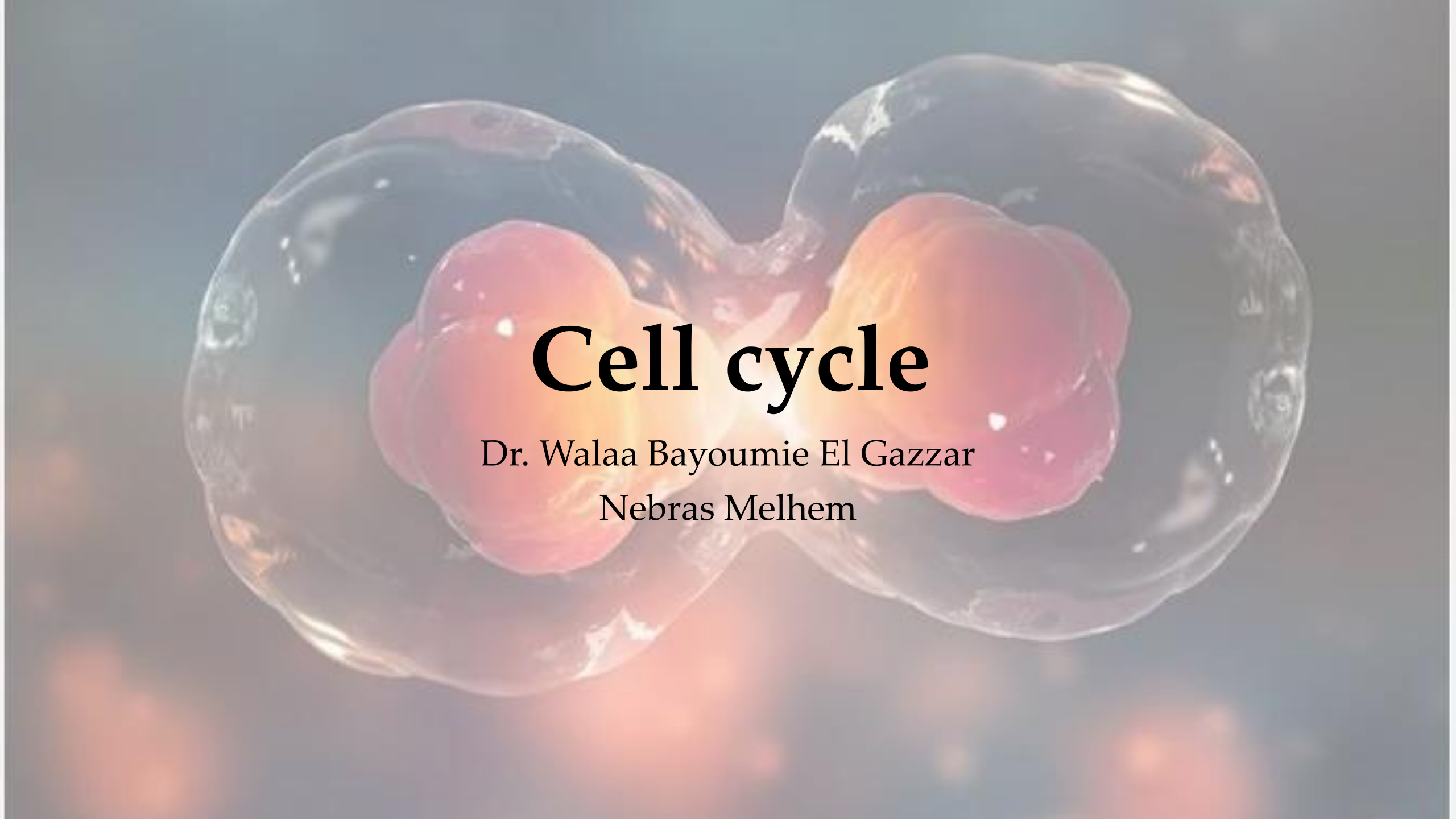


Cell cycle

Dr. Walaa Bayoumie El Gazzar

Nebras Melhem

Cell Cycle

- The term cell cycle describes the **events** that lead to **completion of cell division and formation of two daughter cells as a result of mitosis.**

- **The Resting phase (G_o)**(i.e. Gap zero) represents the **time spent by a cell prior to preparation for active division**.

- Some cells will enter the G_o and may even remain in this phase, a state in which the cells are **viable functional** but are non-proliferative e.g. neuronal cells.

The Cell Cycle

Interphase

The cell grows and copies its DNA

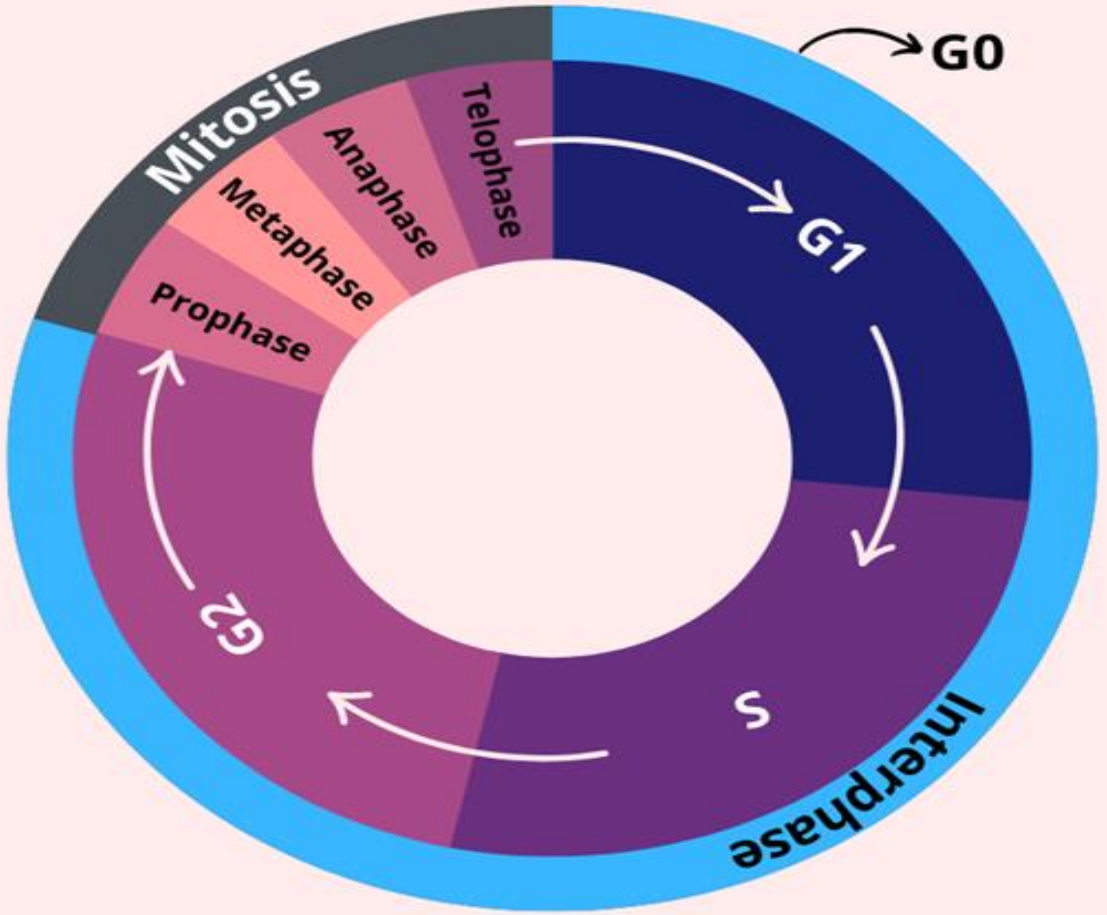
- **G_1**: Cell growth
- **S** : DNA synthesis
- **G_2:** More growth, preparation for mitosis

Mitosis

The cell divides its DNA and cytoplasm, forming two new cells

- **Prophase**
- **Metaphase**
- **Anaphase**
- **Telophase**

G_0: Resting state where the cell performs its functions and is not preparing to divide



Cell Cycle

The cell cycle is divided into 2 main phases:

1. Mitotic phase (M phase)
2. Interphase which is subdivided into:
   - Gap 1 (G1 phase)
   - Synthesis phase (S phase)
   - Gap 2 (G 2 phase)

- The high variability of cell cycle times is due to the variability of the G 1 phase of the cycle.

