle progression through restriction point.

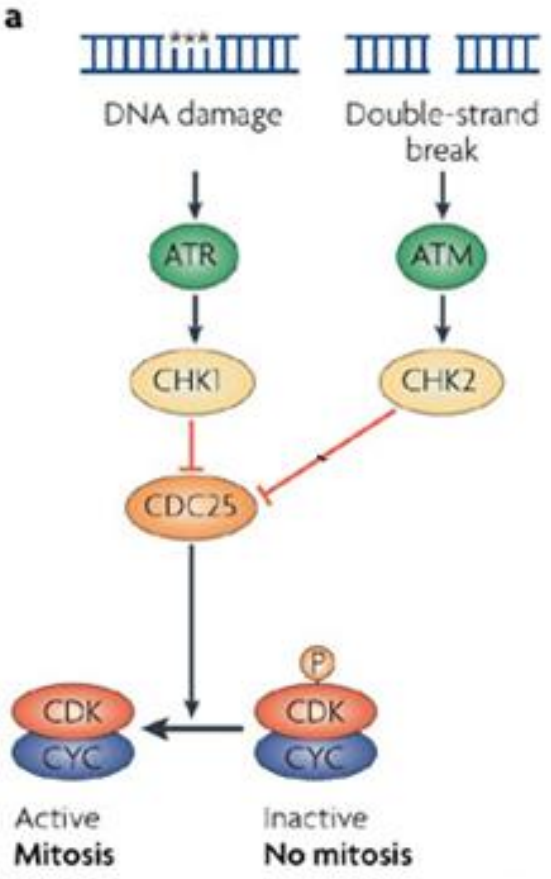


Cell cycle arrest by DNA damage

- ATM and ATR are protein kinases
- ATR is activated by ss DNA damage.
- ATM is activated by ds DNA damage.

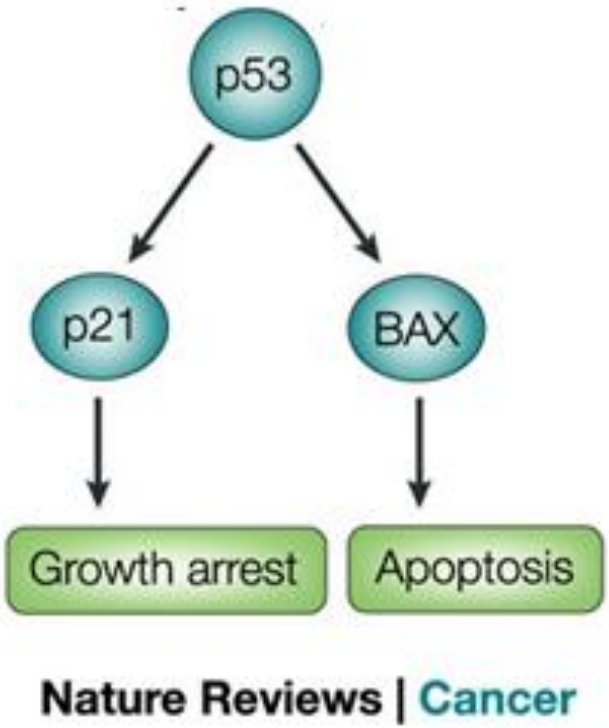
ATR and ATM activate the checkpoint kinases, Chk1 and Chk2, respectively, which inhibit Cdc25 phosphatase.

Phosphatases cannot activate Cdk's causing cell arrest.



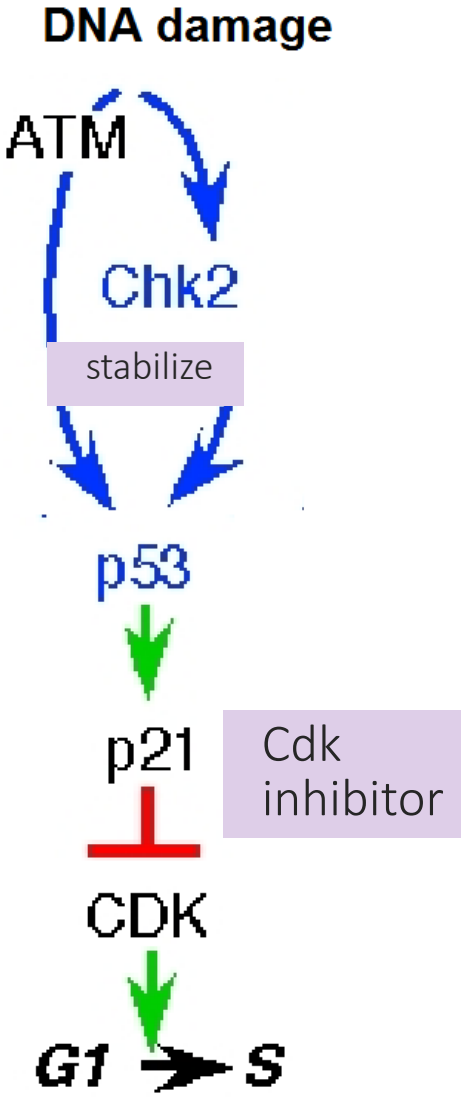
Nature Reviews | Molecular Cell Biology

Role of p53 in cell cycle arrest



- DNA damage results in phosphorylation of p53 protein stabilizing it.

- Activated p53 activates expression of p21, which is a protein that inhibits a Cdk/cyclin complex.
- p53 activates apoptosis



Apoptosis (Programmed cell death)

Is a normal physiological form of cell death.

