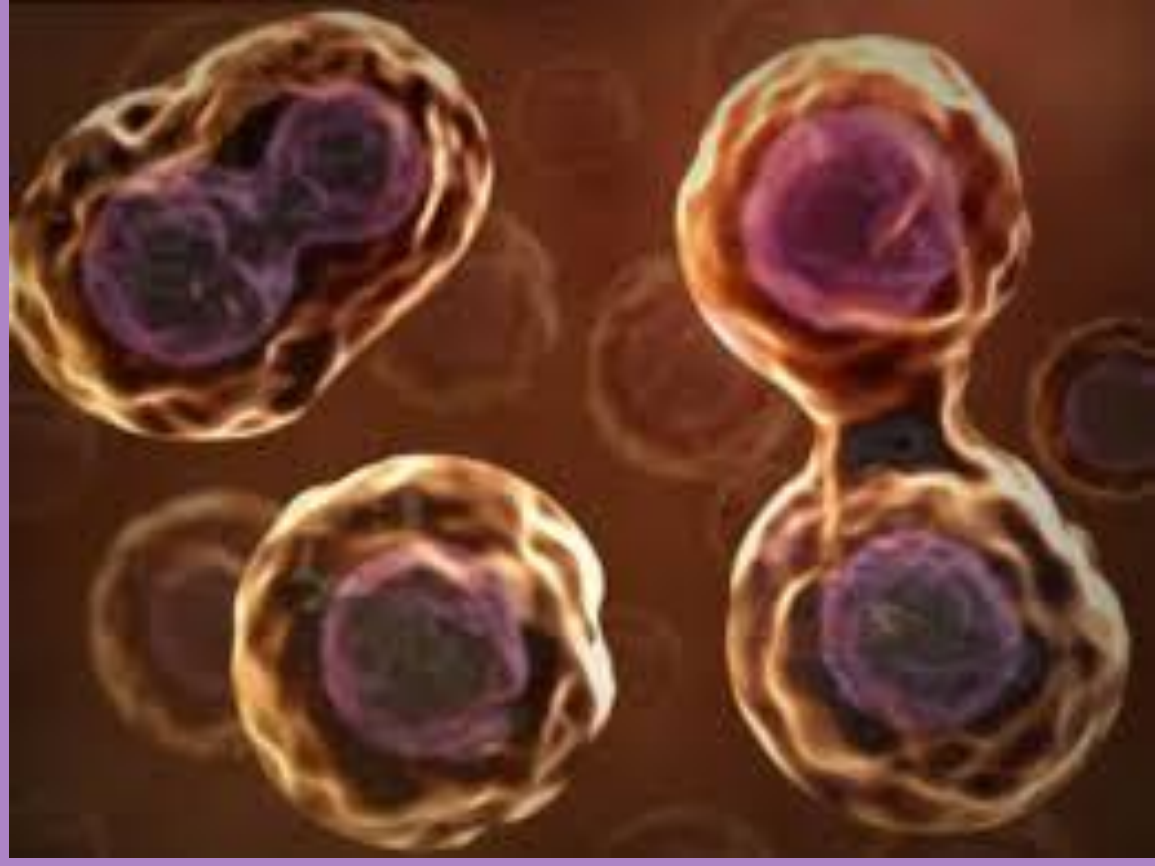
# Cell differentiation cell cycle, proliferation, and death



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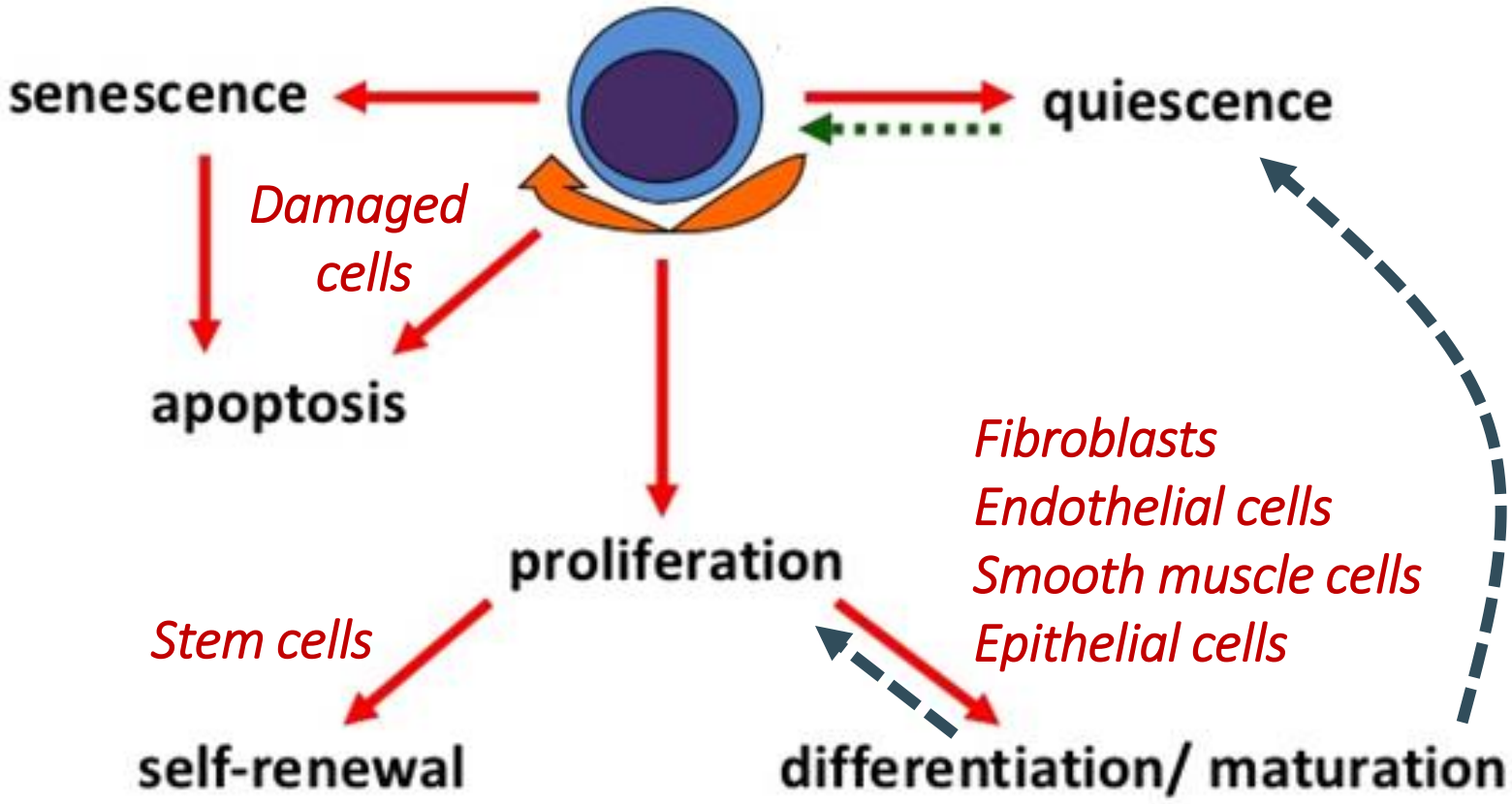
# Differentiation

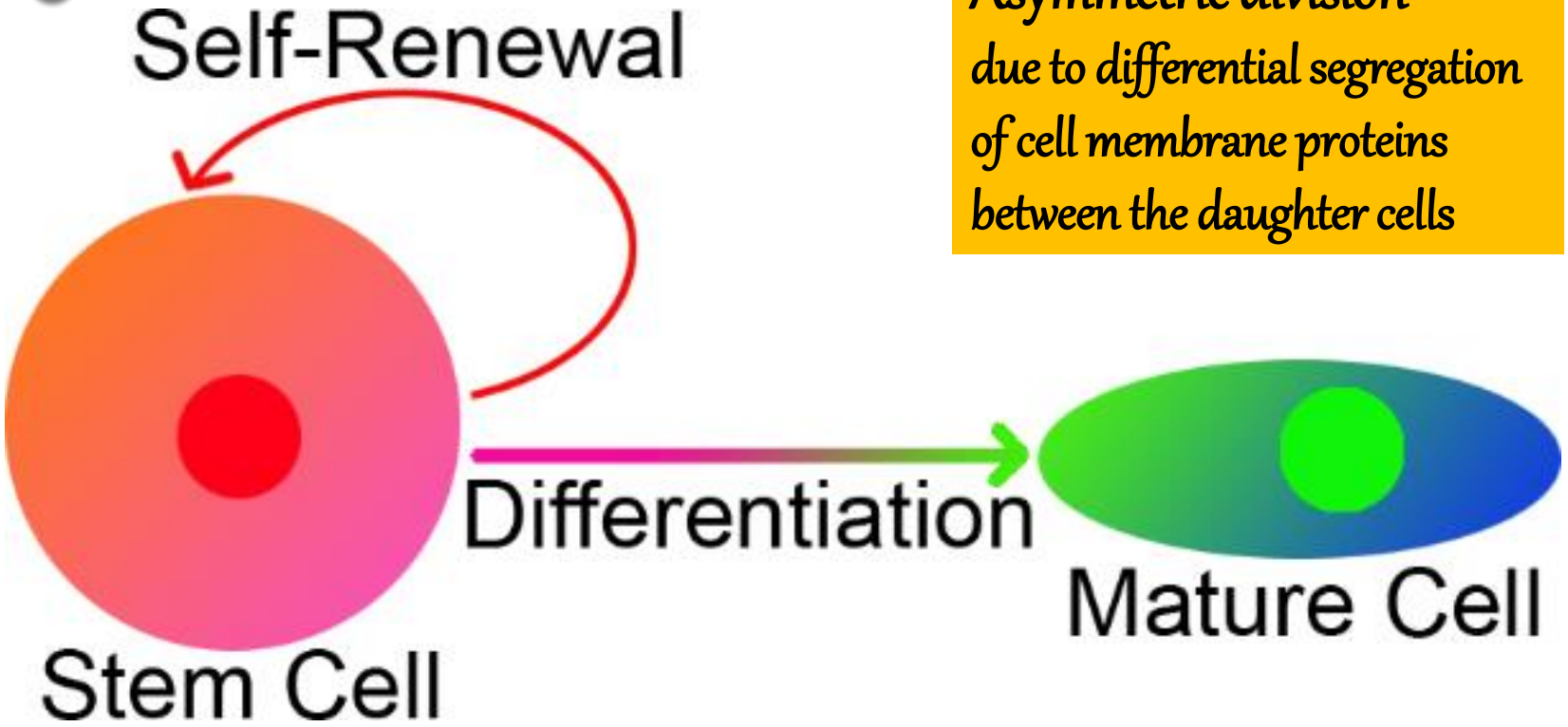
# Cell fate


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

# What are stem cells?

- Are cells that retain the ability to **renew** themselves through cell division and can be **differentiated** into a wide range of specialized cell types.
- All stem cells are unspecialized (**undifferentiated**) cells

# Differentiation vs self renewal

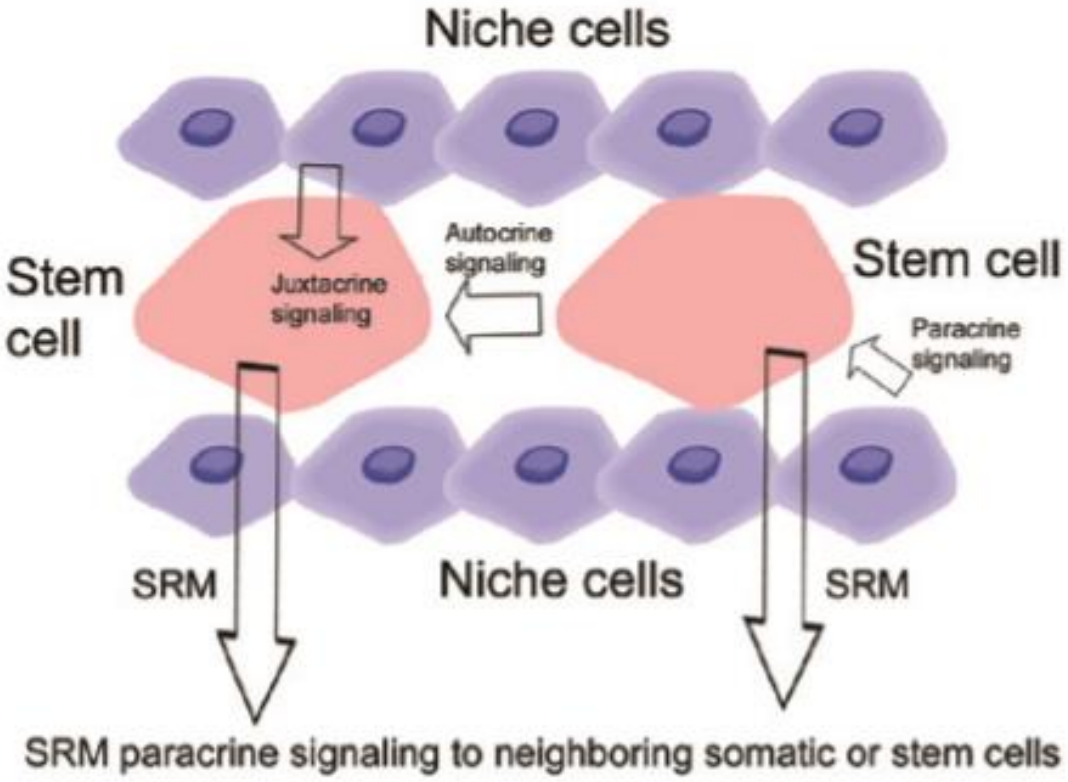



**Asymmetric division**
due to differential segregation of cell membrane proteins between the daughter cells

Self-renewal: The ability to go through numerous cycles of cell division while maintaining the undifferentiated state.

# Stem cell niche

A specialized cellular environment that provides stem cells with the support needed for self-renewal.