Cell Cycle Phases

In rapidly dividing cells, the **cell cycle takes about 24 hours** e.g. hematopoietic & cancer cells.

❖Events for each phase:

➢**G1 phase**:

- The duration of this phase is about **6-12 hours**.
- During this phase, RNA and proteins needed for cell division are synthesized.
  - Active RNA & protein synthesis.

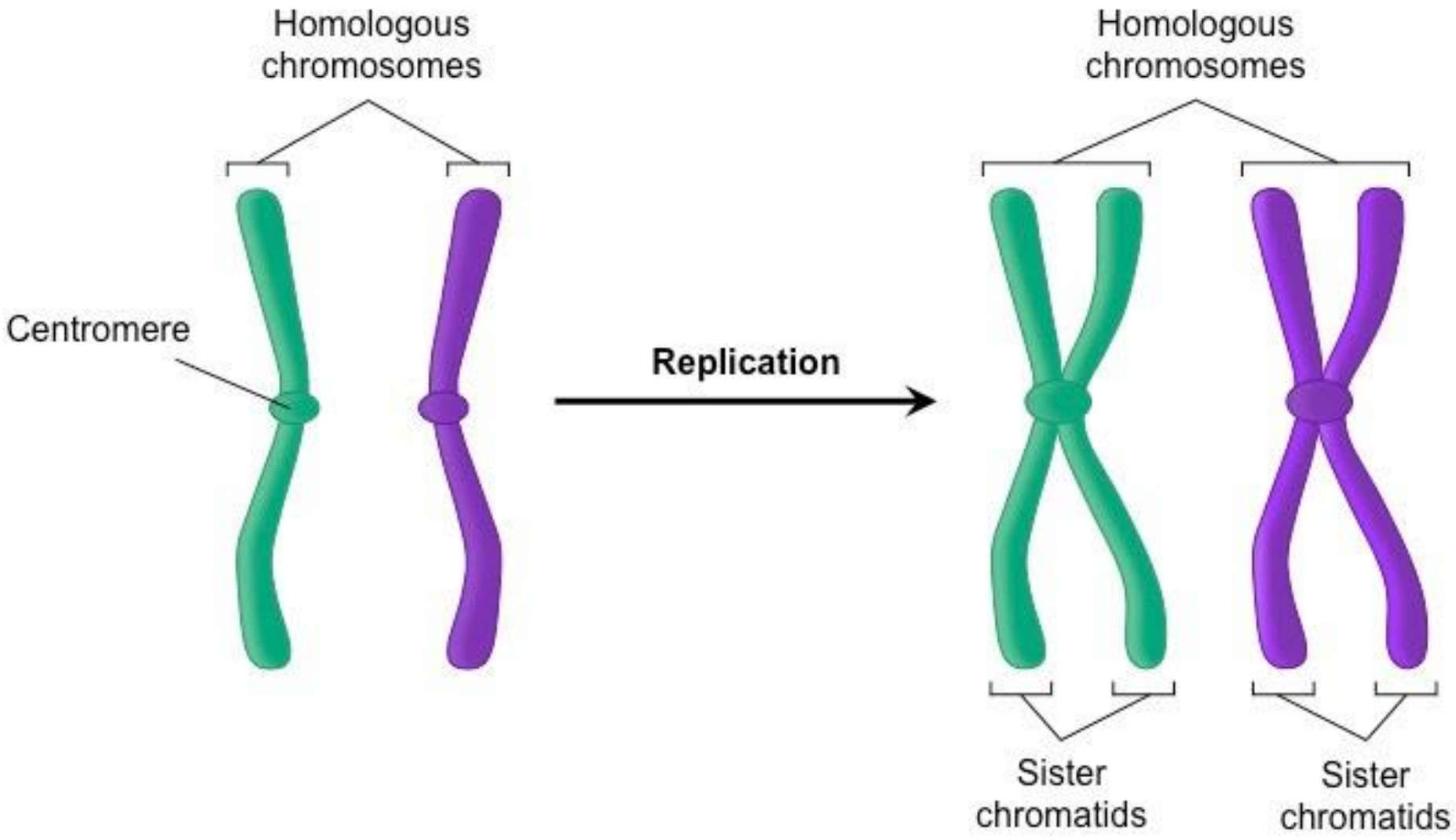
Cell Cycle Phases

➢ **S phase**:

- The duration of this phase lasts about **6 to 8 hours**.
- DNA is replicated (chromosomes are duplicated to become tetraploid).
- These events result in the formation of two sister chromatids attached at the centromere.

➢ **G2 phase**:

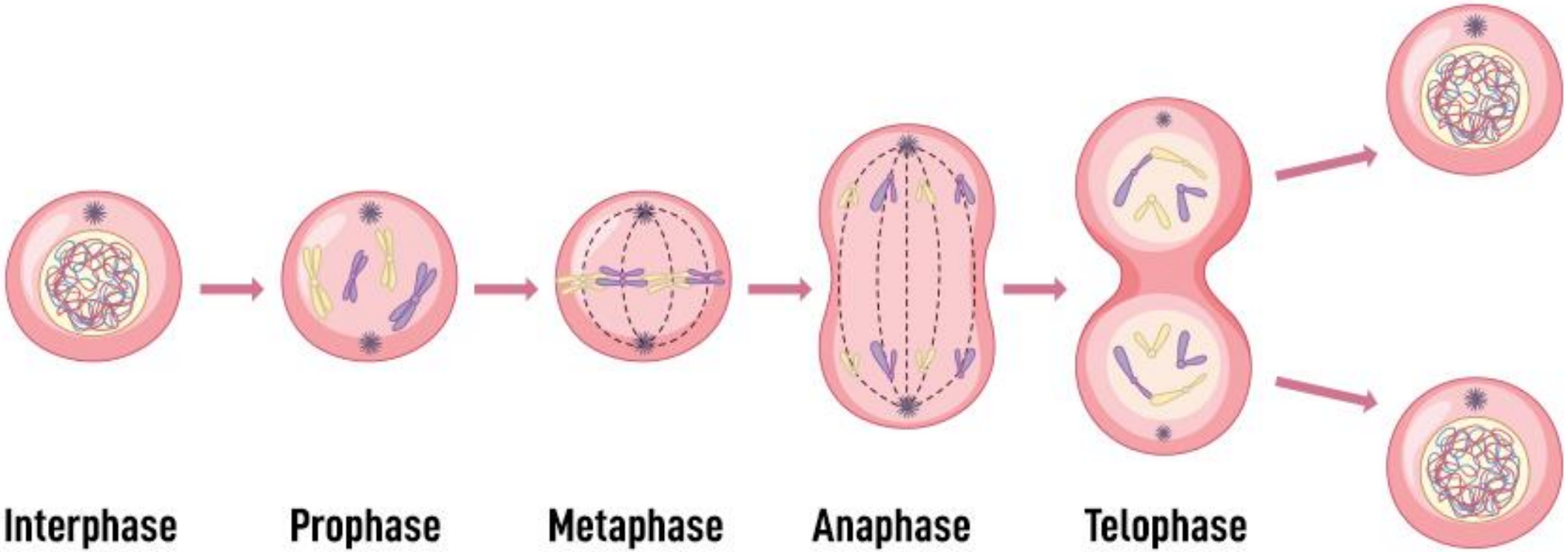
- The duration of this phase lasts about **4 to 5 hours**.
- It is a preparatory phase for M phase. So, **DNA repair occurs in this phase**.
- Also, RNA & protein synthesis are taking place as well as cytoplasmic enlargement. Most of the proteins synthesized are cytosolic proteins (needs to synthesize enough proteins for 2 cells).