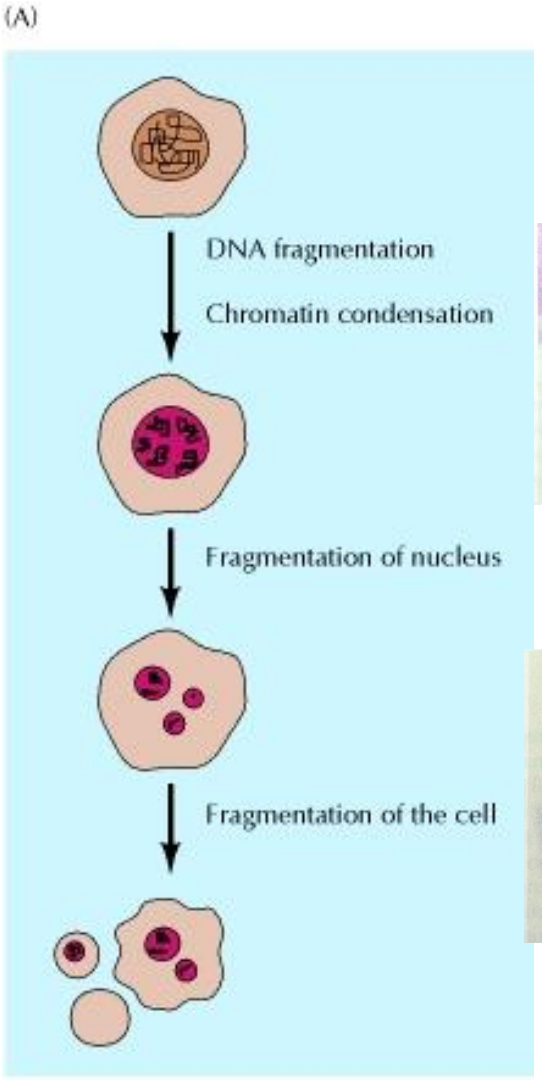
Has a key role in the **maintenance of adult tissues and in embryonic development.**

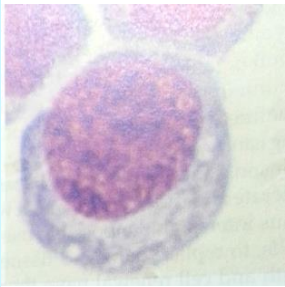
- Renewal of 5×10^{11} blood cells a day
- elimination of nerve cells with faulty connection
- Elimination of damaged and potentially dangerous cells
  - *Cells with DNA damage*
  - *Virus-infected cells*

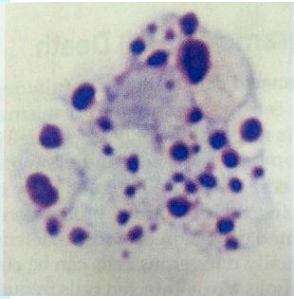
How apoptosis is stimulated?
Intrinsic pathway: simulated by DNA damage
Extrinsic pathway: stimulated by signals from other cells

Features of Apoptosis

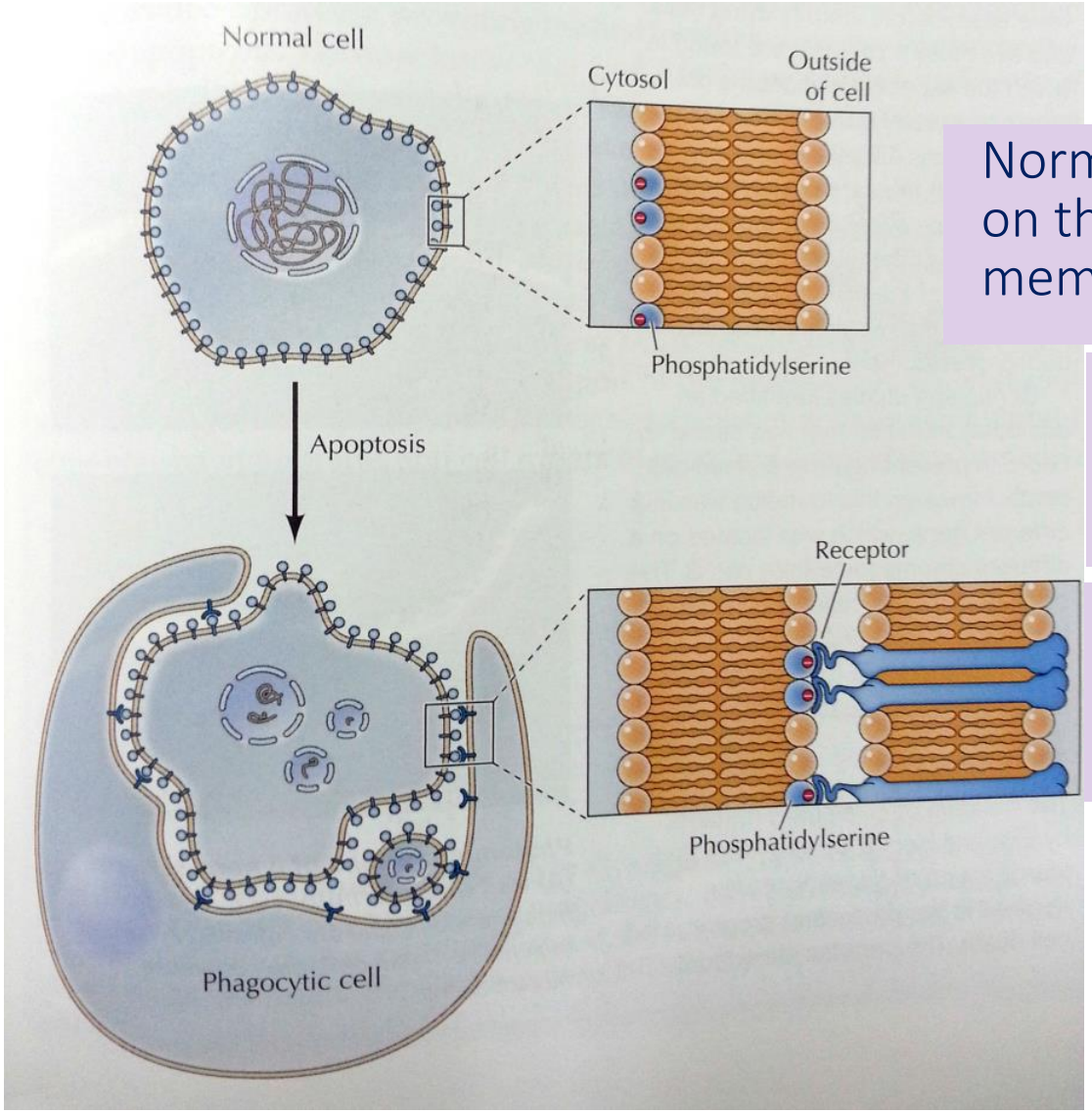
- Fragmentation of chromosomal DNA
- Chromatin condensation
- Breaking up nucleus into small pieces.
- Cell shrinkage
- Cell fragmentation (apoptotic bodies)
- Phagocytosis by macrophages and neighboring cells
- In contrast, cell necrosis results in membrane damage, enlargement of cells, release of intracellular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