# Potency of stem cells

The differentiation potential of the stem cells

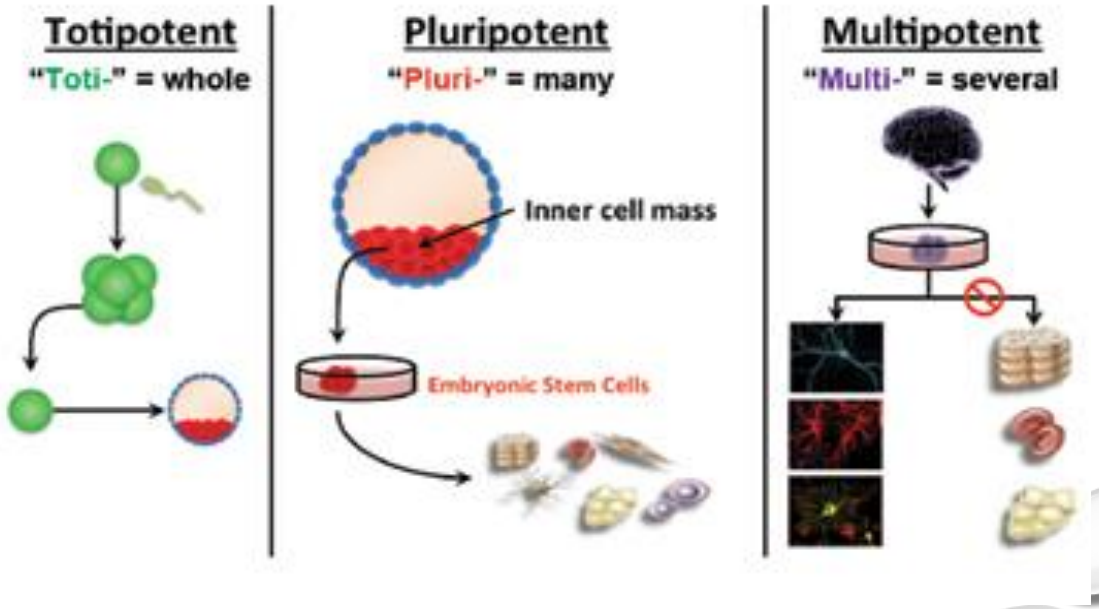
Type of potency :

1-Totipotent

2-Pleuripotent

3-Multipotent

4-Unipotent



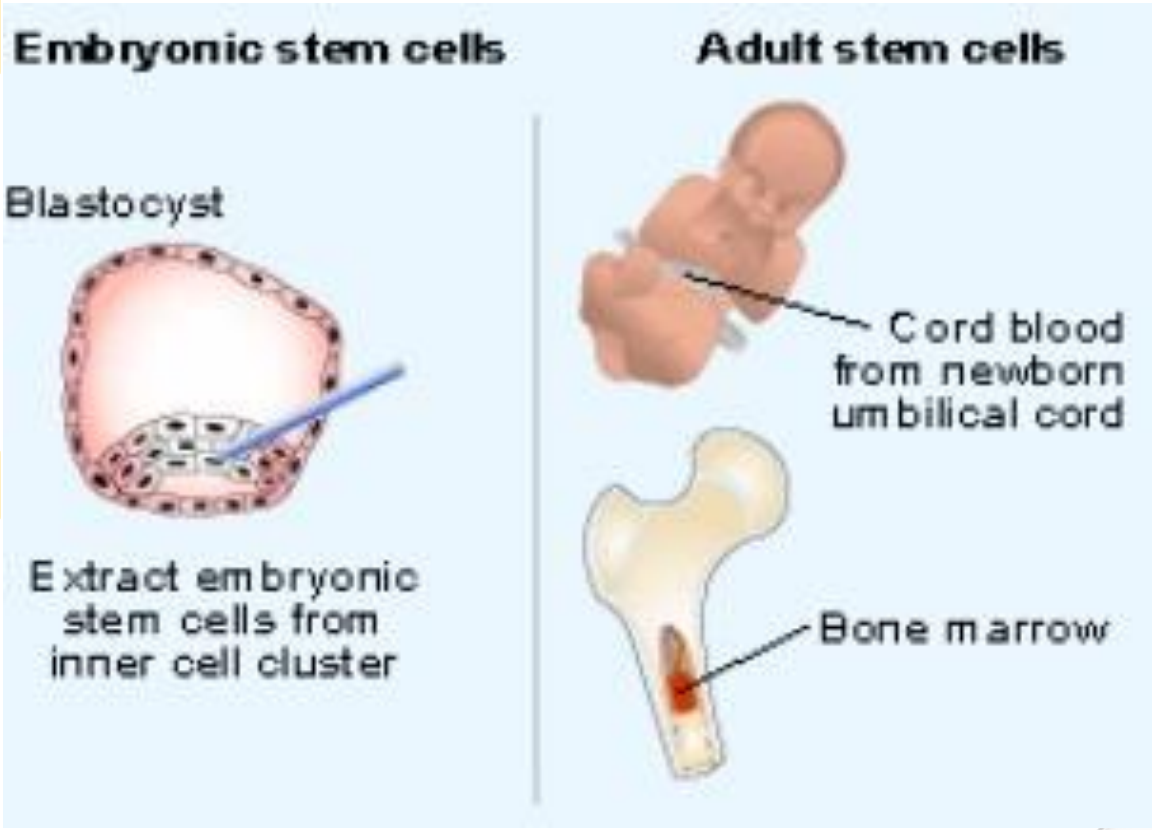
# Types of stem cells

## Embryonic stem cells

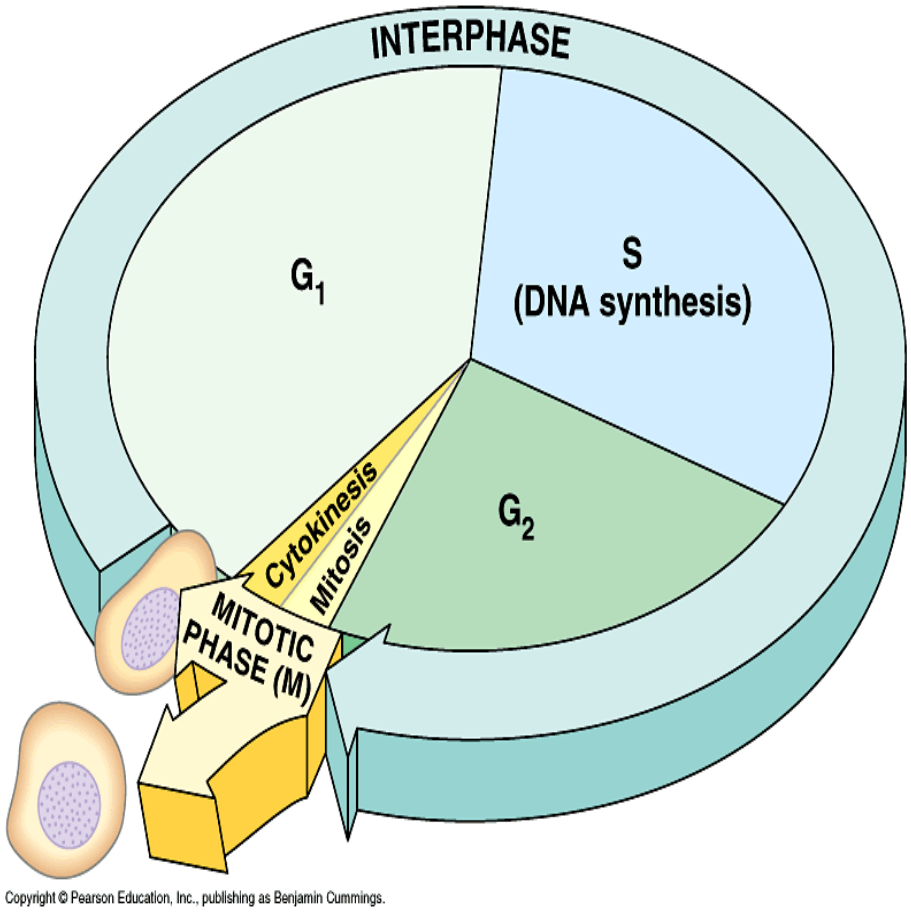
- Are able to differentiate into all the specialized embryonic tissue

## Adult stem cells

- Act as a repair system for the body replacing specialized damaged cells



# The cell cycle



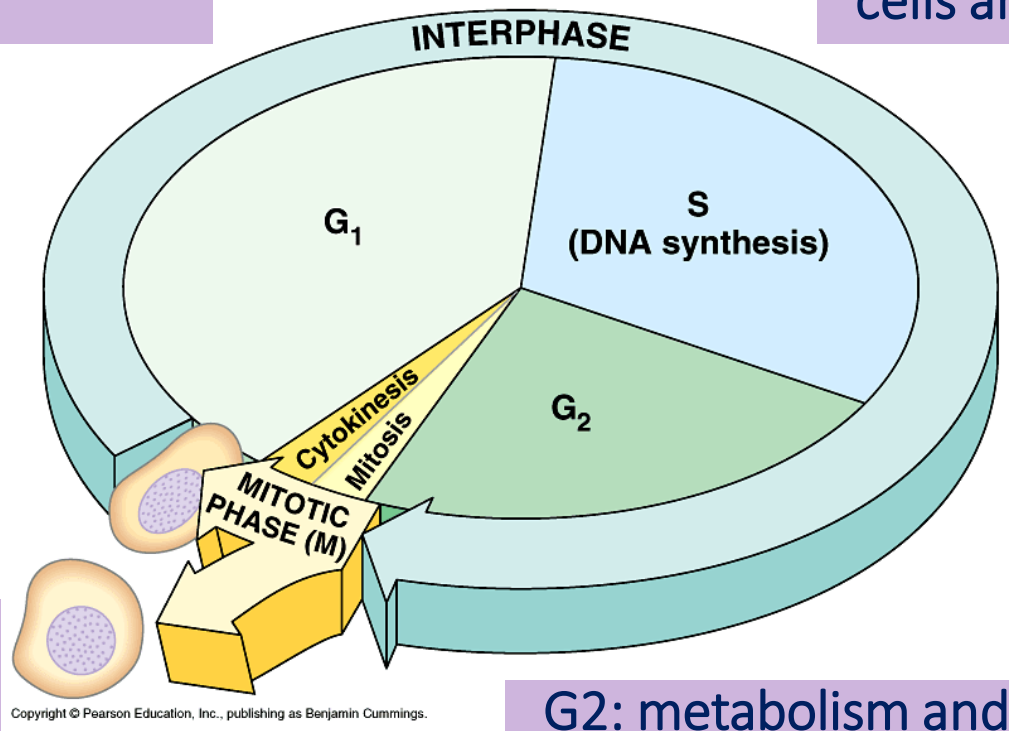


- A typical eukaryotic cell cycle divides ~every 24 hours.
- Mitosis and cytokinesis = ~1 hour
- Interphase: cell growth and DNA replication occur in an orderly manner in preparation for cell division.
- Zygote: no G1 or G2, but rapid S and M phases
- Some cells (nerve cells) enter a quiescent stage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

# Phases of cell cycle

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

S: DNA replication; cells are 2-4n

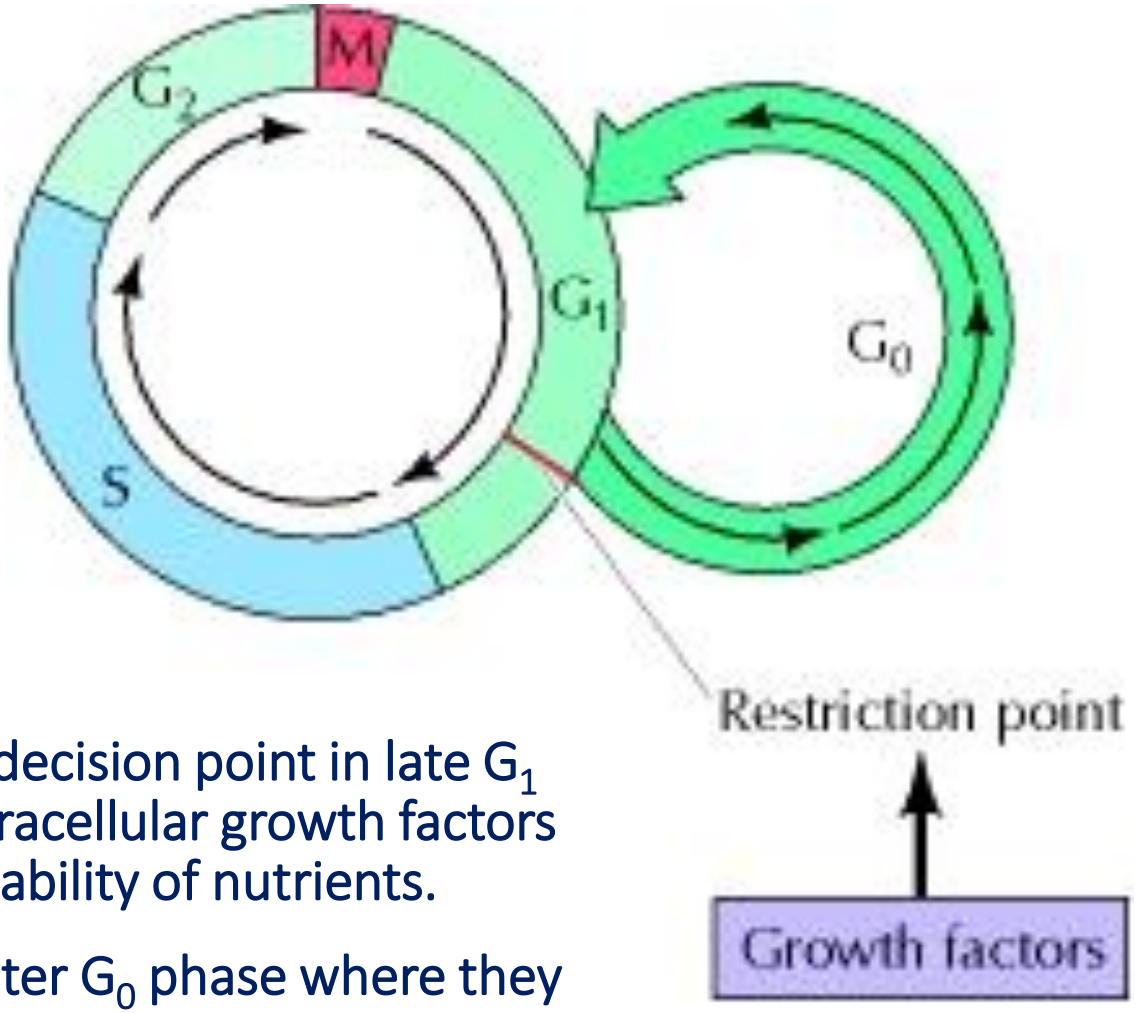





M: chromosomal segregation, nuclear and cell division (4n)