Homologous chromosomes
Centromere
Replication
Homologous chromosomes
Sister chromatids
Sister chromatids

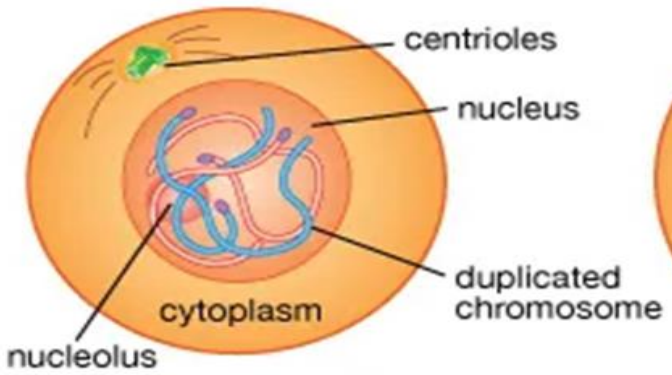
Cell Cycle Phases

➢**M phase**:

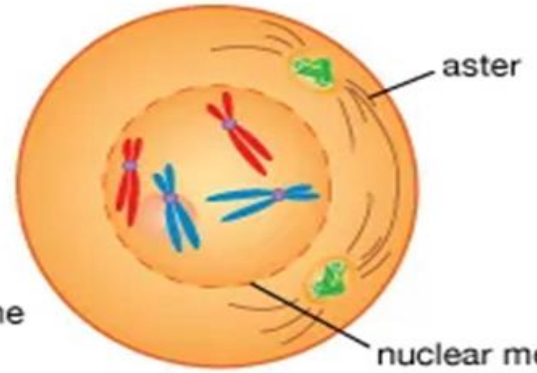
- It is the shortest phase taking about **one hour**.
- During this phase, the **2 sister chromatids segregate** and move to the opposite poles of the mitotic spindle i.e. segregating one of the two sister chromatids to each daughter cell.
- The later cells either enter into G_0 (Resting, undividing, dormant or gab zero phase) or reenter the cell cycle again when there is need for cell growth & repair.


Interphase
Prophase
Metaphase
Anaphase
Telophase

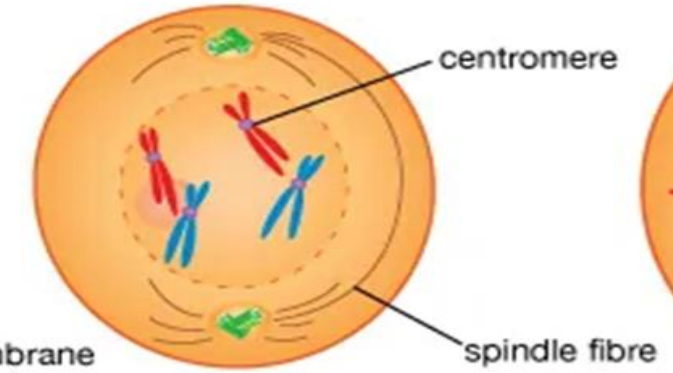
Mitosis, or somatic cell division



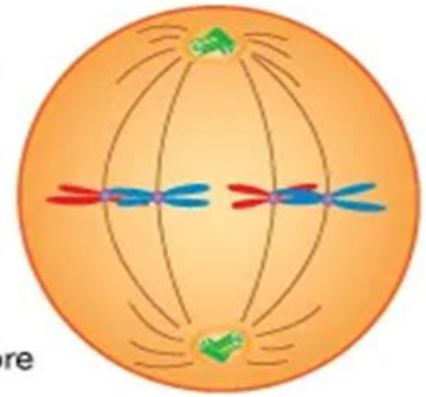
Prior to mitosis, each chromosome makes an exact duplicate of itself. The chromosomes then thicken and coil.



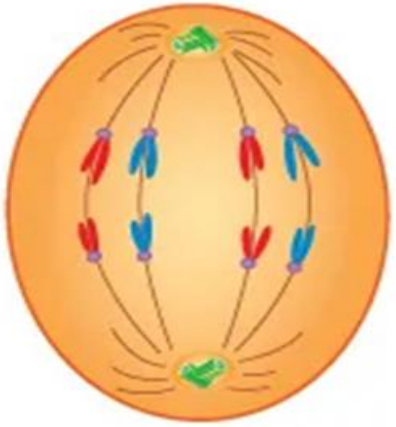
In early prophase the centrioles, which have divided, form asters and move apart. The nuclear membrane begins to disintegrate.



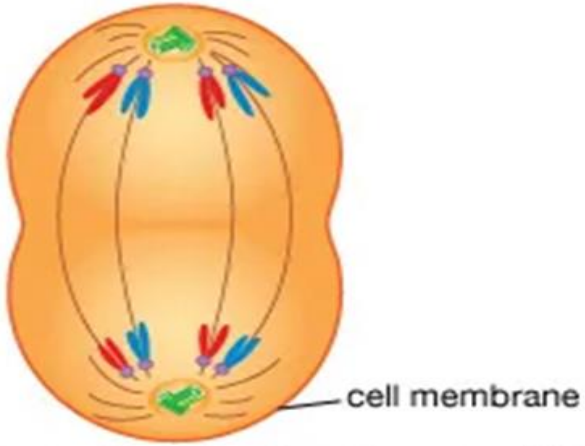
In late prophase the centrioles and asters are at opposite poles. The nucleolus and nuclear membrane have almost completely disappeared.



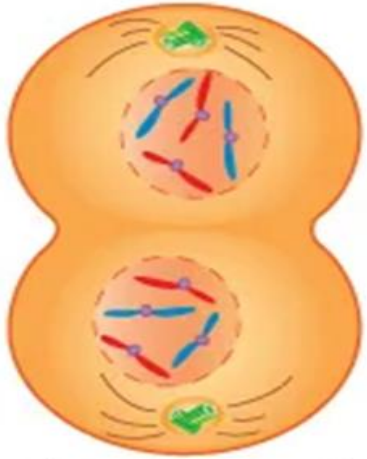
The doubled chromosomes—their centromeres attached to the spindle fibres—line up at mid-cell in metaphase.



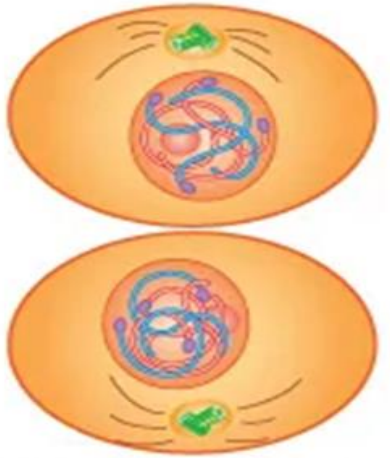
In early anaphase the centromeres split. Half the chromosomes move to one pole, half to the other pole.



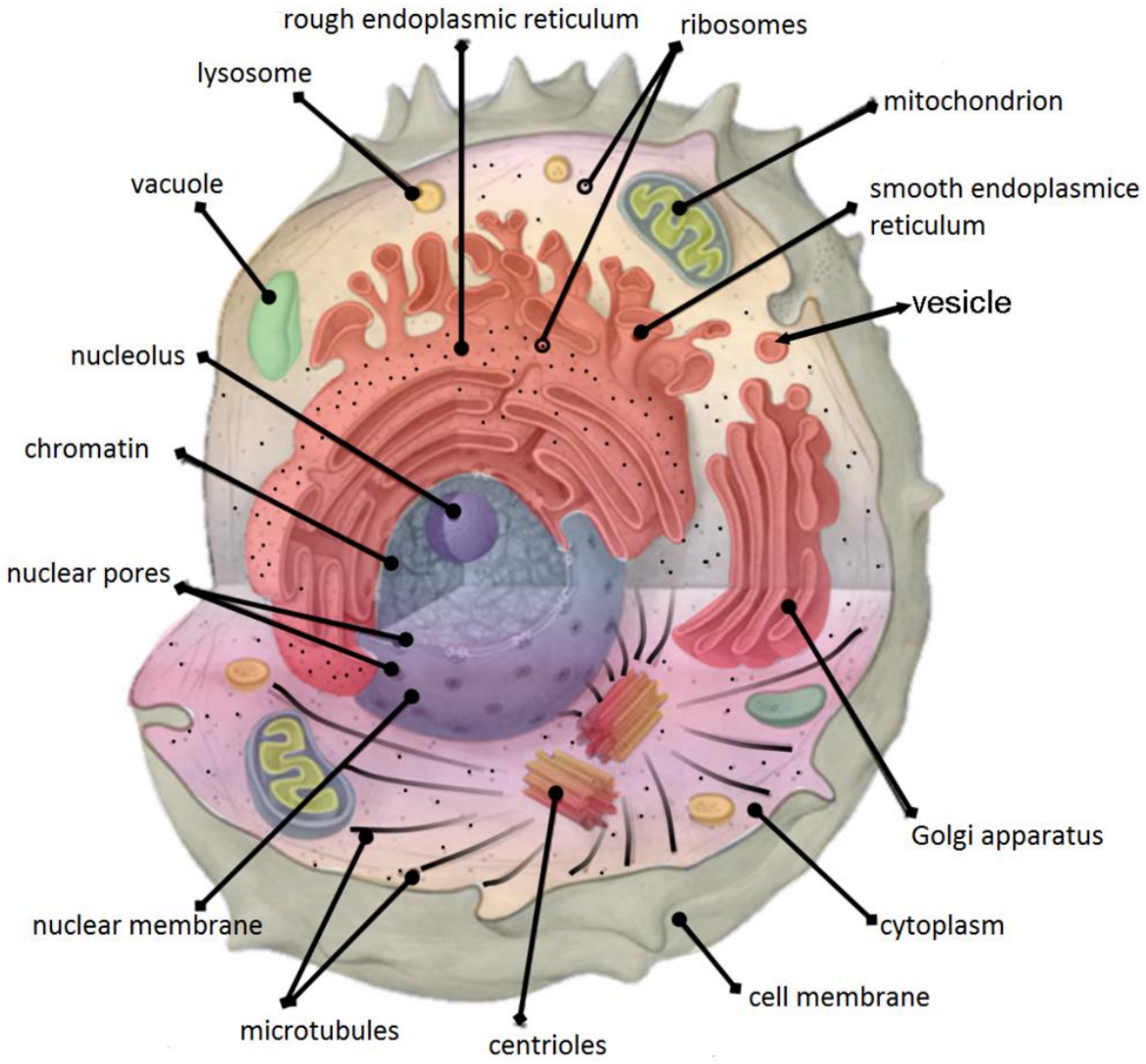
In late anaphase the chromosomes have almost reached their respective poles. The cell membrane begins to pinch at the centre.