Role of phosphatidylserine (PS)



Normally, PS is expressed on the inner leaflet of cell membrane.

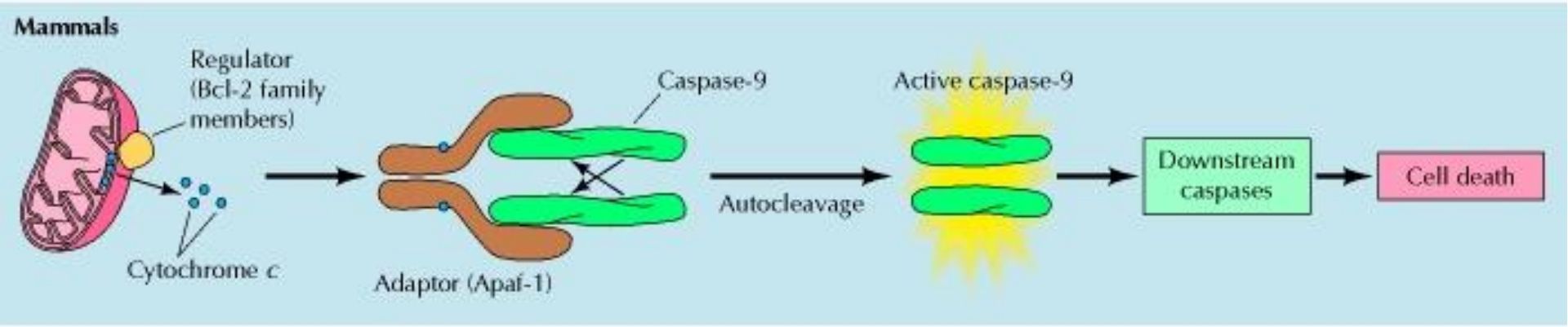
During the initiation of apoptosis, PS is flipped to the outer leaflet.

It is then recognized by phagocytic cells.

The molecular activation of 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

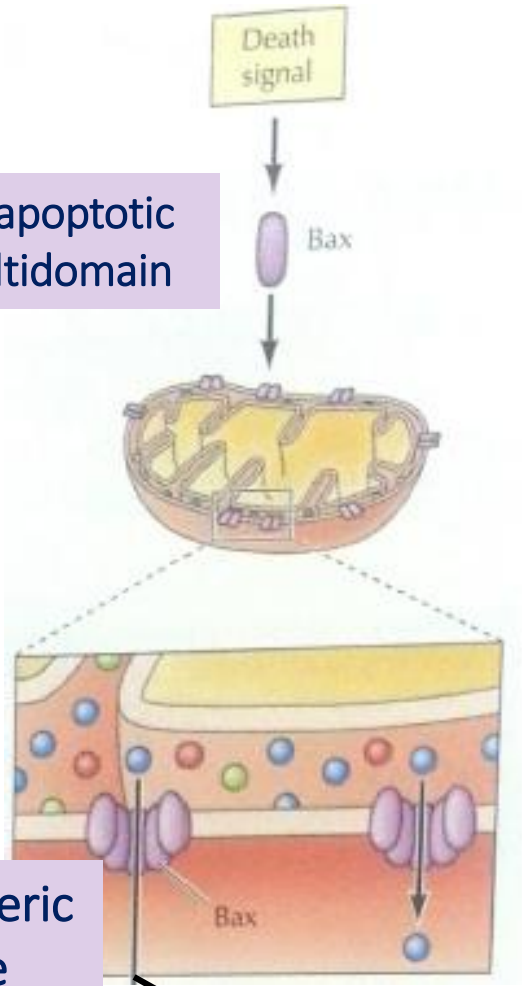
Release of cytochrome *c* from mitochondria activates caspase-9, which then activates downstream caspases to induce apoptosis.