G2: metabolism and cell growth; cells are 4n

# Regulation of cell cycle

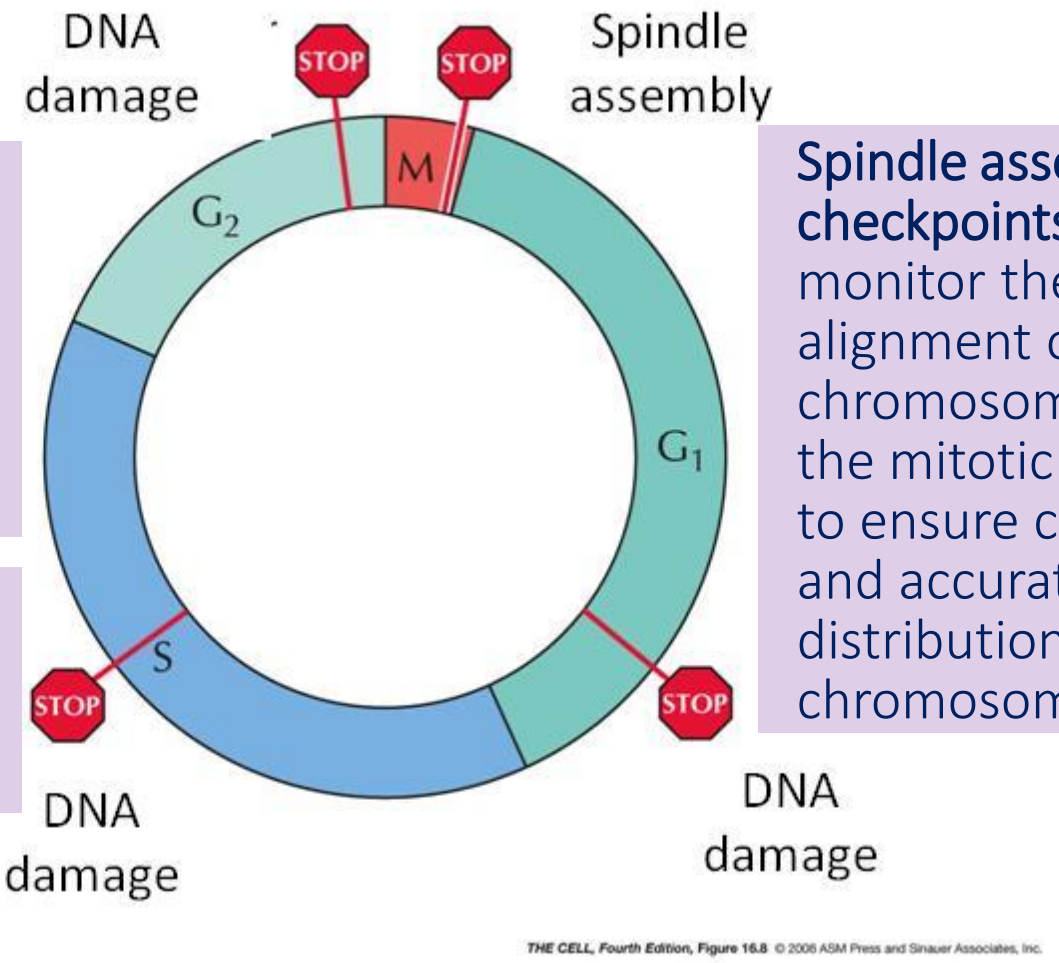



- Restriction point: a decision point in late $G_1$ regulated by the extracellular growth factors rather than the availability of nutrients.
- If not there, cells enter $G_0$ phase where they are metabolically active without growth.

# 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

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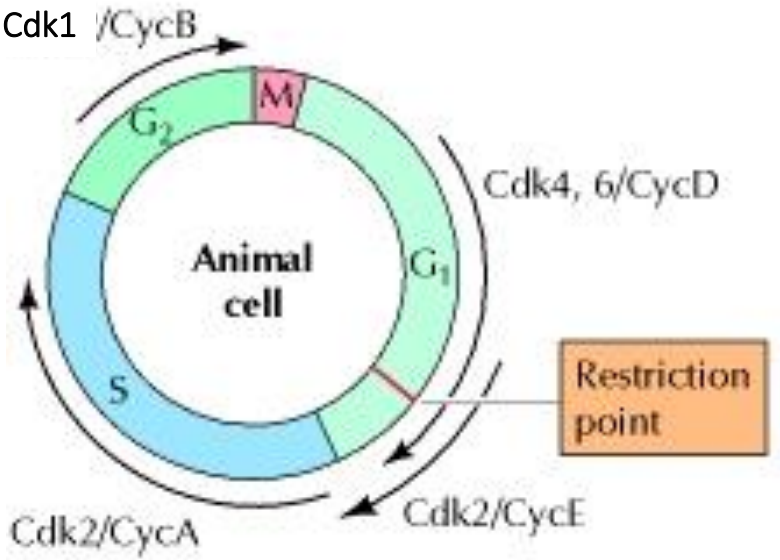
**Spindle assembly checkpoints** monitor the alignment of chromosomes on the mitotic spindle to ensure complete and accurate distribution of chromosomes.

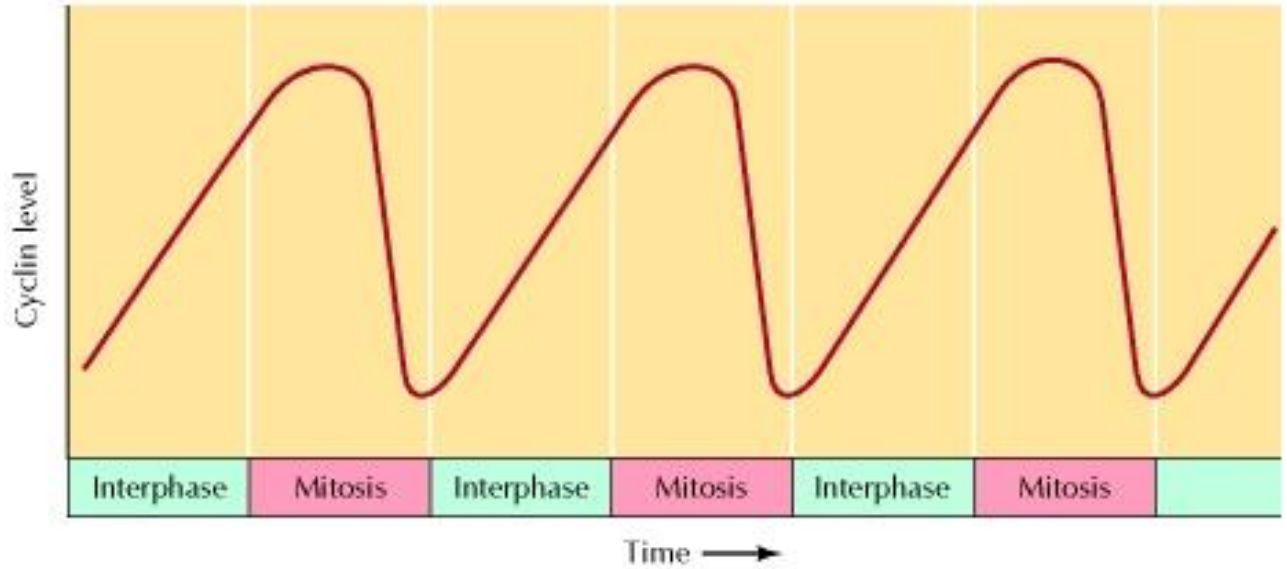
# Regulators of cell cycle

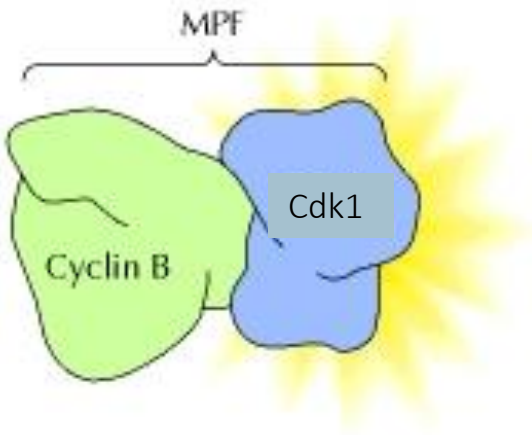
Cyclins are proteins that accumulate throughout the interphase and are rapidly degraded toward the end of mitosis.