The cell membrane completes constriction in telophase. Nuclear membranes form around the separated chromosomes.



At mitosis completion, there are two cells with the same structures and number of chromosomes as the parent cell.


rough endoplasmic reticulum
ribosomes
lysosome
mitochondrion
vacuole
smooth endoplasmice reticulum
vesicle
nucleolus
chromatin
nuclear pores
Golgi apparatus
nuclear membrane
cytoplasm
cell membrane
microtubules
centrioles

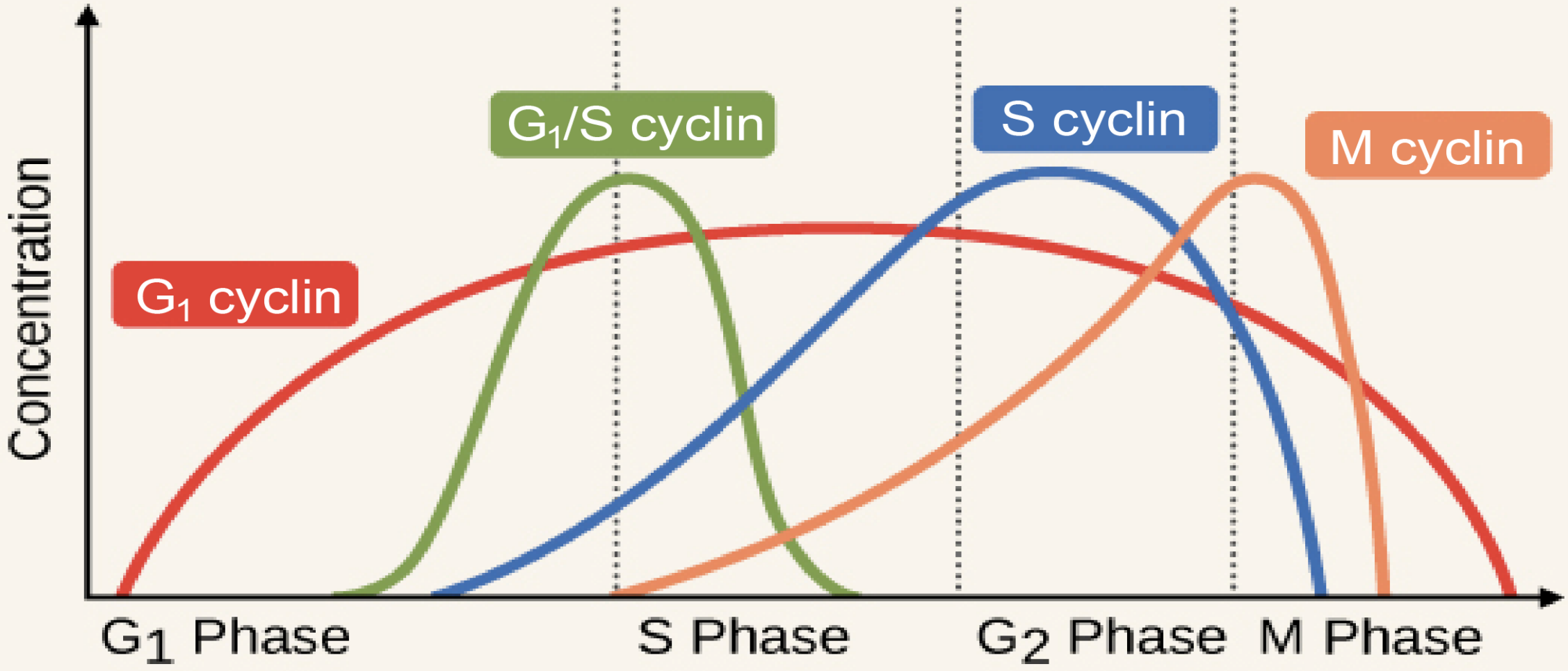
Control of cell cycle
(The molecular basis for cell cycle regulation)

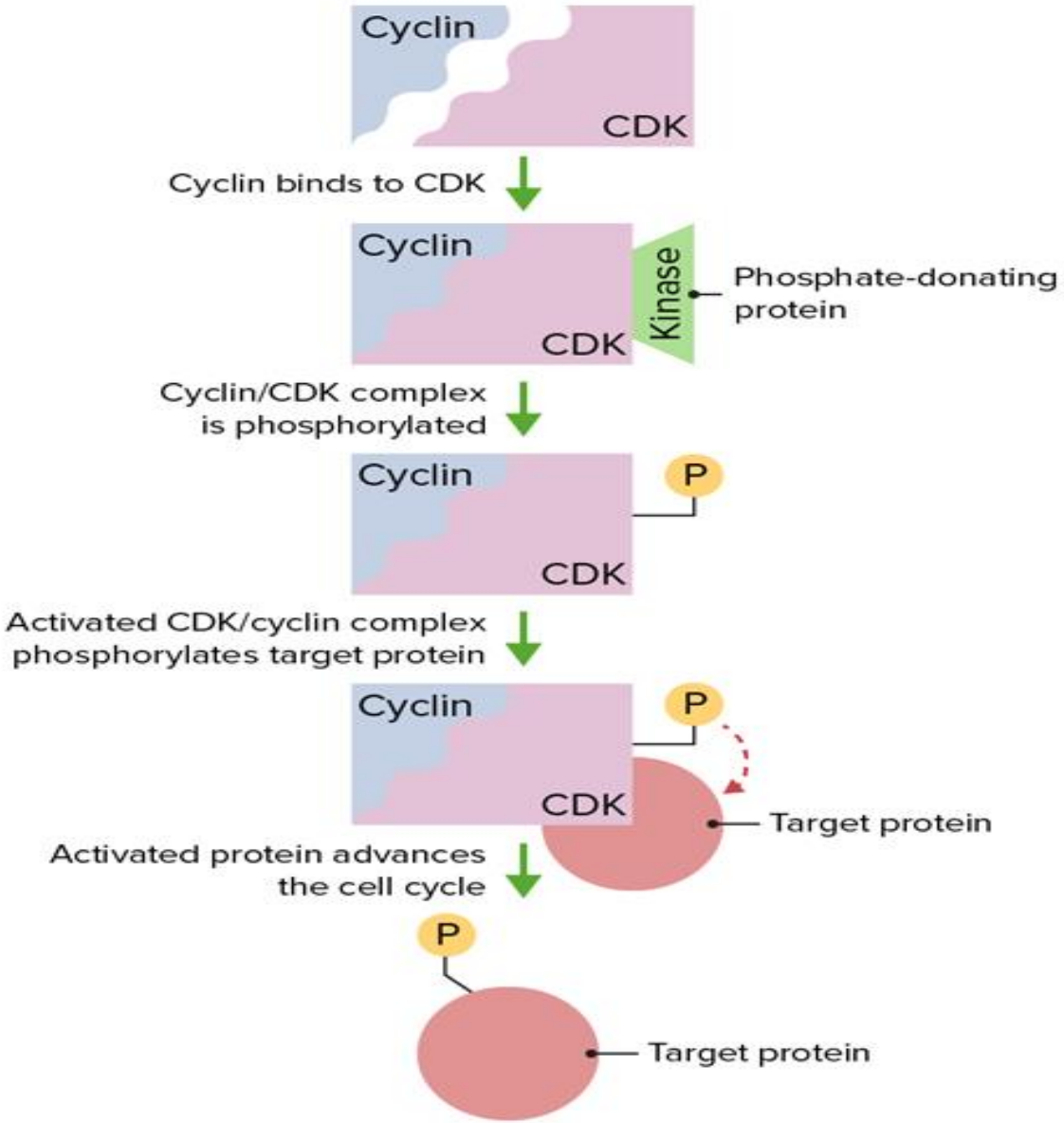
- A family of proteins called **cyclins** governs the transition of a cell from one phase to another.