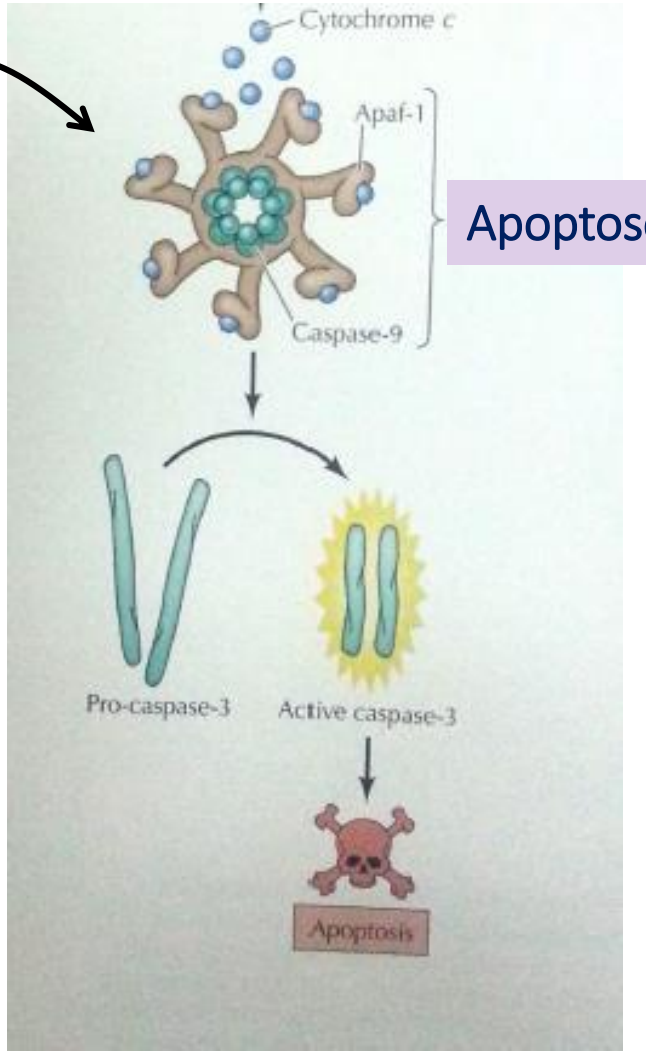


How is cytochrome c released form mitochondria?