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

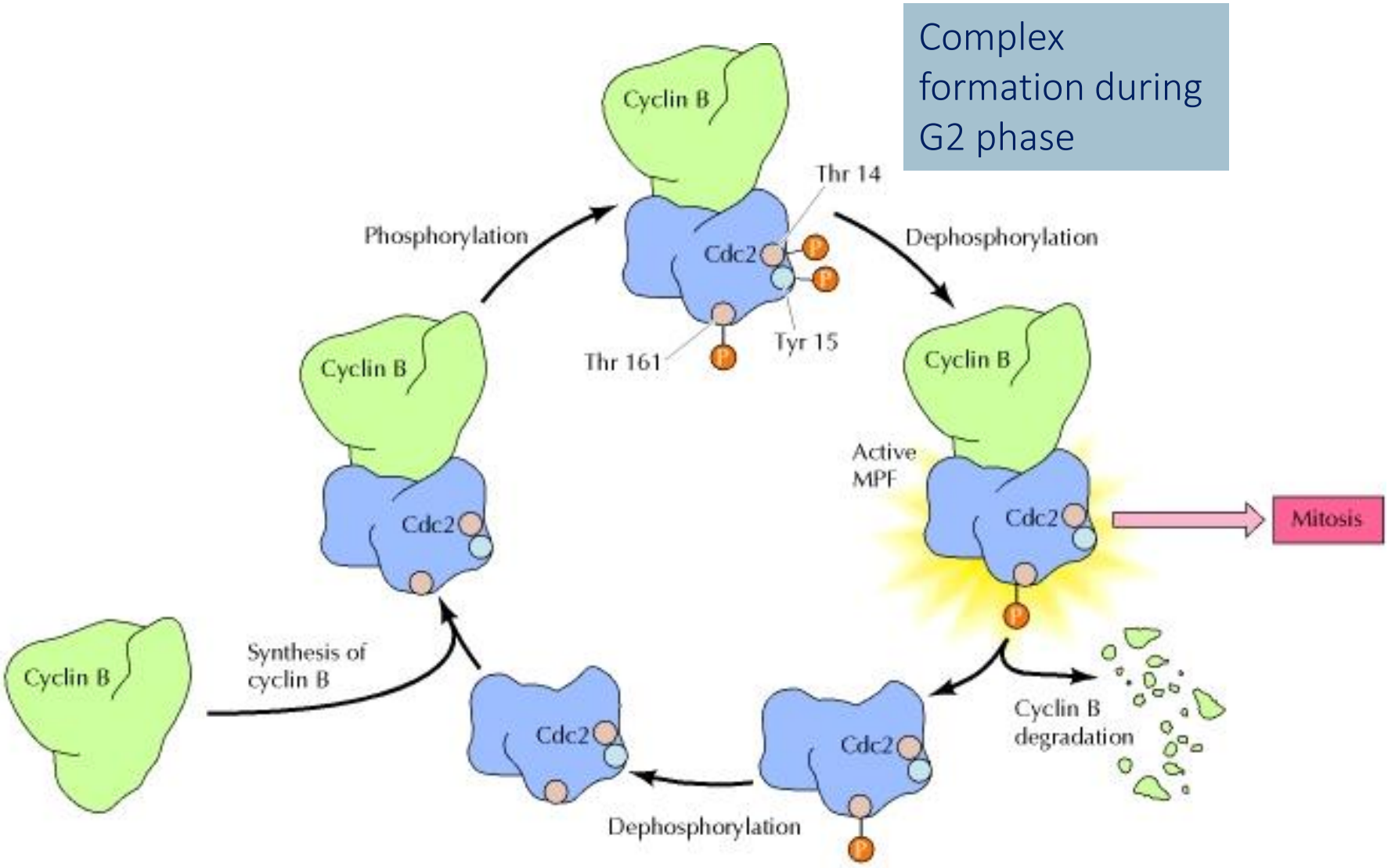
Cdk inhibitors: inhibit Cdk activity



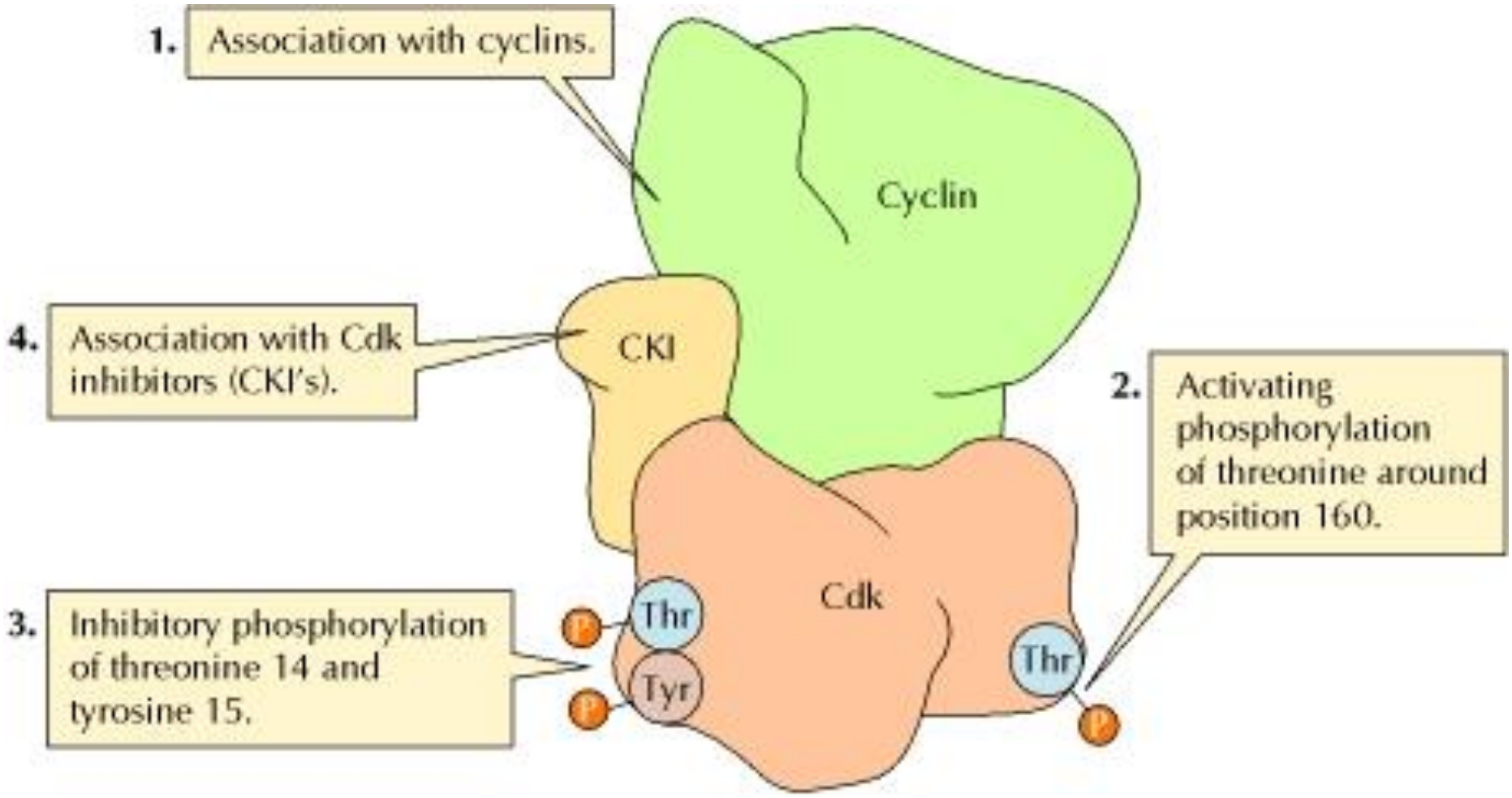



# Regulation of cell cycle progression



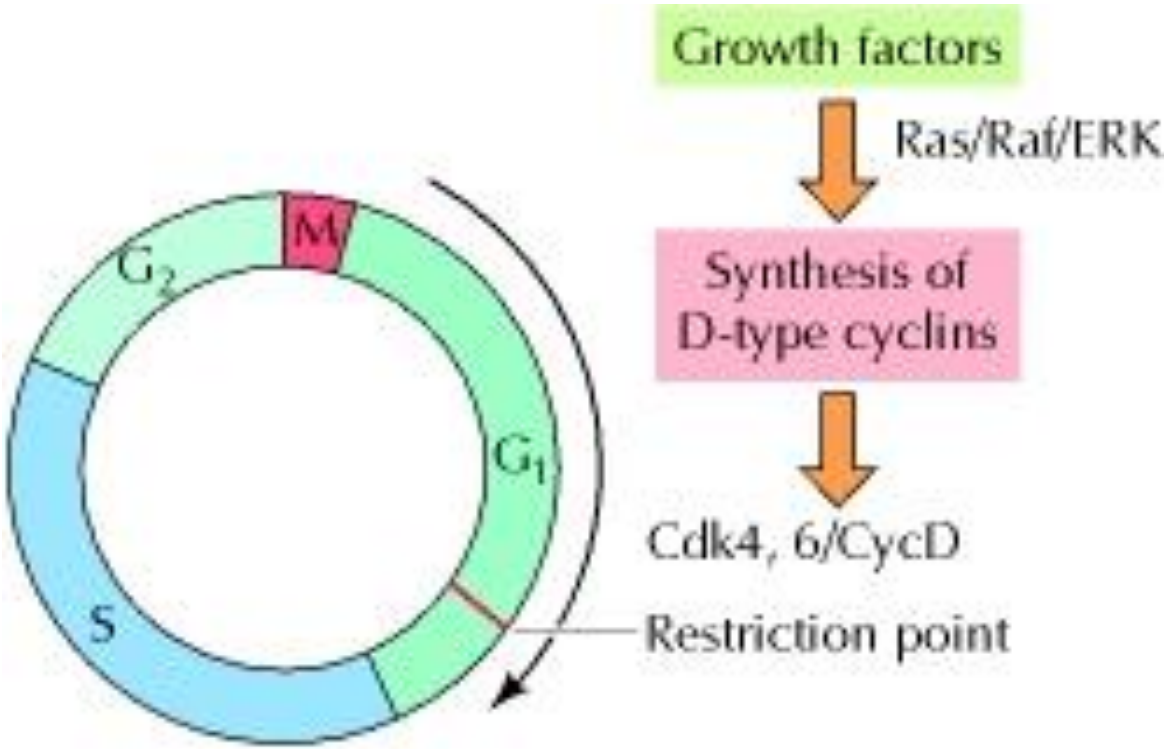
# Mechanisms of Cdk regulation



# 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.

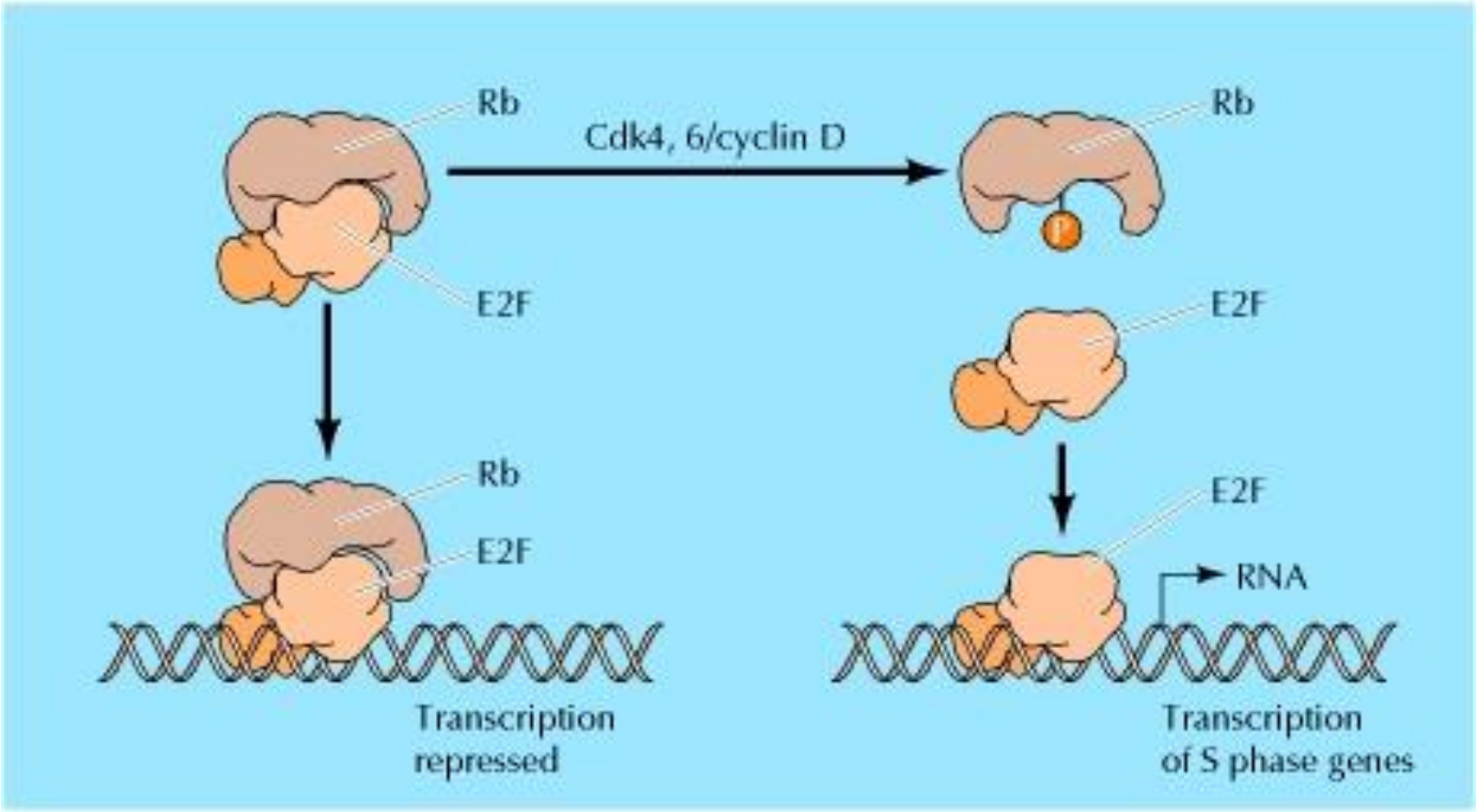
Defects in cyclin D regulation lead to the loss of growth regulation that is characteristic of cancer cells.



# 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.

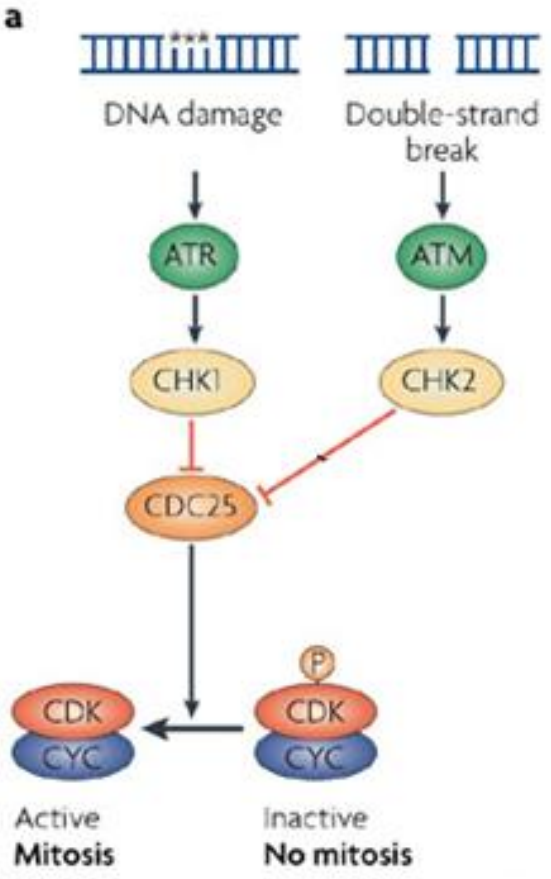


# Cell cycle arrest by DNA damage

- 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.

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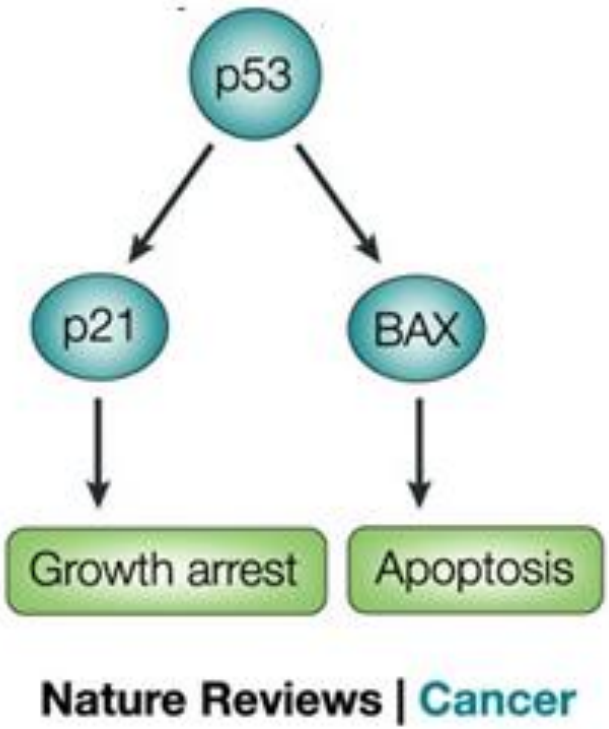
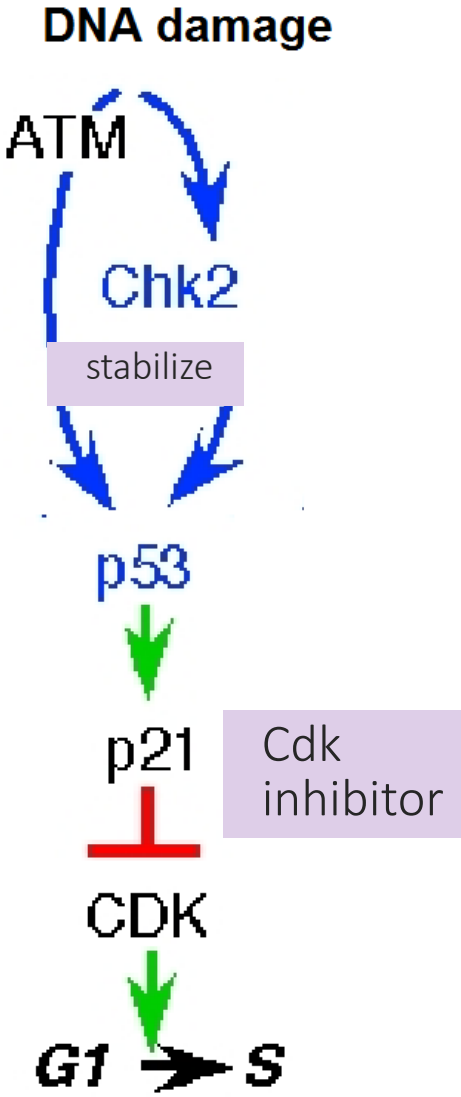
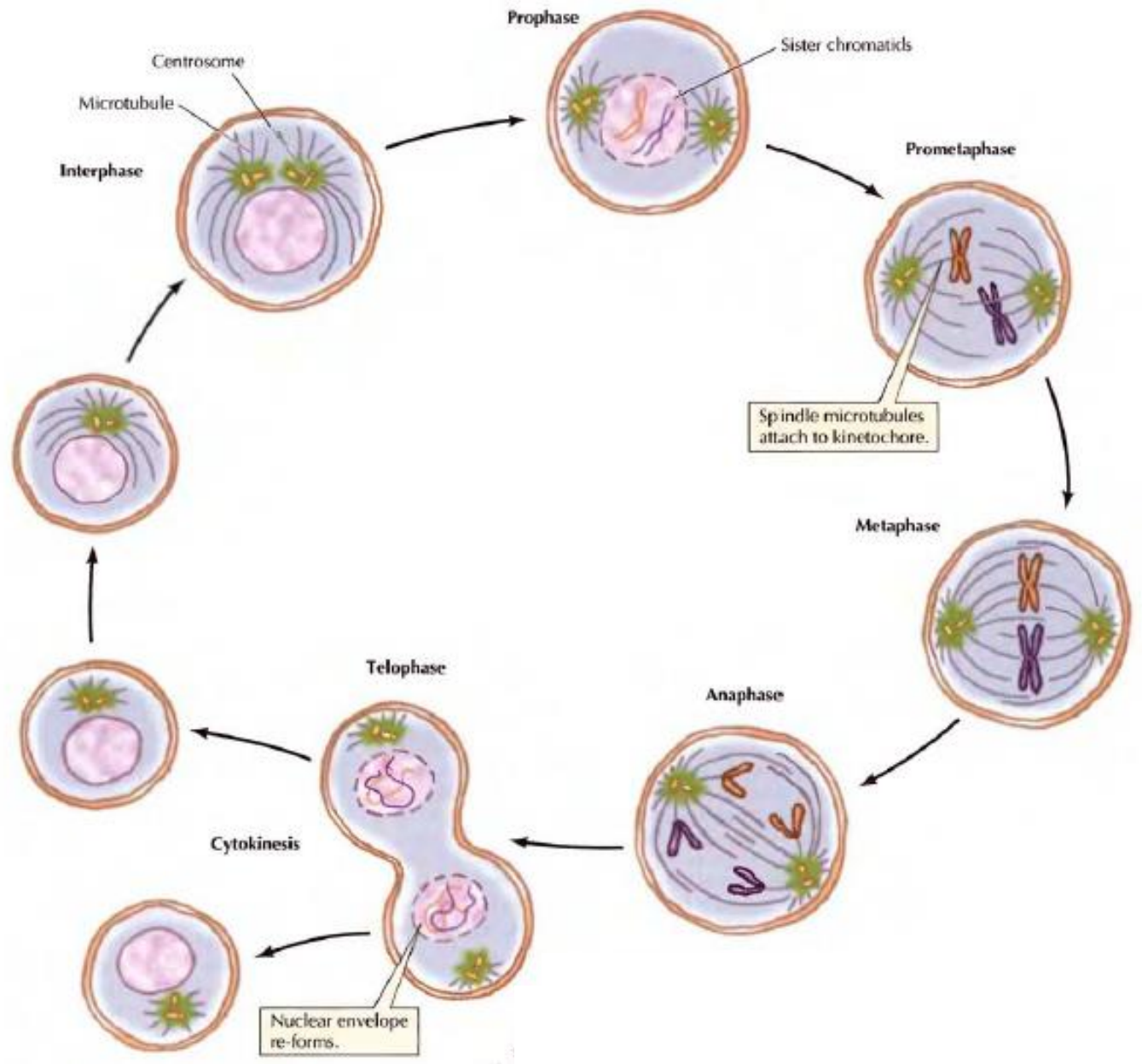
# Role of p53 in cell cycle arrest