- The concentration of different cyclins **increases & decreases during different phases** of the cell cycle, and hence their name.

- The cyclins act by **activating** certain **cyclin-dependent protein kinases** (CDKs) that **phosphorylate** substrates essential for the passage of the cell from one phase to another.

Cyclin Expression Cycle



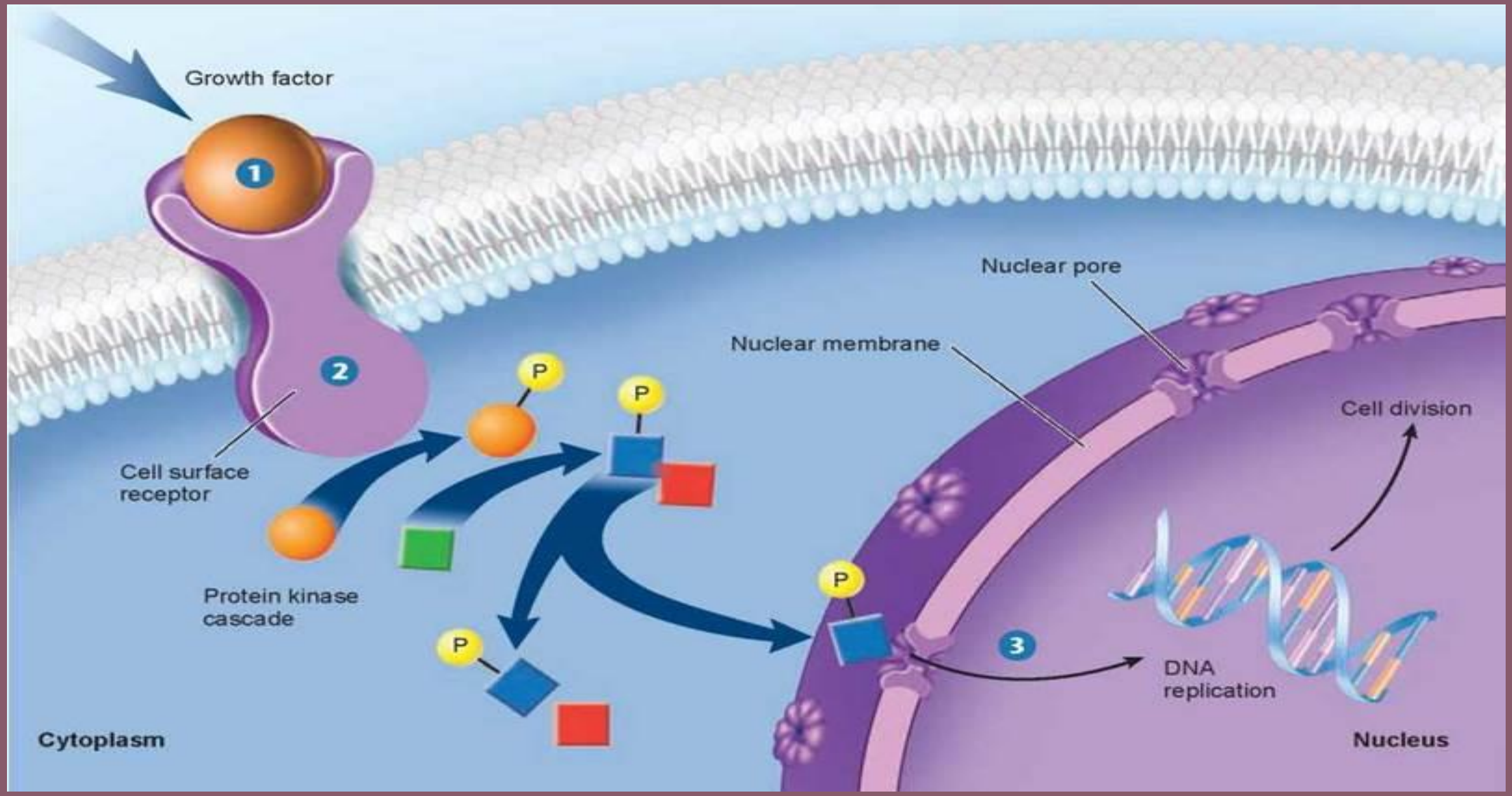

Cyclin
CDK
Cyclin binds to CDK
Cyclin
CDK
Kinase
Phosphate-donating protein
Cyclin/CDK complex is phosphorylated
Cyclin
CDK
P
Activated CDK/cyclin complex phosphorylates target protein
Cyclin
CDK
P
Target protein
Activated protein advances the cell cycle
P
Target protein

Control of cell cycle

- The cell cycle is initiated by the **binding of a growth factor** to **growth factor receptor** on the plasma membrane of the cell.

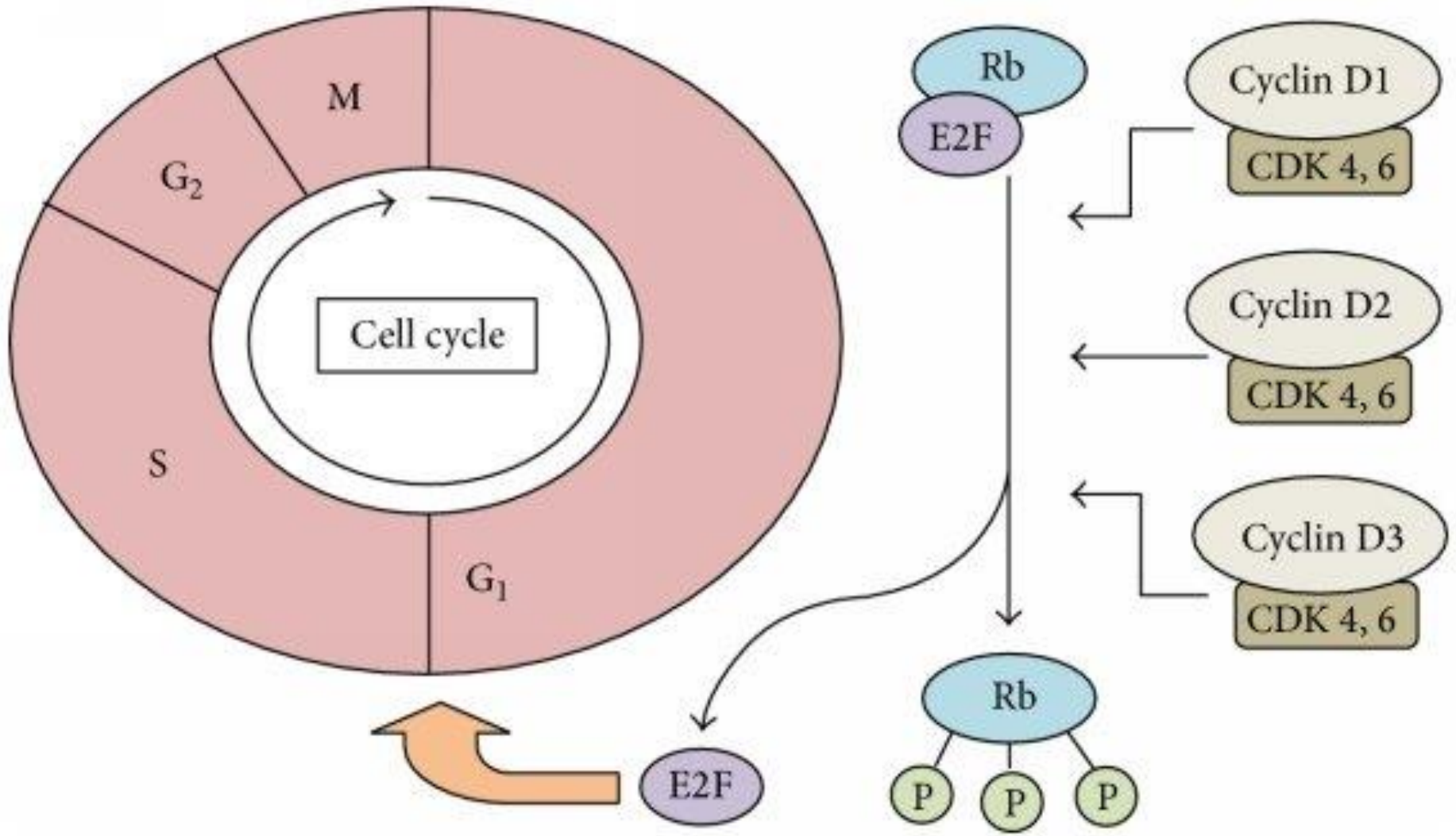
- The **growth factor receptor** undergoes **autophosphorylation on tyrosine residues** (have intrinsic protein-tyrosine kinases (TRKs) in their cytosolic domains) and becomes **active protein tyrosine kinase** that **can catalyze phosphorylation** of certain target proteins (receptor substrates) on tyrosine residues.