Proapoptotic multidomain

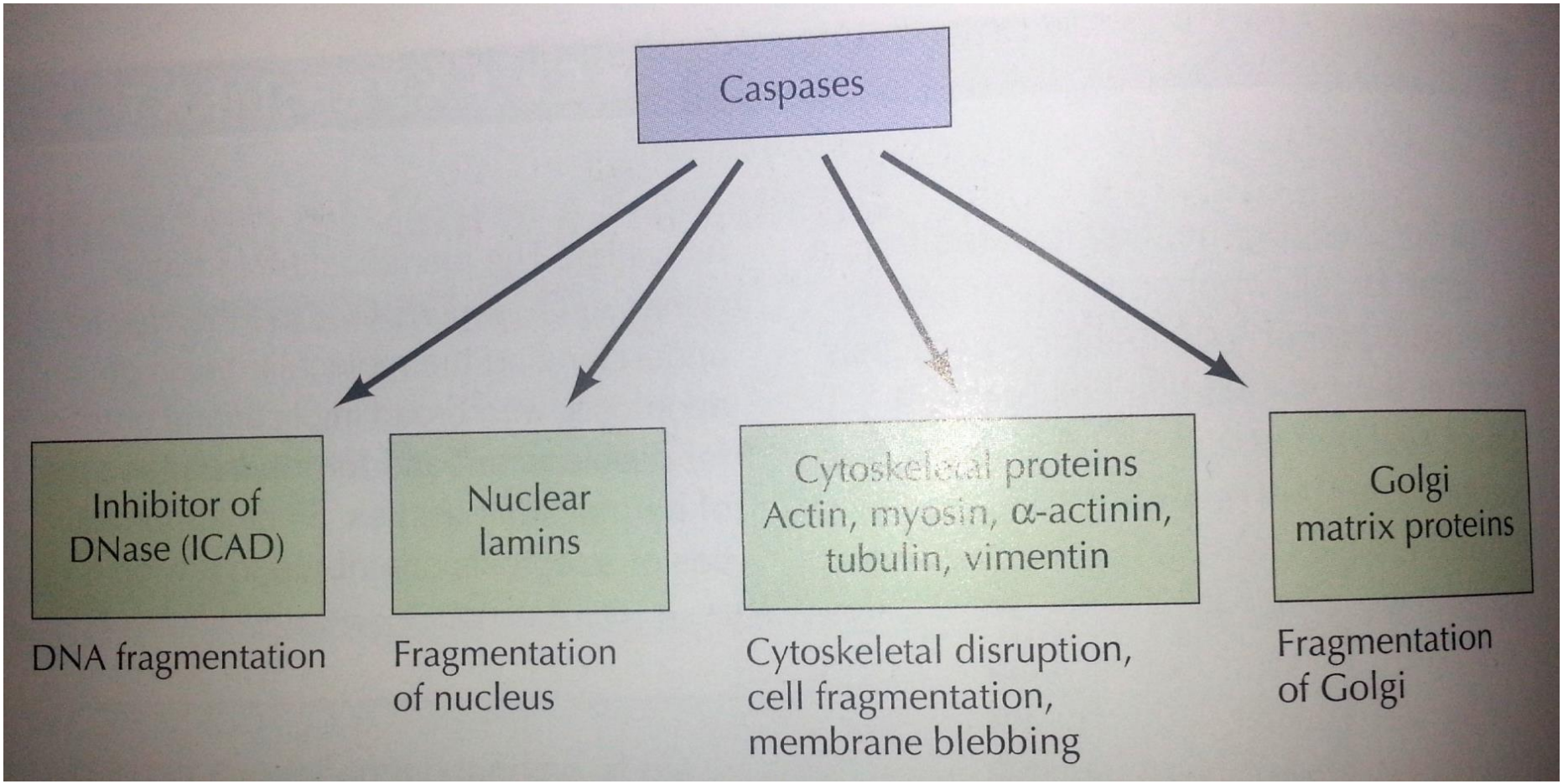
Oligomeric pore formation





Apoptosome

Caspases roles



Bcl-2 family

Anti-apoptotic Bcl-2 proteins

Multi-domain pro-apoptotic effectors

Pro-apoptotic BH3-only

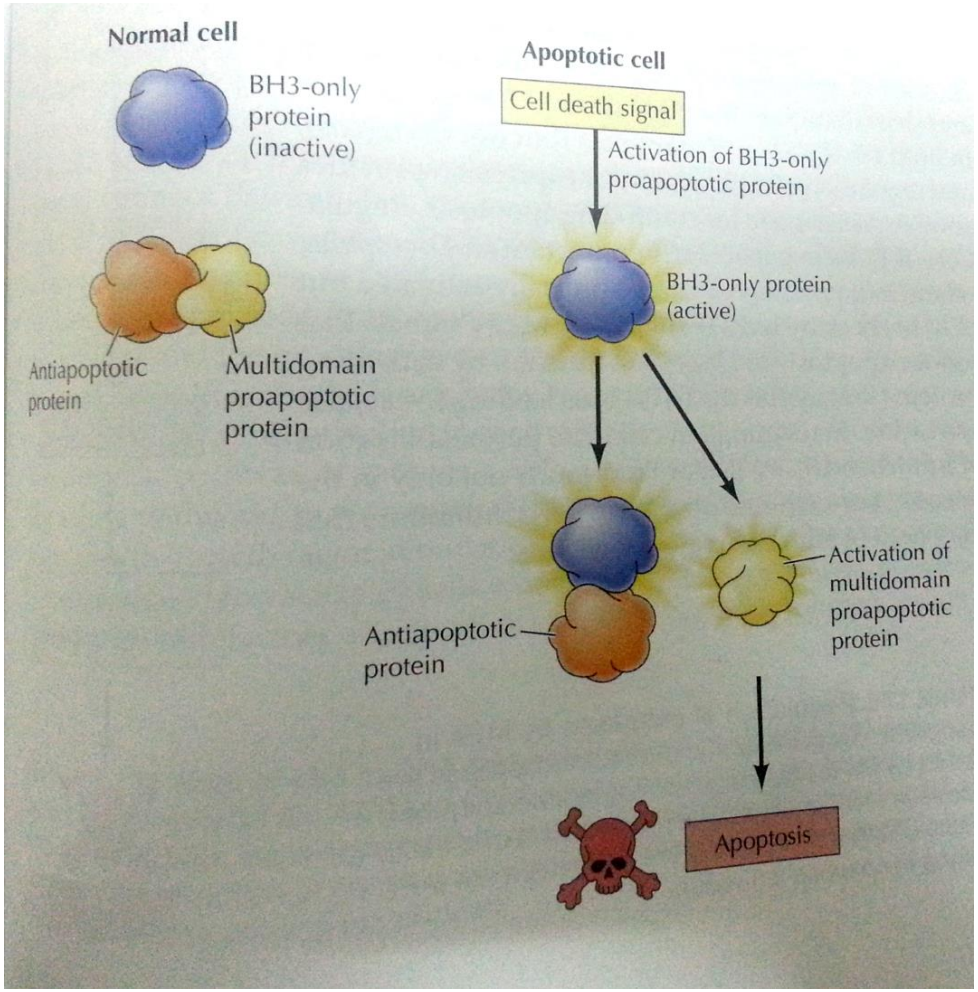
- There are three classes of Bcl-2 according to their domains and apoptotic effect:

1. Anti-apoptotic proteins
2. Proapoptotic proteins:
   - *Multi-domain*
   - *BH3-only domain*

How is apoptosis activated upstream?

- **Normally**, BH3-only protein is inactive and the multi-domain proapoptotic protein is inactivated by the anti-apoptotic protein.