- 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

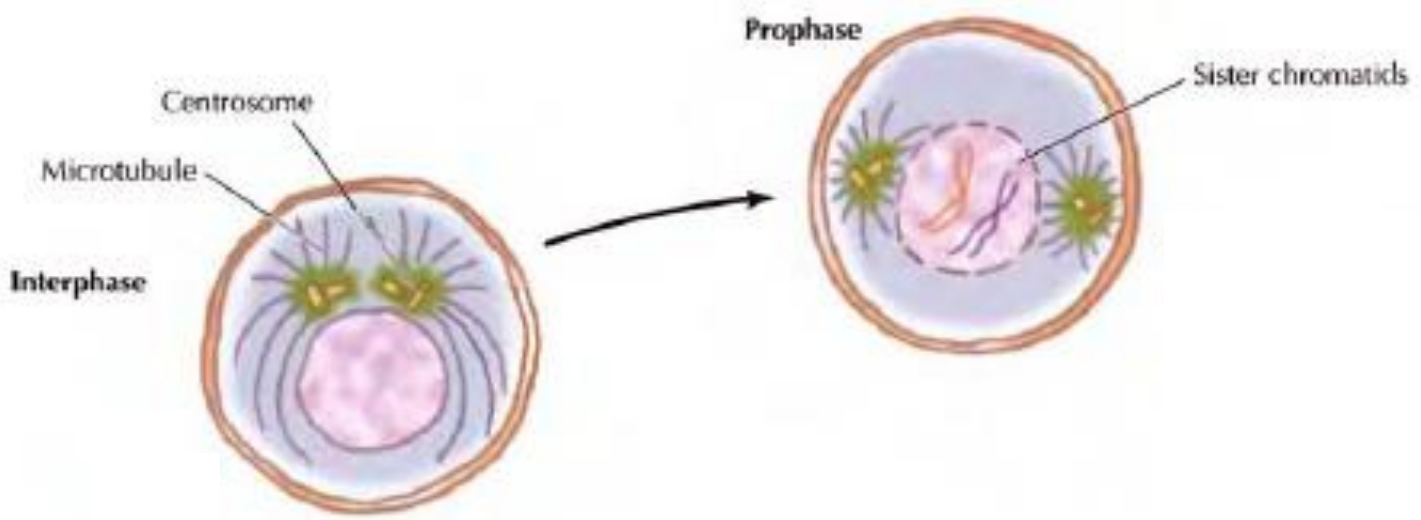


# Phases of Cell Division



# Phases of Cell Division

## Prophase

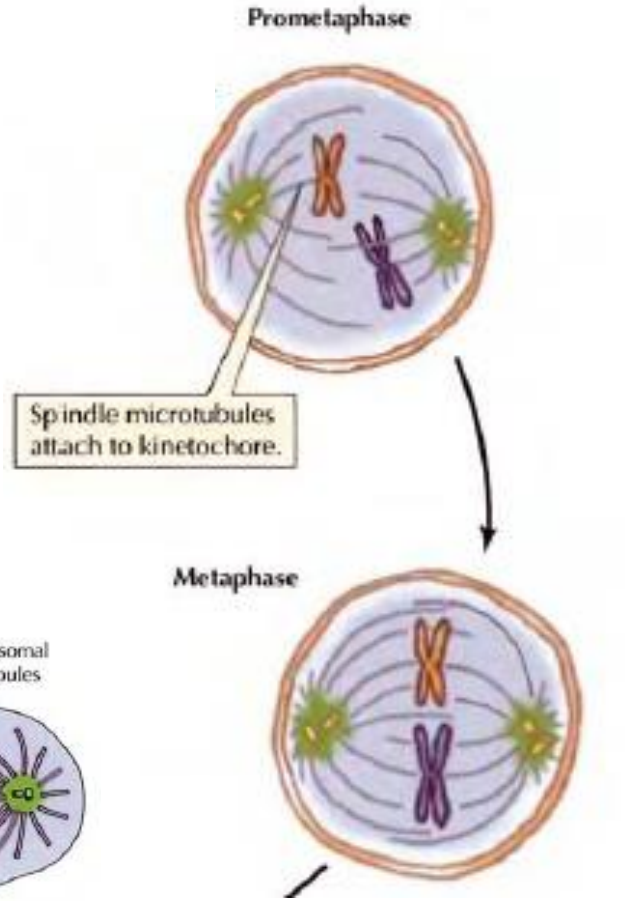


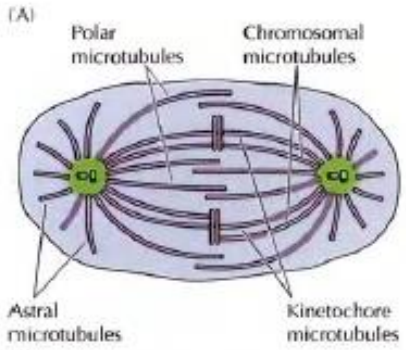

- Condensed chromosomes held by centromeres, condensation to allow separation by spindle later on without being broken or twisted around each other
- Centromere is a DNA sequence to which proteins bind to form kinetochore that is the site of spindle attachment
- Centromeres duplicate during interphase and separate to opposite sides of the nucleus in prophase to serve as poles of mitotic spindle
- Spindle pole bodies are embedded in the nuclear envelope

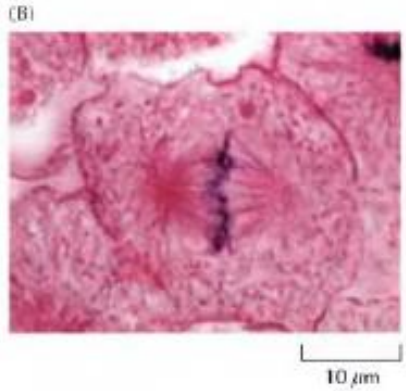
# Phases of Cell Division

## Prometaphase and metaphase

- Attachment of microtubules of the mitotic spindle to kinetochores of condensed chromosomes
- The kinetochores of sister chromatids orient in opposite directions to attach to the microtubules of different poles of the spindle
- Chromosomes shuffle back and forth until they align on metaphase plate and starting metaphase



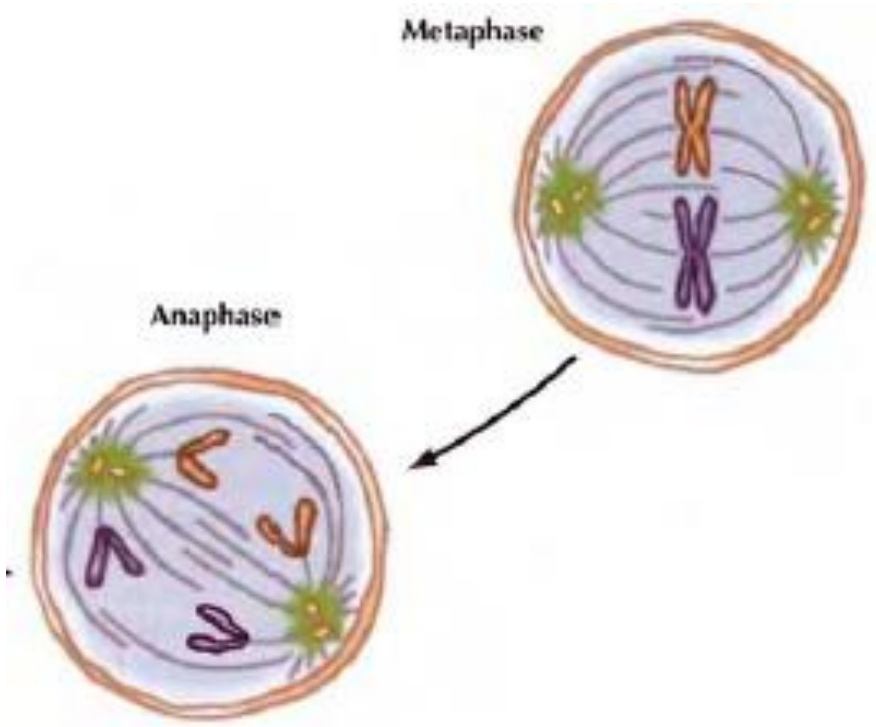



# Phases of Cell Division

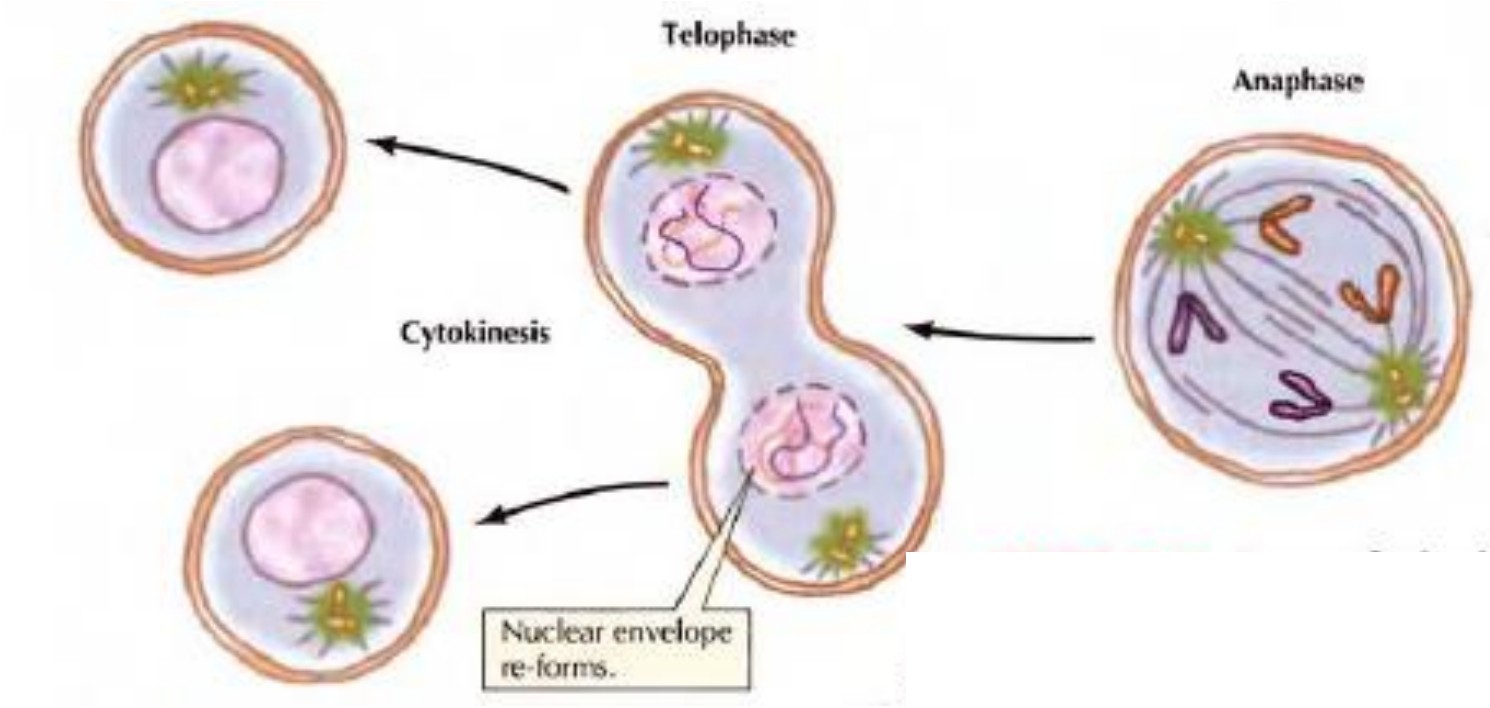
## Anaphase

- Anaphase is triggered by the breakage of the link between sister chromatids to allow their movement to opposite poles of the spindle



# Phases of Cell Division

## Telophase




- Nuclei reform and chromosomes decondense
- After division of nuclei (mitosis), division of the cell (cytokinesis) occurs

# Phases of Cell Division

## Cytokinesis

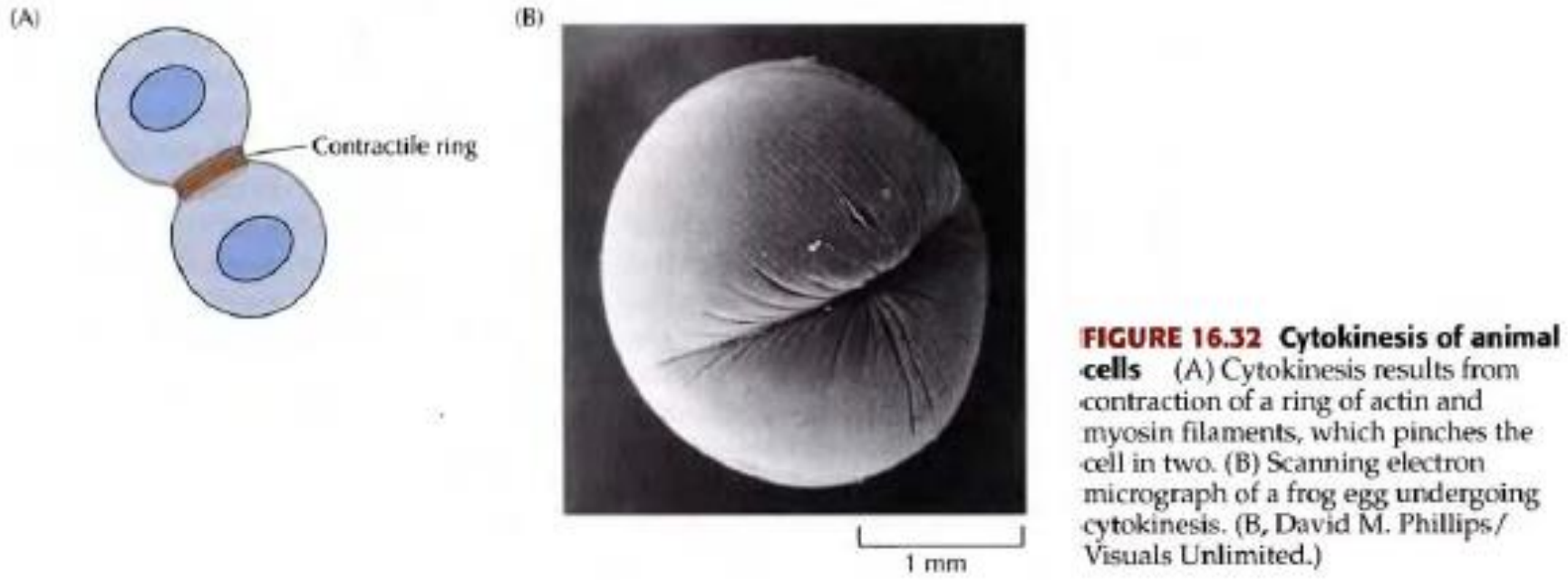



**FIGURE 16.32 Cytokinesis of animal cells** (A) Cytokinesis results from contraction of a ring of actin and myosin filaments, which pinches the cell in two. (B) Scanning electron micrograph of a frog egg undergoing cytokinesis. (B, David M. Phillips/ Visuals Unlimited.)