- **Phosphorylated target proteins mediate an intracellular signal that finally induces the production of cyclins.**


Growth factor
1
2
Cell surface receptor
Protein kinase cascade
P
P
P
P
Nuclear pore
Nuclear membrane
Cell division
3
DNA replication
Cytoplasm
Nucleus

Control of cell cycle

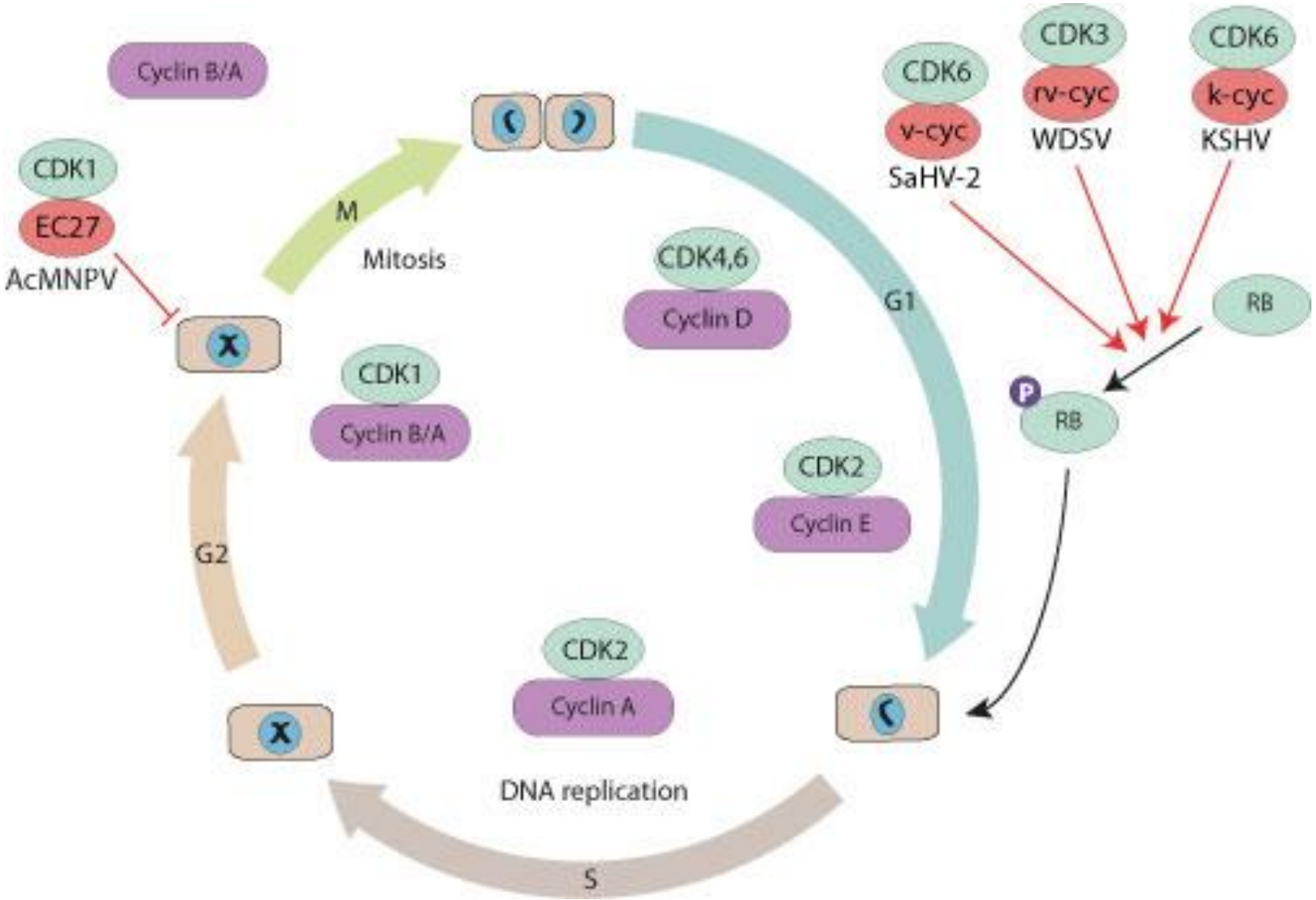
- Cyclin D increases late in the G1 phase. It **activates and forms a complex with CDK4 and CDK6** (these two kinases are also synthesized during G1 in cells undergoing active division).
- The **dephosphorylated Rb protein binds to &** inactivates **a protein called transcription factor E2F.**
- The **cyclin D-CDK4/CDK6 complex catalyzes phosphorylation of the retinoblastoma (Rb) protein**.
- When the **Rb protein is phosphorylated** by **CDK4 or CDK6** it becomes separated from E2F which **becomes now active**.
- E2F is **required** for the transcription of genes that code for proteins needed for progression from G1 to S phase (traverse the G1-S restriction point).


M
G2
S
G1
Cell cycle
Rb
E2F
Cyclin D1
CDK 4, 6
Cyclin D2
CDK 4, 6
Cyclin D3
CDK 4, 6
Rb
P
P
P
E2F

Control of cell cycle

- Other cyclins CDKs are involved in different aspects of cell cycle progression.
- **Cyclin E & CDK2** forms a complex in **late G1**.
- Cyclin E rapidly degraded, and the released **CDK2 then forms a complex with cyclin A.**
- This sequence is **necessary for the initiation of DNA synthesis in S phase.**
- The **B cyclins** are produced **late in the G2 phase**.

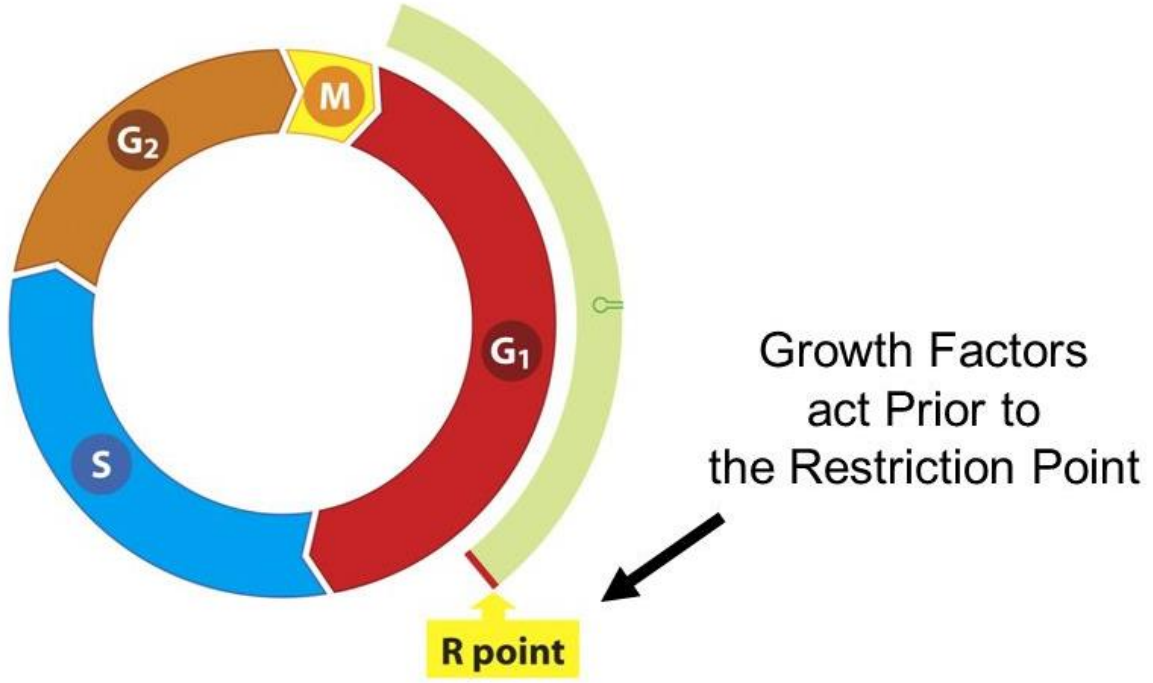
❖A complex between **cyclin B & CDK1 is rate limiting for the G2/M transition in eukaryotic cells.**