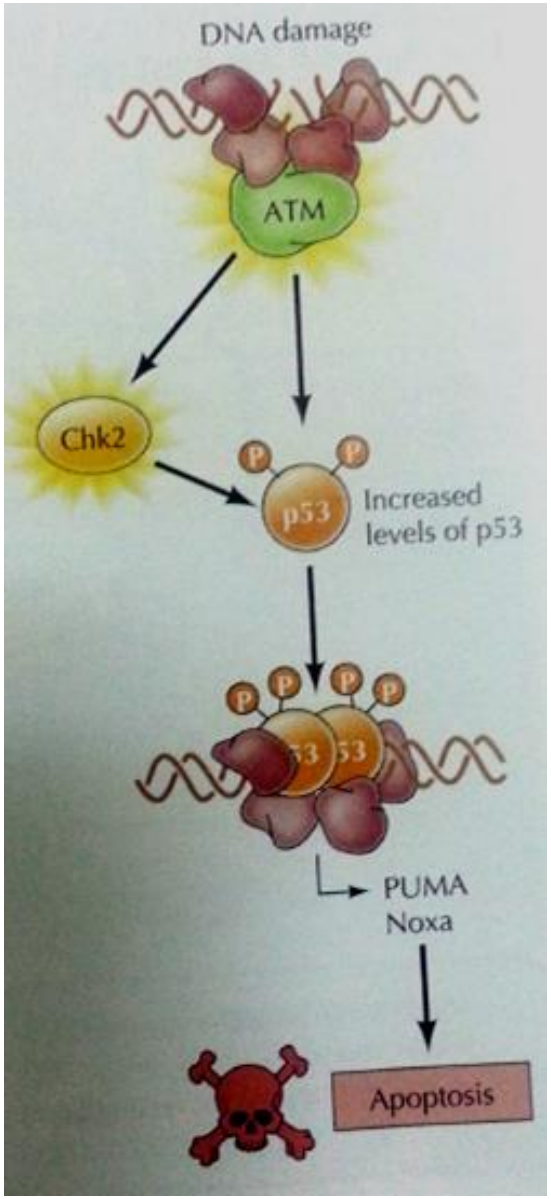
- **Death signals** activate the BH3-only protein, which inactivates the antiapoptotic proteins resulting in the release and activation of the multi-domain proapoptotic protein.



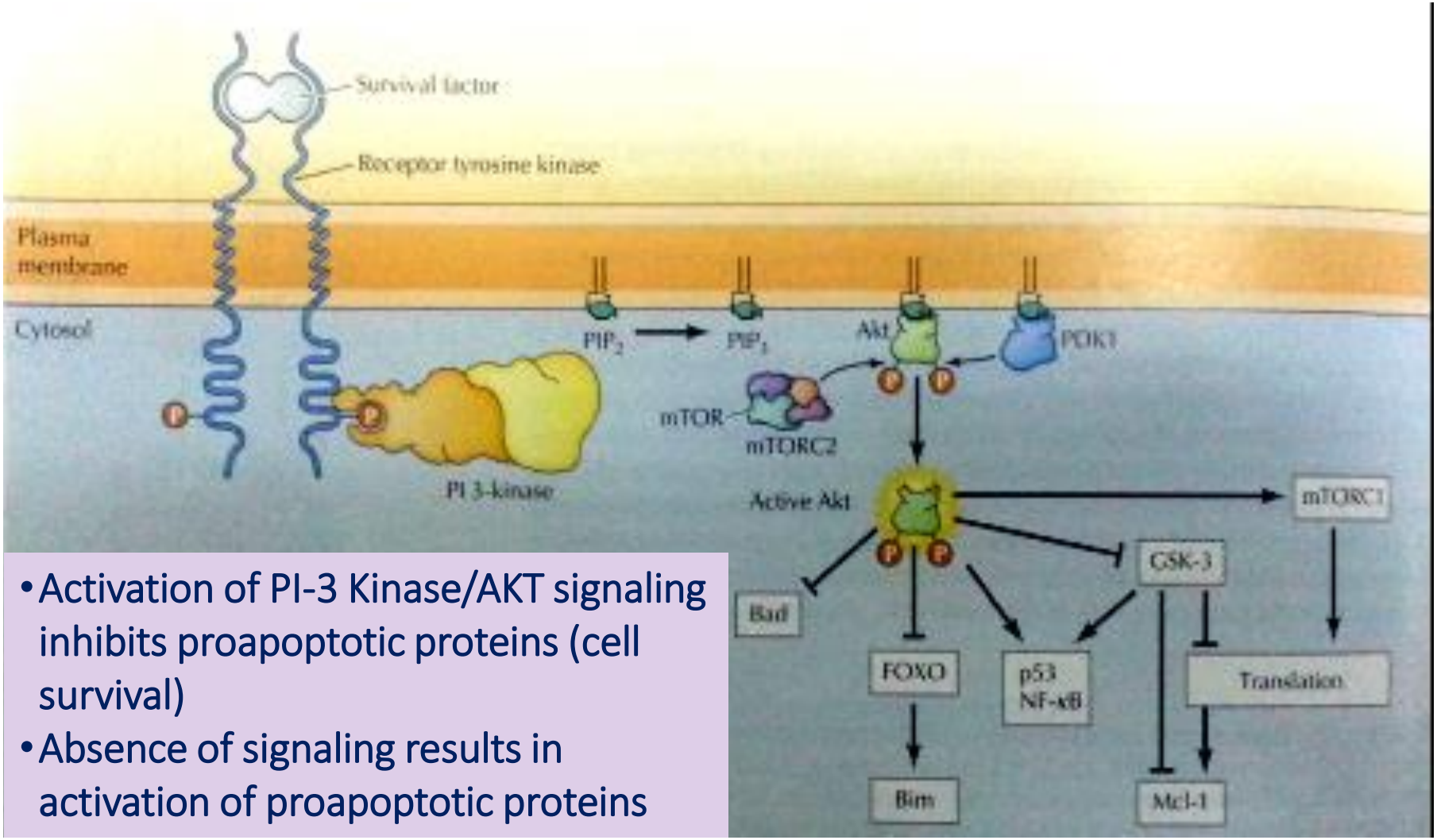
Internal pathway

ATM/Chk2 signaling stimulates p53 phosphorylation

Phosphorylated p53 induce the expression of BH3-only proteins.