- Is mediated by contractile ring of actin and myosin formation

# Holding sister chromatids together

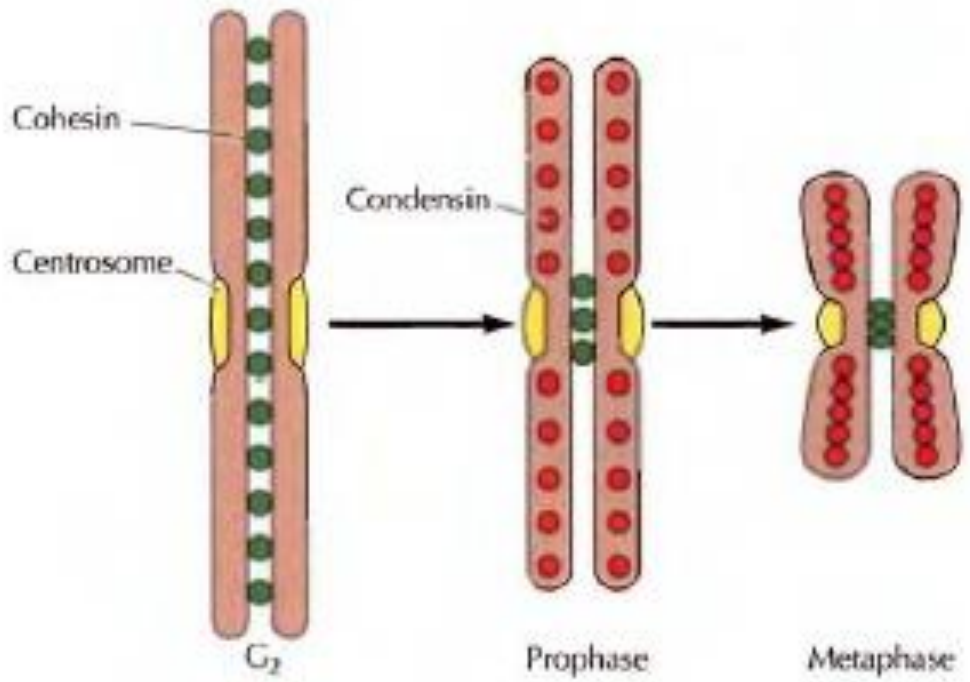
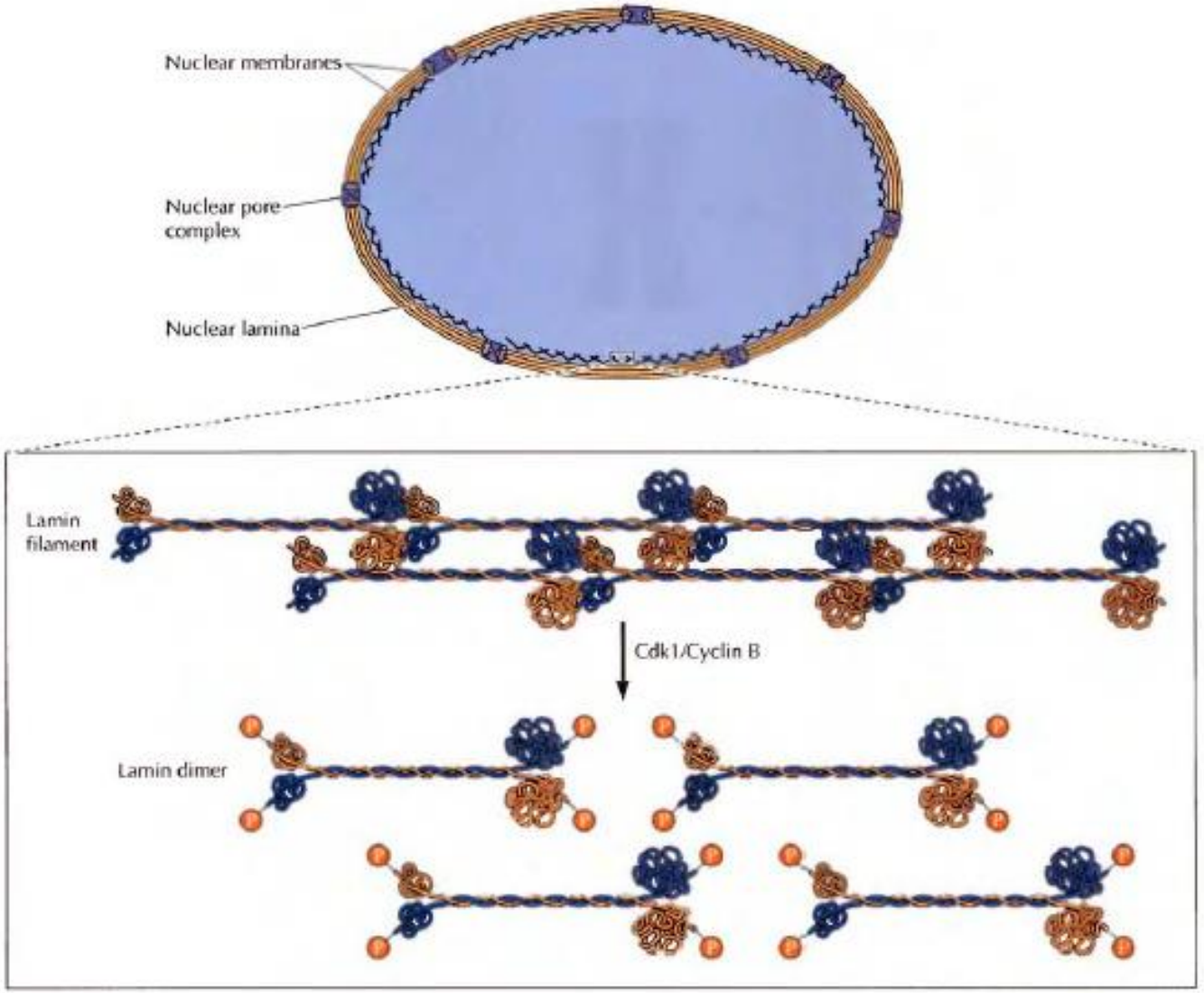



**FIGURE 16.26 The action of cohesins and condensins** Cohesins bind to DNA during S phase and maintain the linkage between sister chromatids following DNA replication in S and $G_2$. As the cell enters M phase, the cohesins are replaced by condensins along most of the chromosome, remaining only at the centromere. Phosphorylation by Cdk1 activates the condensins, which drive chromatin condensation.

# Breakdown of nuclear envelope

- Phosphorylation by Cdk1 results in:
- Nuclear membranes fragmentation
- Pore complex dissociation
- Nuclear lamina depolymerization



# Apoptosis (Programmed cell death)

Is a normal physiological form of cell death.

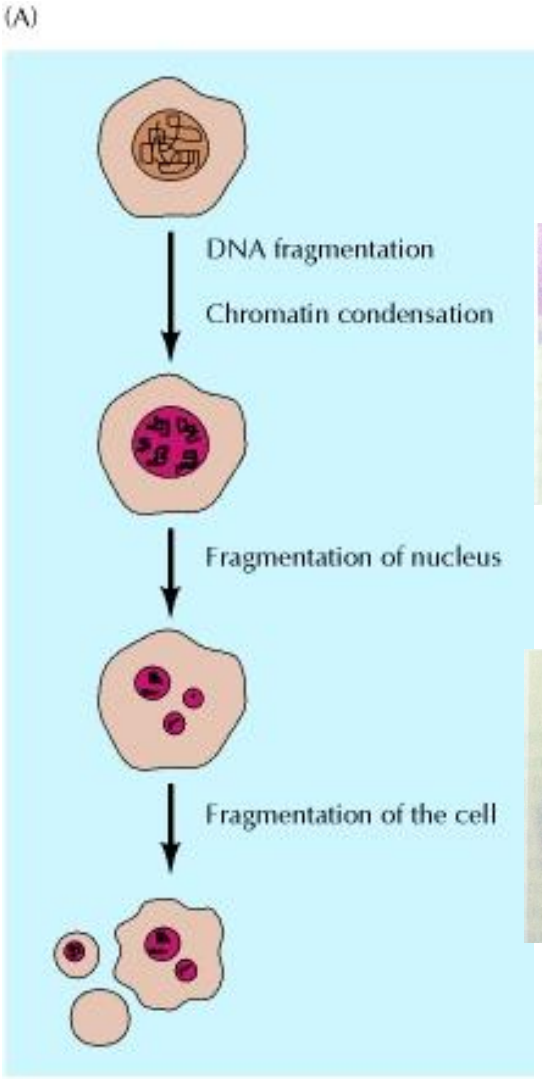
Has a key role in the **maintenance of adult tissues and in embryonic development.**

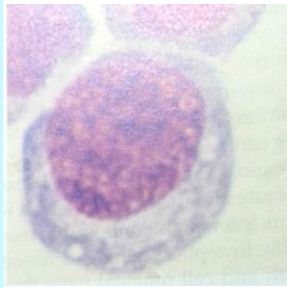
- Renewal of $5 \times 10^{11}$ blood cells a day
- elimination of nerve cells with faulty connection
- Elimination of damaged and potentially dangerous cells
  - *Cells with DNA damage*
  - *Virus-infected cells*

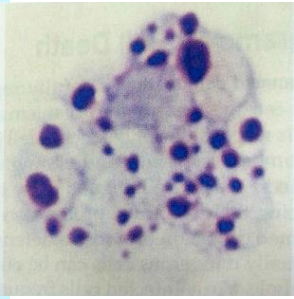
How apoptosis is stimulated?
Intrinsic pathway: simulated by DNA damage
Extrinsic pathway: stimulated by signals from other cells

# Features of Apoptosis

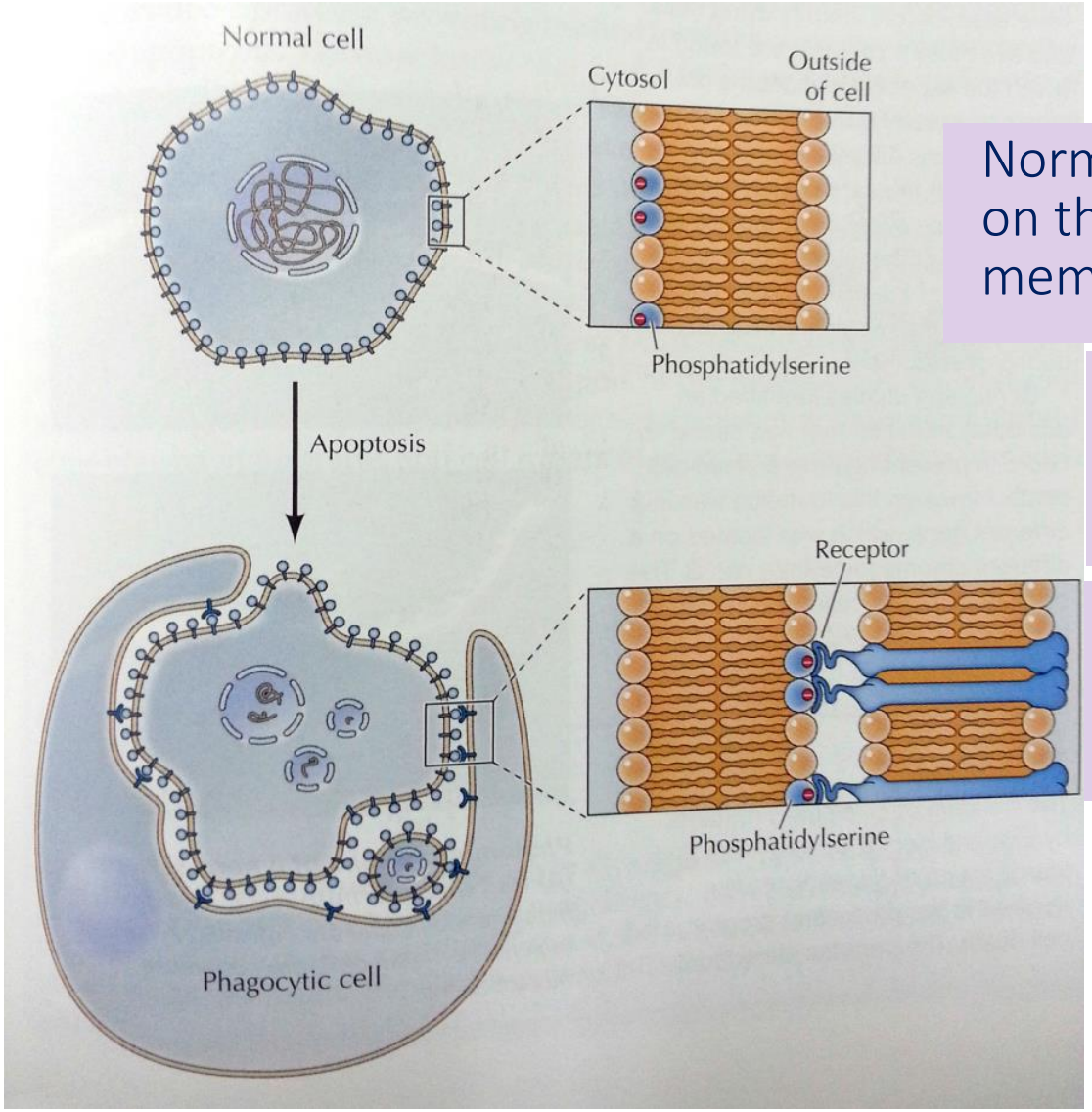
- Fragmentation of chromosomal DNA
- Chromatin condensation
- Breaking up nucleus into small pieces.
- Cell shrinkage
- Cell fragmentation (apoptotic bodies)
- Phagocytosis by macrophages and neighboring cells
- In contrast, cell necrosis results in membrane damage, enlargement of cells, release of intracellular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