Cyclin B/A
CDK1
EC27
AcMNPV
M
Mitosis
CDK4,6
Cyclin D
G1
CDK6
v-cyc
SaHV-2
CDK3
rv-cyc
WDSV
CDK6
k-cyc
KSHV
RB
P
RB
CDK1
Cyclin B/A
CDK2
Cyclin E
G2
CDK2
Cyclin A
DNA replication
S

Restriction point

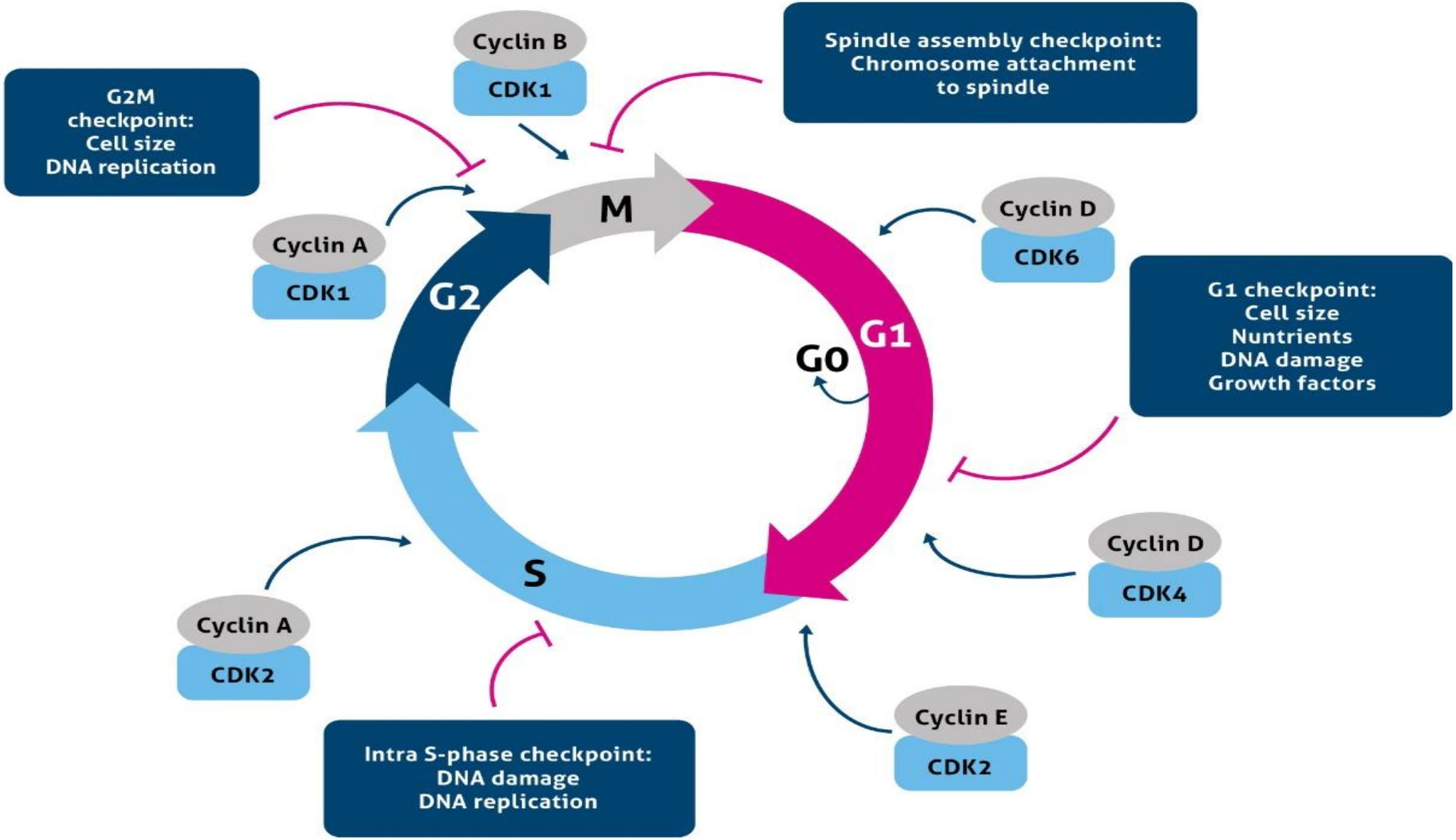
- In the cell cycle there is a **restriction point** (in late G1) at which the cells become committed to enter the S phase and to complete the cycle independent on the presence of growth factors.

- If cultured mammalian cells are removed from medium containing growth factors to one lacking growth factors before they have passed the restriction point, the cells do not enter the S phase.



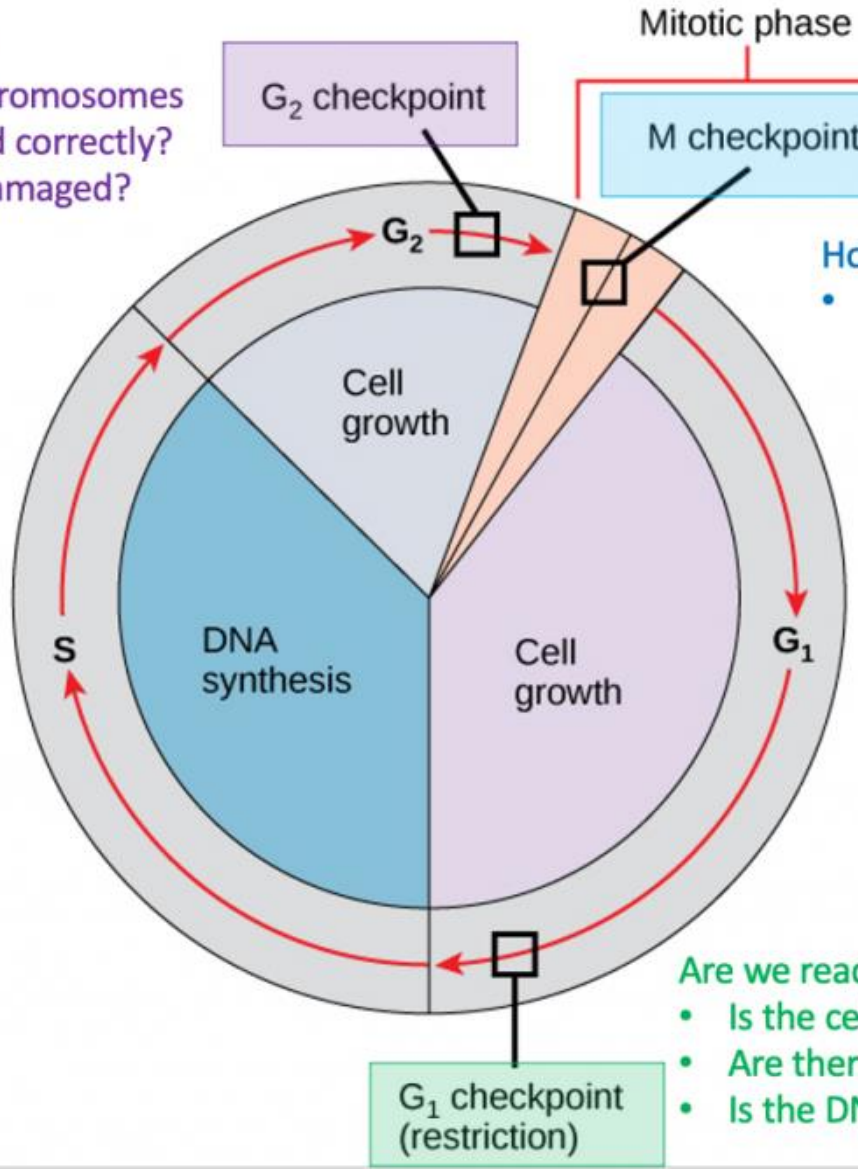
Cell cycle check points

- DNA, chromosome, chromosome segregation integrity is continuously monitored throughout the cell cycle in **4 check points**.
- ***DNA damage*** is detected in G1 & G2 phases.
- Completeness of ***replication*** is detected late in the S phase.
- Proper ***chromosomal segregation*** machinery is detected in the M phase.
- Cells will not progress through the phase of the cycle in which defects are detected. In some cases, if the damage cannot be repaired, such cells undergo programmed cell death (apoptosis).