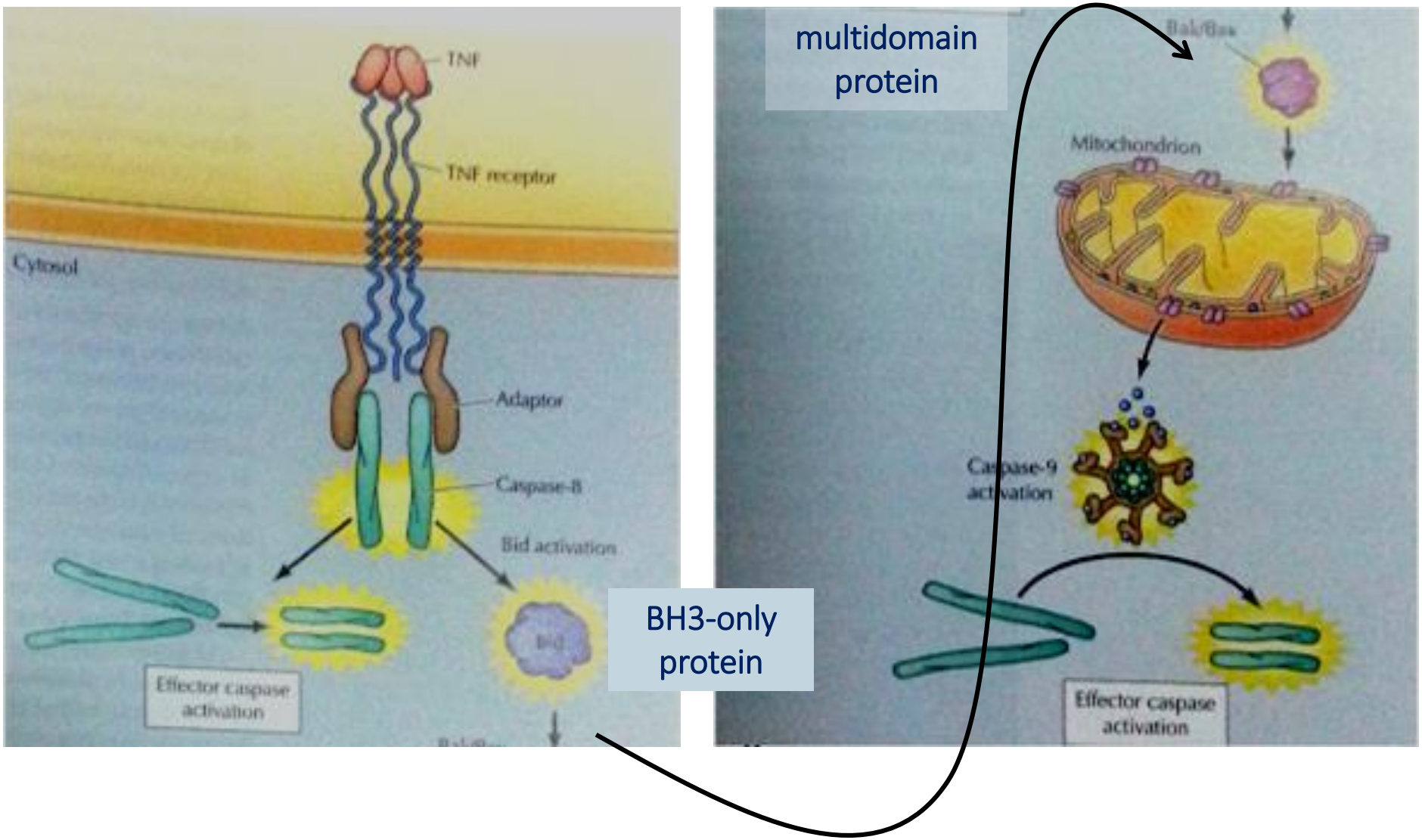


External signaling (1): pro-survival



- 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



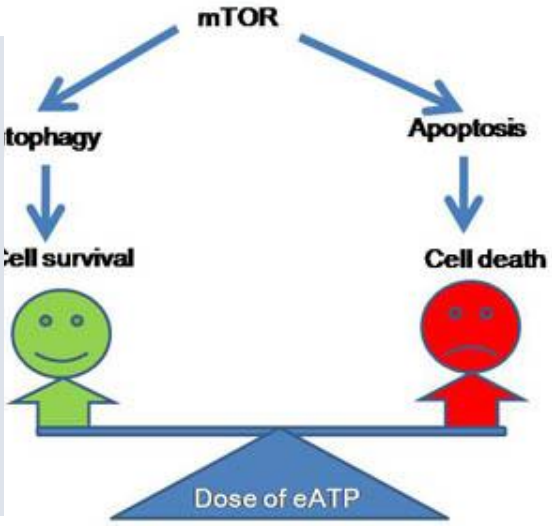
Autophagy

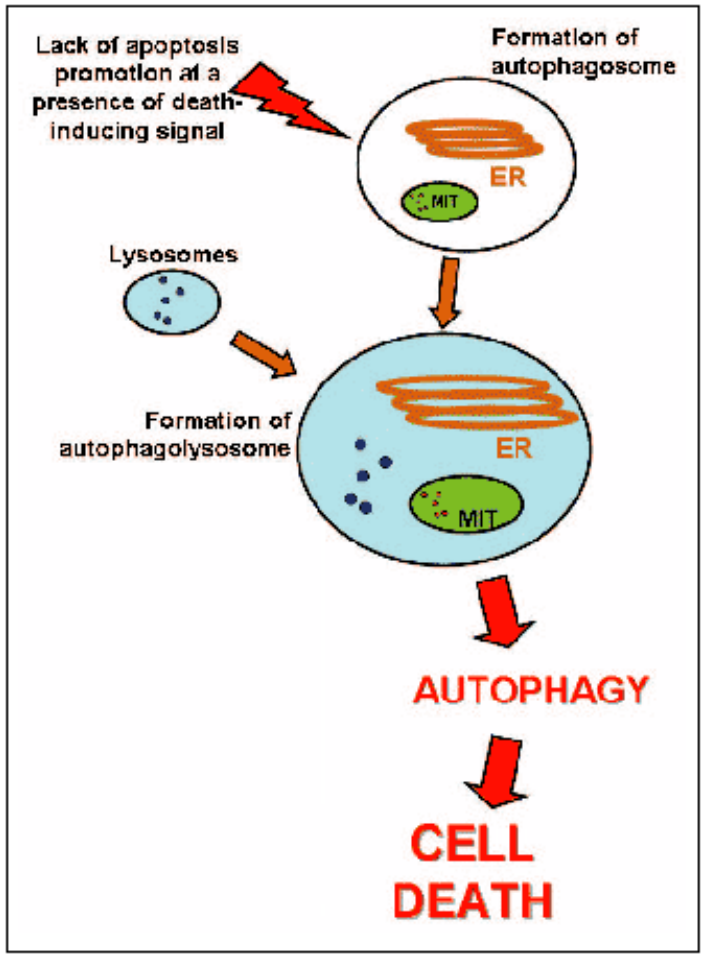
Apoptosis can be caspase-independent, but mediated by autophagy through mTOR signaling.