# Role of phosphatidylserine (PS)




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

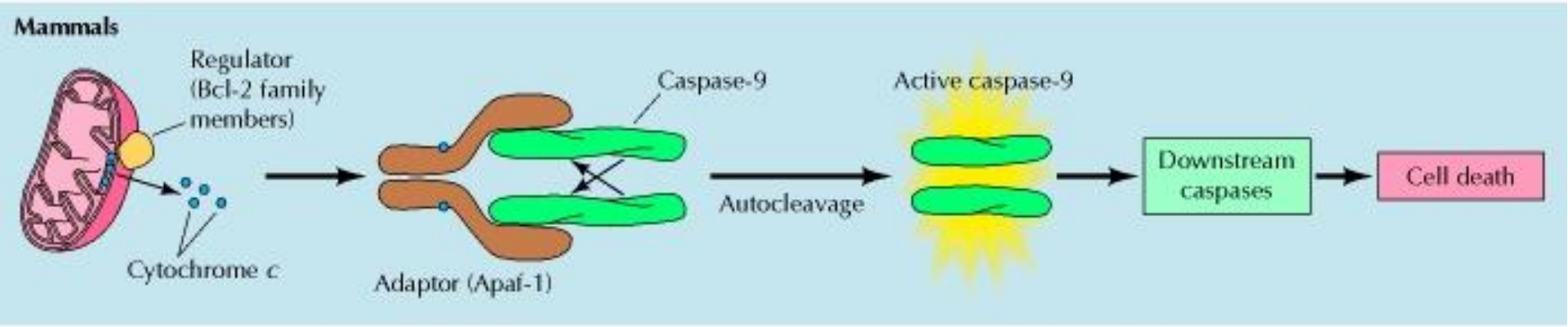
During the initiation of apoptosis, PS is flipped to the outer leaflet.

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

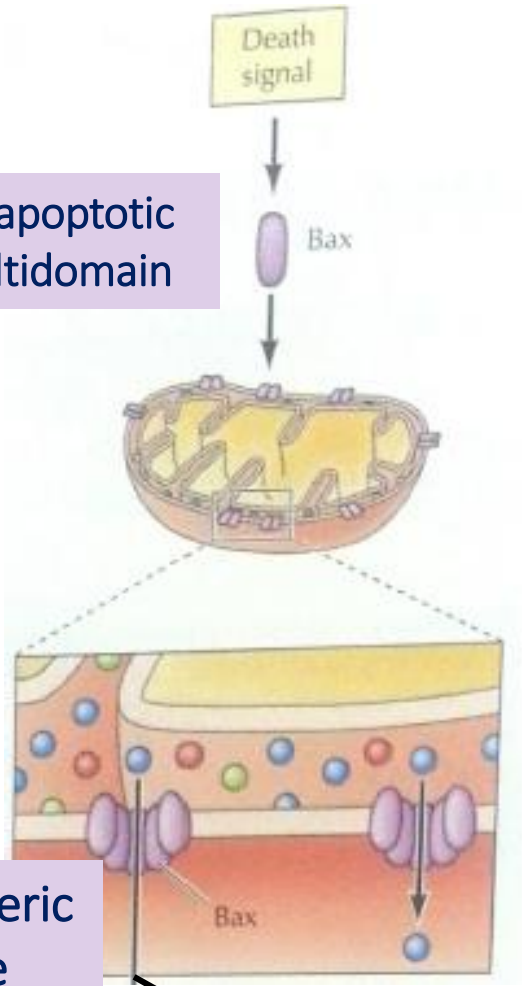
Release of cytochrome *c* from mitochondria activates caspase-9, which then activates downstream caspases to induce apoptosis.

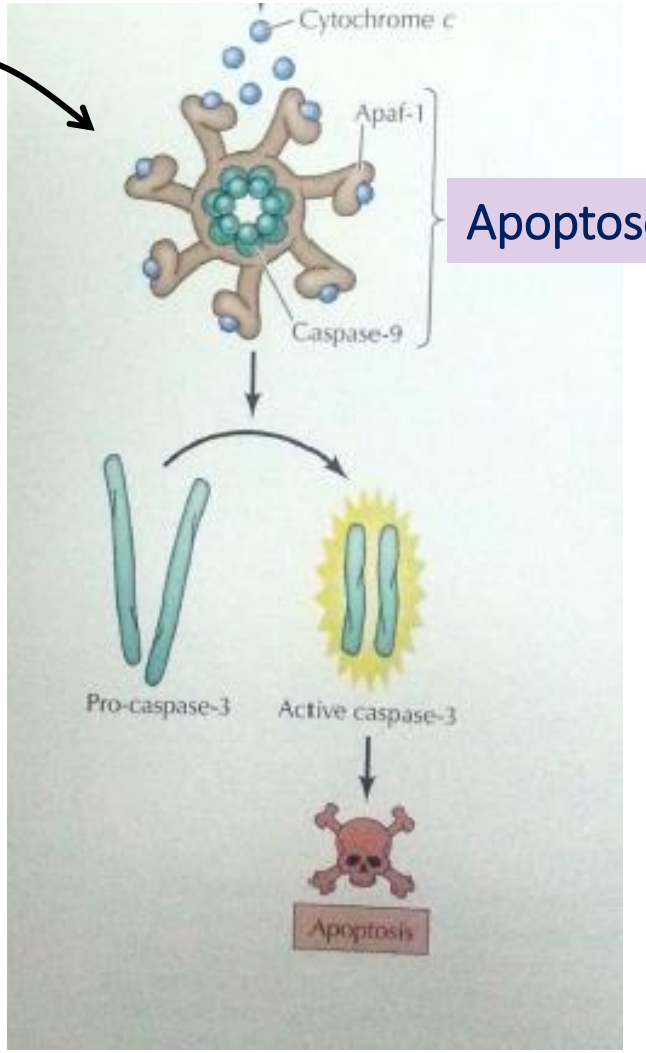


# How is cytochrome c released form mitochondria?

Proapoptotic multidomain

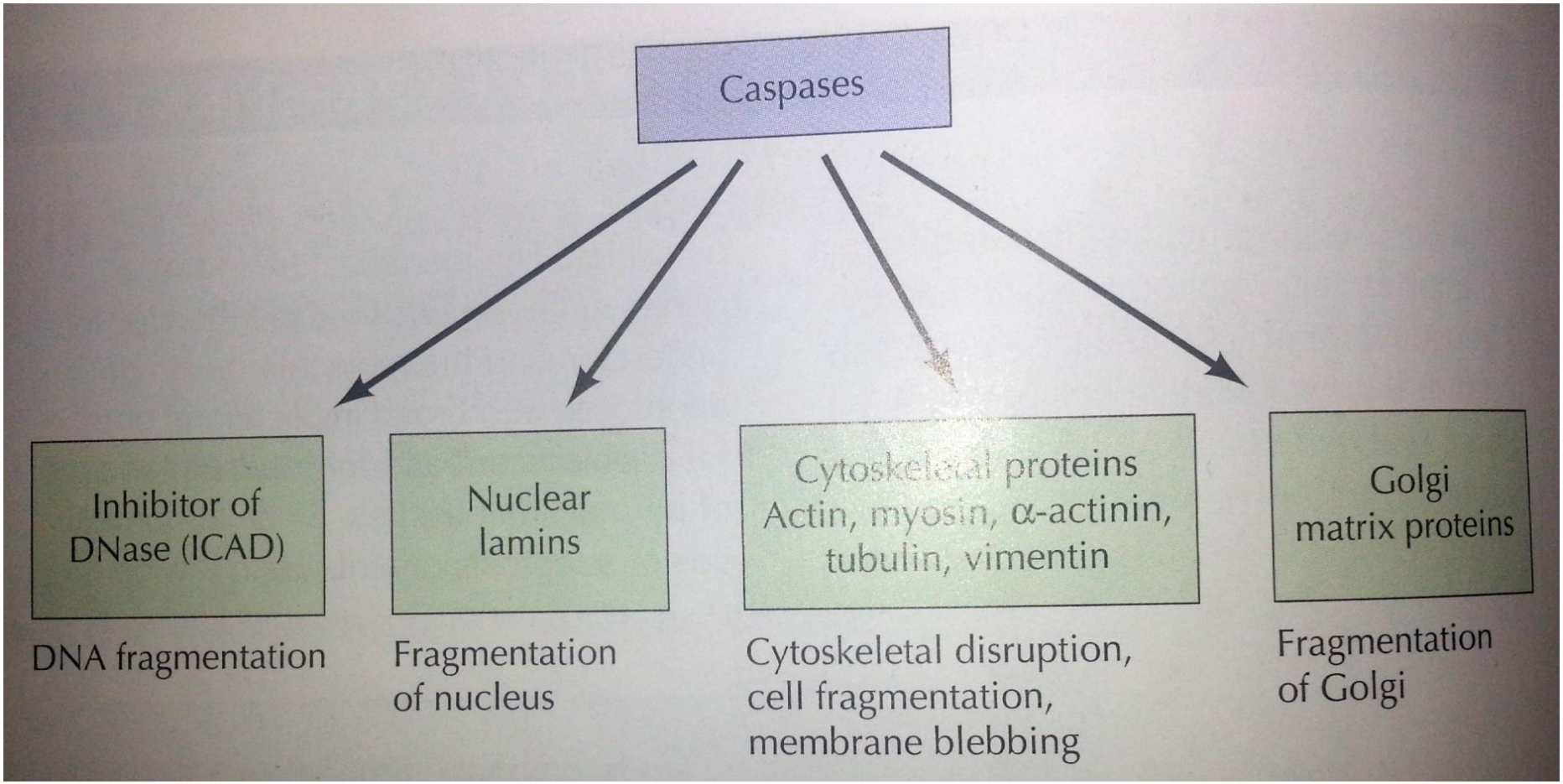
Oligomeric pore formation




Apoptosome

# Caspases roles



# Bcl-2 family


**Anti-apoptotic Bcl-2 proteins**


**Multi-domain pro-apoptotic effectors**


**Pro-apoptotic BH3-only**

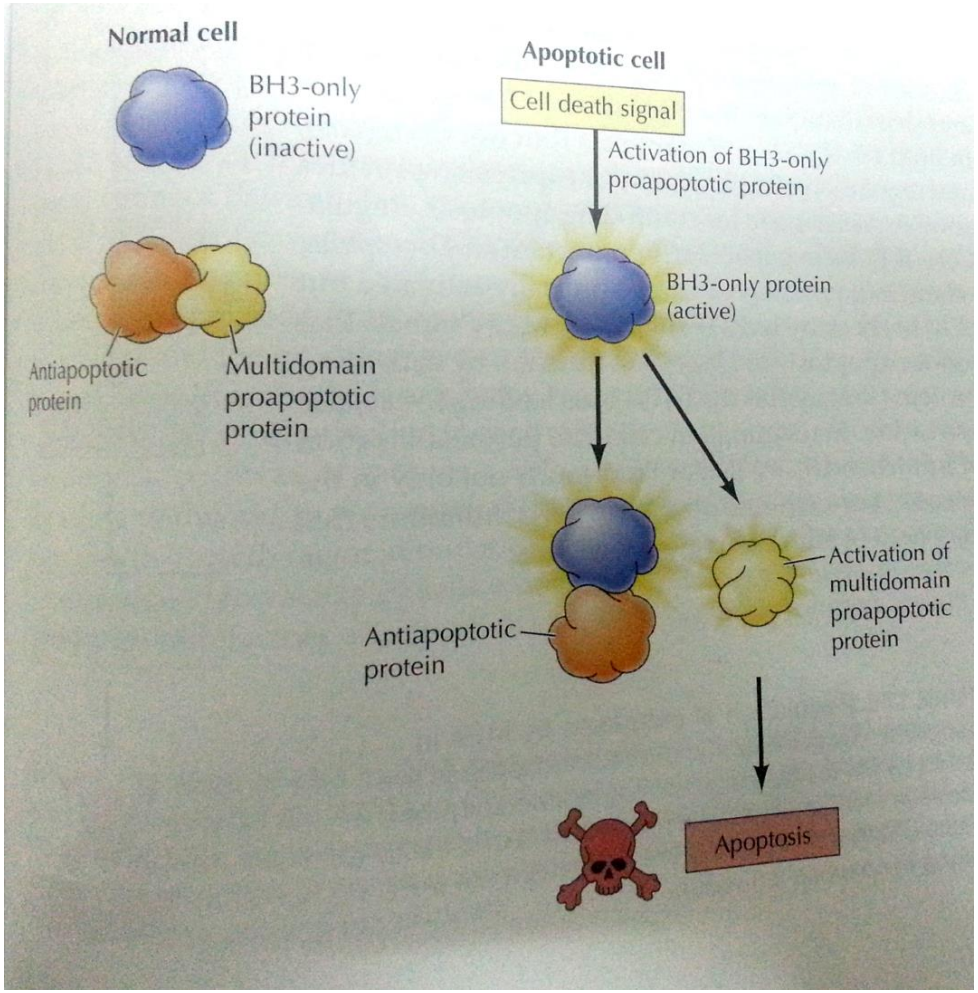
- There are three classes of Bcl-2 according to their domains and apoptotic effect:

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.