Cyclin B
CDK1
Spindle assembly checkpoint:
Chromosome attachment
to spindle
G2M
checkpoint:
Cell size
DNA replication
M
Cyclin A
CDK1
Cyclin D
CDK6
G2
G1
G0
G1 checkpoint:
Cell size
Nuntrients
DNA damage
Growth factors
Cyclin D
CDK4
S
Cyclin A
CDK2
Cyclin E
CDK2
Intra S-phase checkpoint:
DNA damage
DNA replication

How's our DNA?

- Did all the chromosomes get replicated correctly?
- Is the DNA damaged?



How's our chromosomal alignment?

- Did all the chromosomes line up in the center of the cell, ready to be pulled apart?

Are we ready to divide?

- Is the cell big enough?
- Are there enough energy and other reserves?
- Is the DNA damaged?

Apoptosis

- Apo = off, ptosis = falling

- The cells carry in their nucleus **genetic program for suicide** that can be turned on to get rid of a specific cell, so it is called cell suicide or programmed cell death.

Apoptosis

It can be induced by several stimuli as follows:

❖Receptor mediated apoptosis results from the **interaction of a ligand** with a specific transmembrane receptor, the most important are the **Fas receptor** and **tumor necrosis factor receptor 1** (TNFR).

- Radiation, hypoxia, free radicals and chemical agents as chemotherapy **produce DNA damage**.

- These changes **produce activation of p53** which produces **arrest of cell cycle** and **allows for DNA repair** or **activate the apoptotic pathway** through activation of the apoptotic gene i.e. **Bax gene**.

Apoptosis

- Loss of protein Bax function as a result of gene mutation is associated with cancer development e.g. **gastric adenocarcinoma**.

- **Bcl-2** is an **antiapoptotic protein** that acts through binding with **protein Bax** and produces its **inactivation**.

- Increased level of Bcl-2 is associated with cancer development.

- In normal cells, both **Bax** and **Bcl-2** are present in balance **(the ratio of apoptosis inhibitors to apoptosis stimulators makes death decision).**

Apoptosis

Mechanism of apoptosis:

- Apoptosis is initiated by **activation** of certain proapoptotic protein factors that results in the following cascade:

1. Release of cytochrome c from the mitochondria to the cytosol.

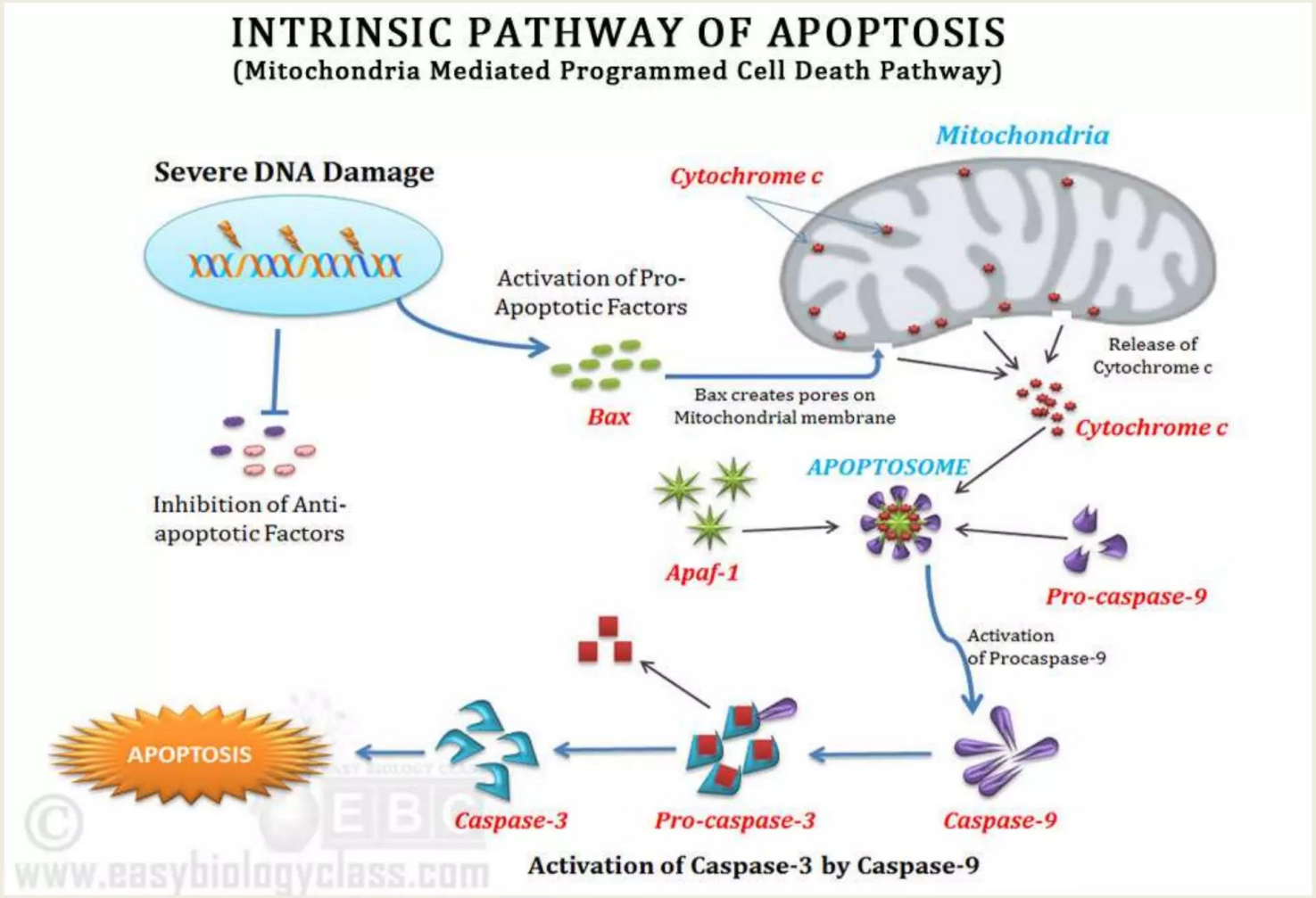
2. The **release of cytochrome c** produces an **activation cascade** that leads to **activation of caspases** (group of enzymes that split cellular proteins).

- They derive their name from the "c" from cysteine amino acid present in the catalytic site of the enzyme and **caspase** refers to their unique ability to cleave the substrate after aspartic acid residue.

Apoptosis

3. **Caspases produce activation of endonucleases** that **split DNA**, termed caspase activated Dnase (CAD).

- CAD produces a series of DNA fragments varying in length by approximately 200 bp (nucleosomal fragments and their multiplies), these fragments have characteristic ladder appearance on gel electrophoresis (it is a diagnostic test).


INTRINSIC PATHWAY OF APOPTOSIS
(Mitochondria Mediated Programmed Cell Death Pathway)
Mitochondria
Severe DNA Damage
Cytochrome c
Activation of Pro-Apoptotic Factors
Release of Cytochrome c
Bax creates pores on Mitochondrial membrane
Bax
Cytochrome c
APOPTOSOME
Inhibition of Anti-apoptotic Factors
Apaf-1
Pro-caspase-9
Activation of Procaspase-9
APOPTOSIS
Caspase-3
Pro-caspase-3
Caspase-9
Activation of Caspase-3 by Caspase-9
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