The dying cell does not go through the same morphological features, but accumulate lysosomes.

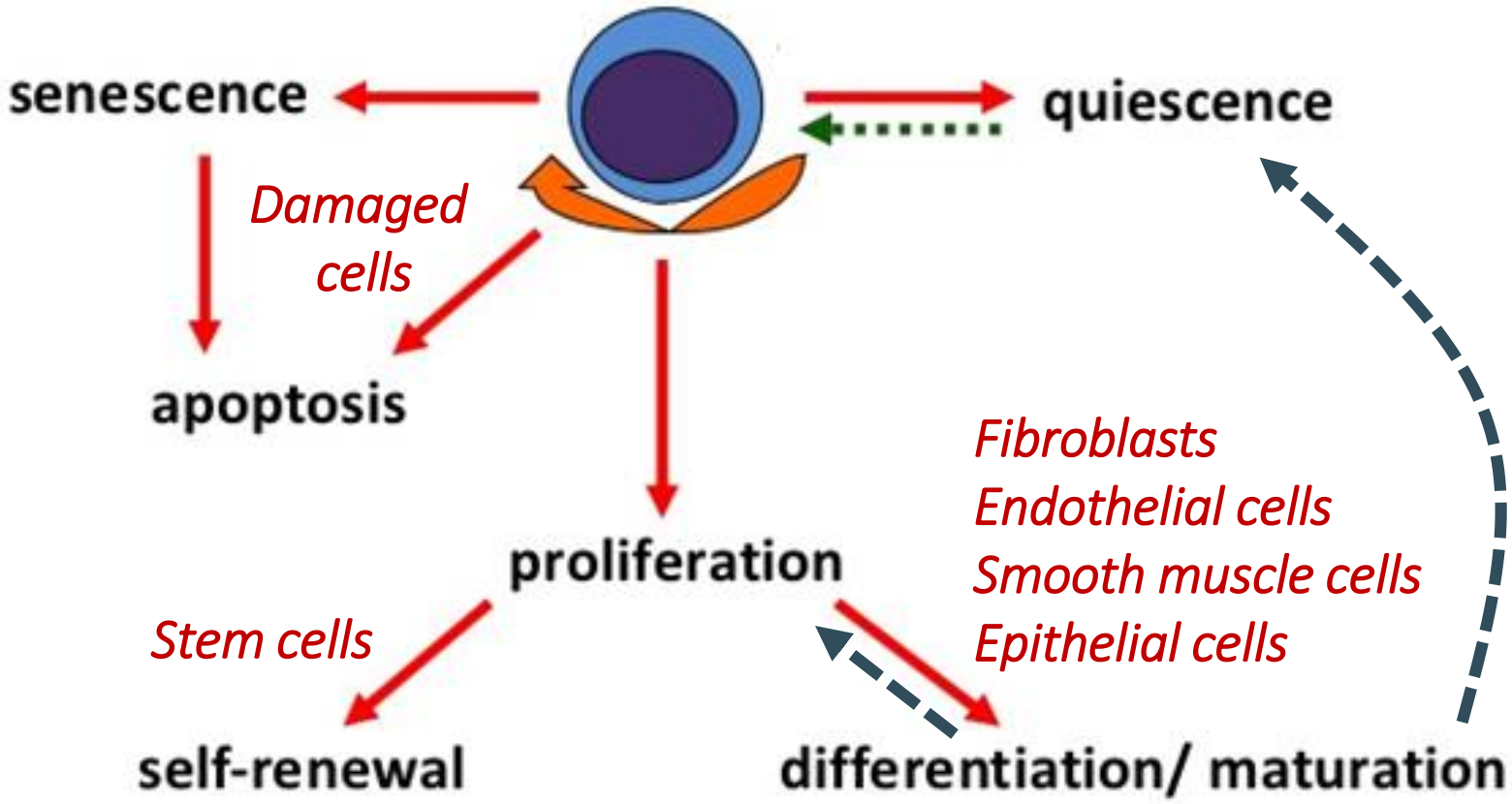
Advantages:

- When cells lack molecular machinery of apoptosis
- It provides cells with an opportunity to repair the damage prior to death





Cell fate


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