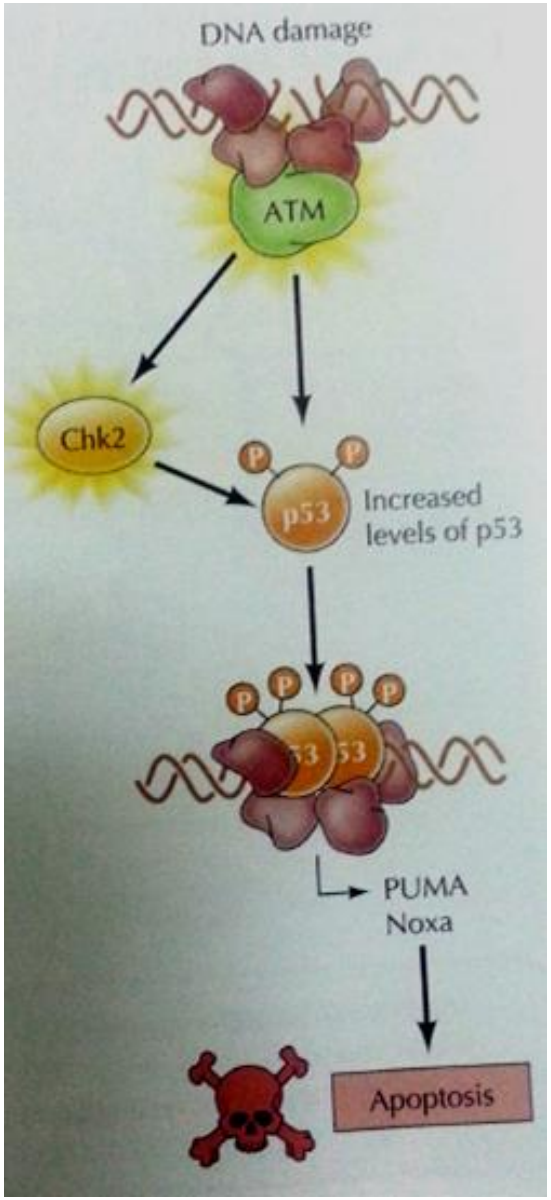
- **Death signals** activate the BH3-only protein, which inactivates the antiapoptotic proteins resulting in the release and activation of the multi-domain proapoptotic protein.



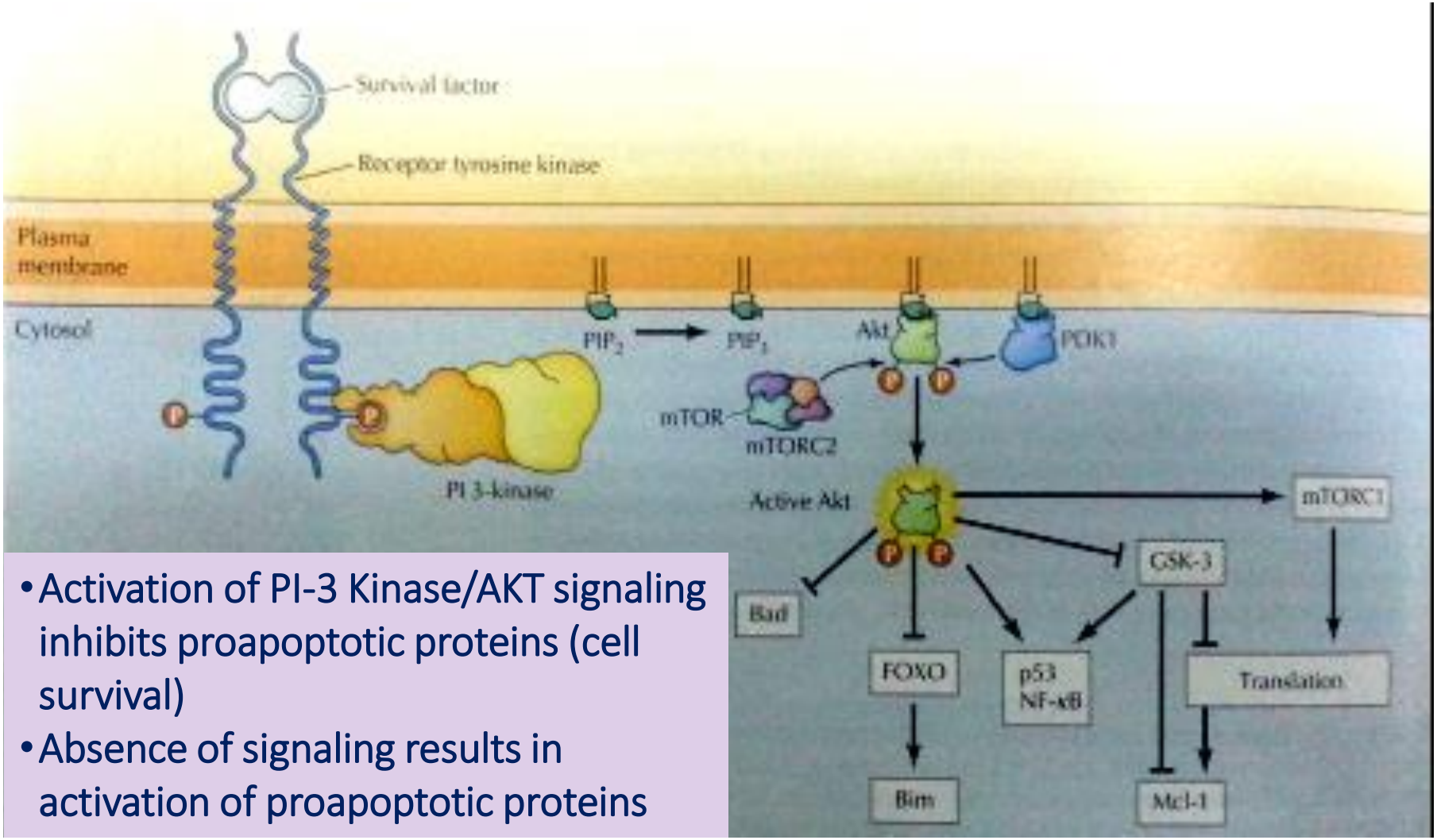
# Internal pathway

ATM/Chk2 signaling stimulates p53 phosphorylation

Phosphorylated p53 induce the expression of BH3-only proteins.

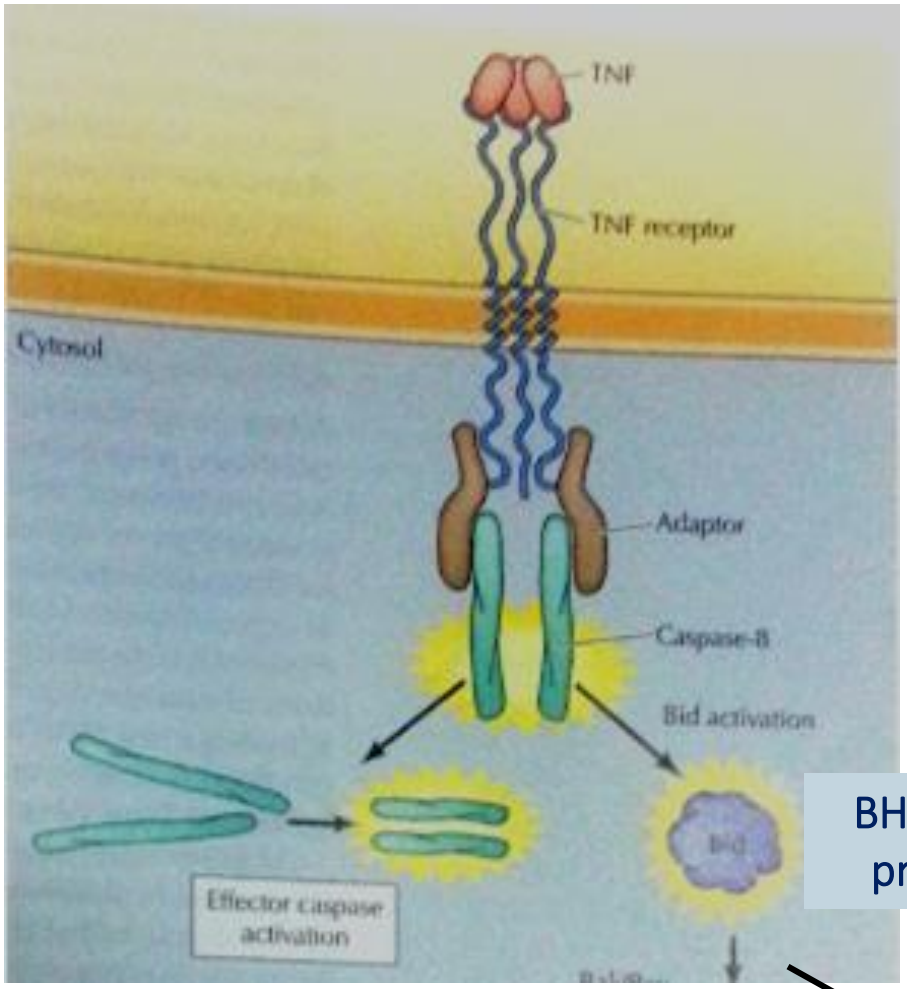


# External signaling (1): pro-survival

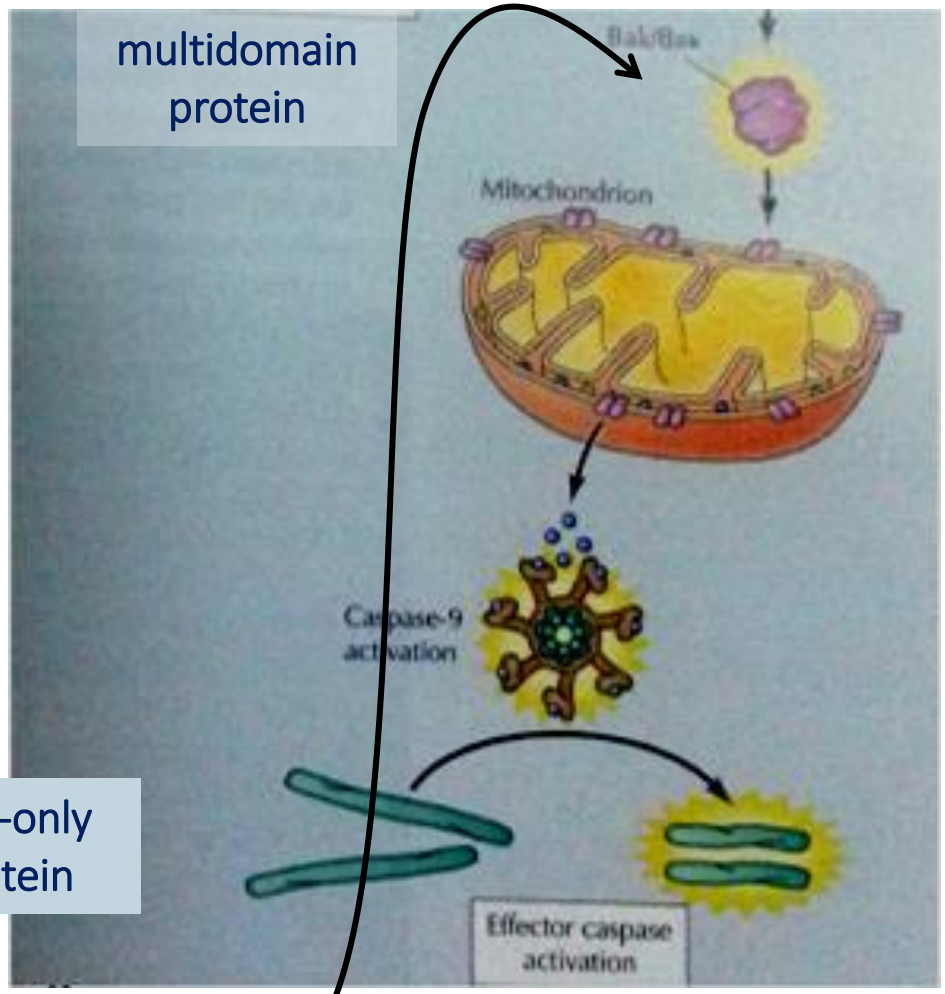



- Activation of PI-3 Kinase/AKT signaling inhibits proapoptotic proteins (cell survival)
- Absence of signaling results in activation of proapoptotic proteins

# External signaling (2): pro-death



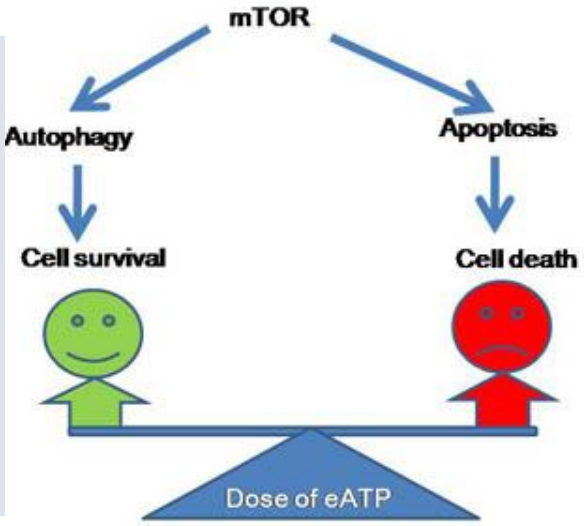

BH3-only protein

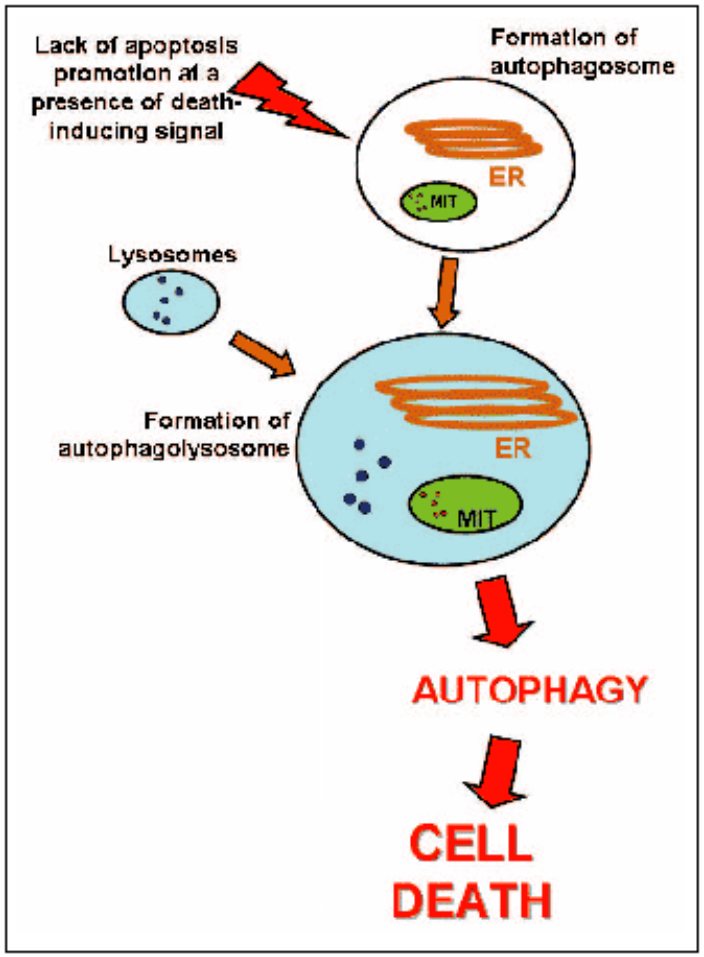


# Autophagy

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