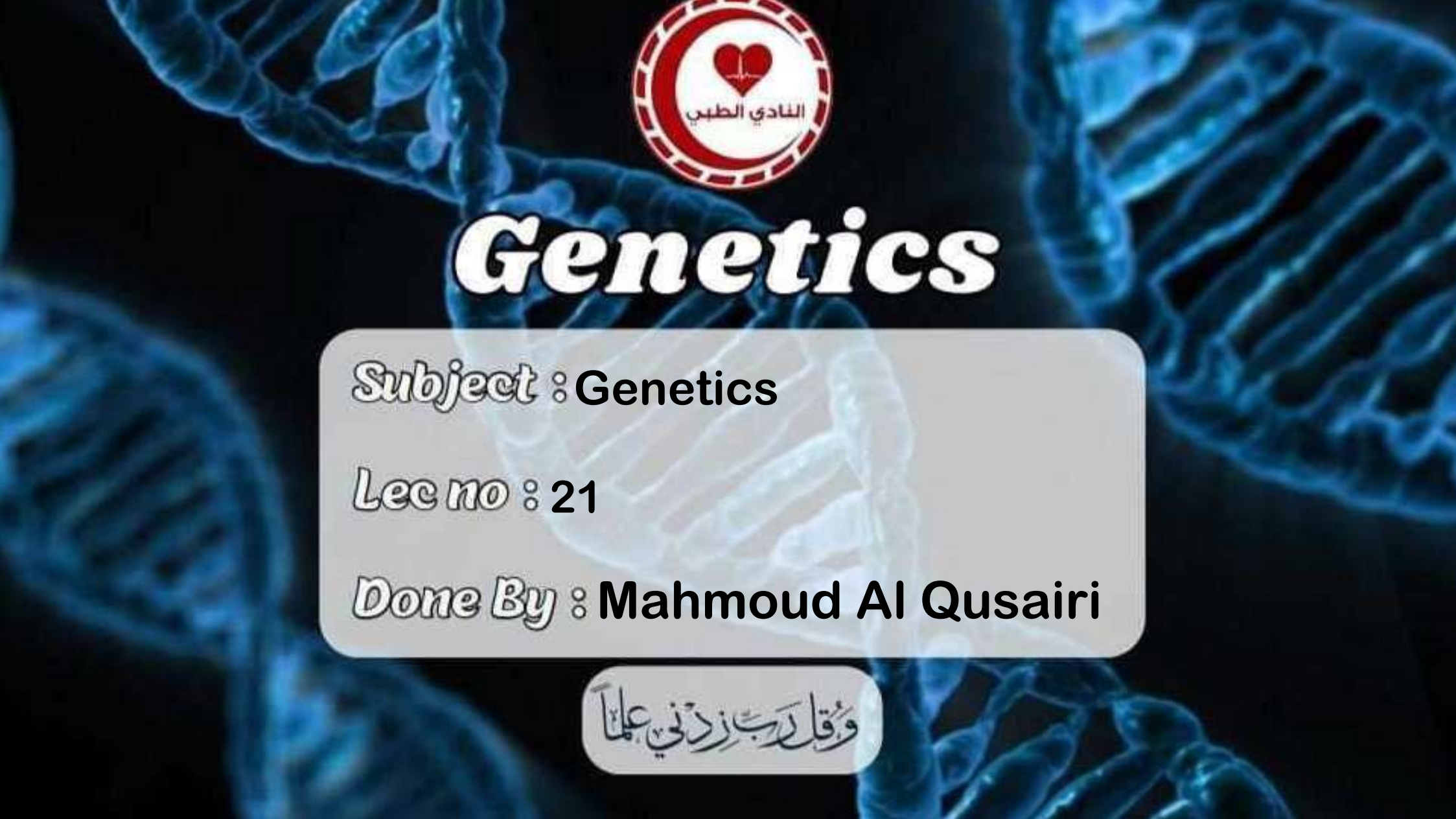
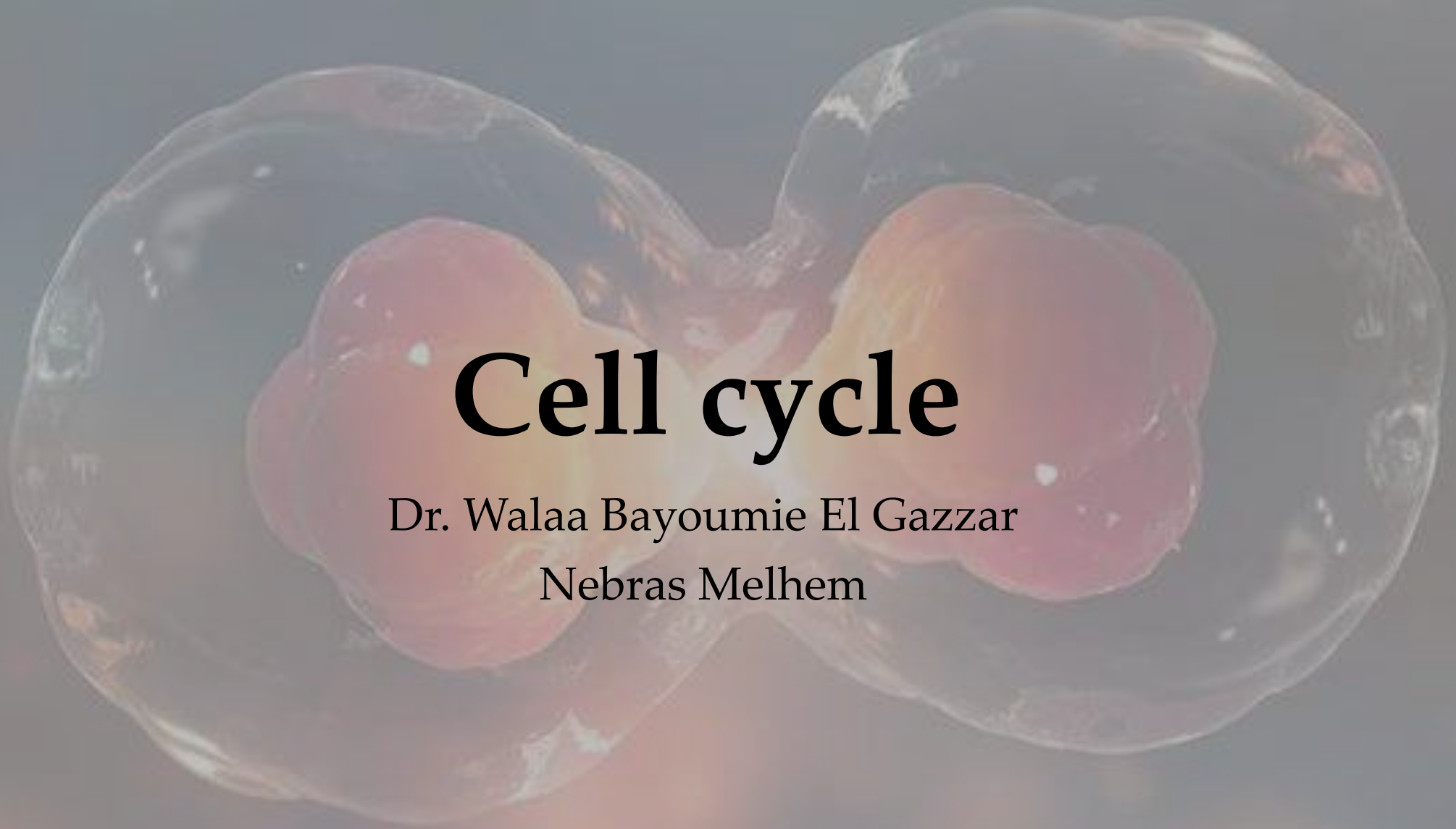

النادي الطبي
Genetics
Subject : Genetics
Lec no : 21
Done By : Mahmoud Al Qusairi
وقل رب زدني علما



Cell cycle

Dr. Walaa Bayoumie El Gazzar

Nebras Melhem

damage حصل اذا ← مهمة للغاية cell cycle *
و الـ cell ماتت فأنا بحكم
خلية اخرى (نفس الخلية هذه)
فبالتالي بتصير cell cycle

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.**

Cardiac cells Muscle cells Neuronal cells
permanent cells

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

يوجد خلايا تبقى في هذه phase مثل

Interphase مرحلة ما قبل

- 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

2 phases

First phase **Interphase**

It contains 3 sub-phases

The cell grows and copies its DNA

1. **G_1**: Cell growth
2. **S**: DNA synthesis
3. **G_2**: More growth, preparation for mitosis

to be able to divide to 2 daughter cells

Second phase **Mitosis**

Contains four sub-subdivisions

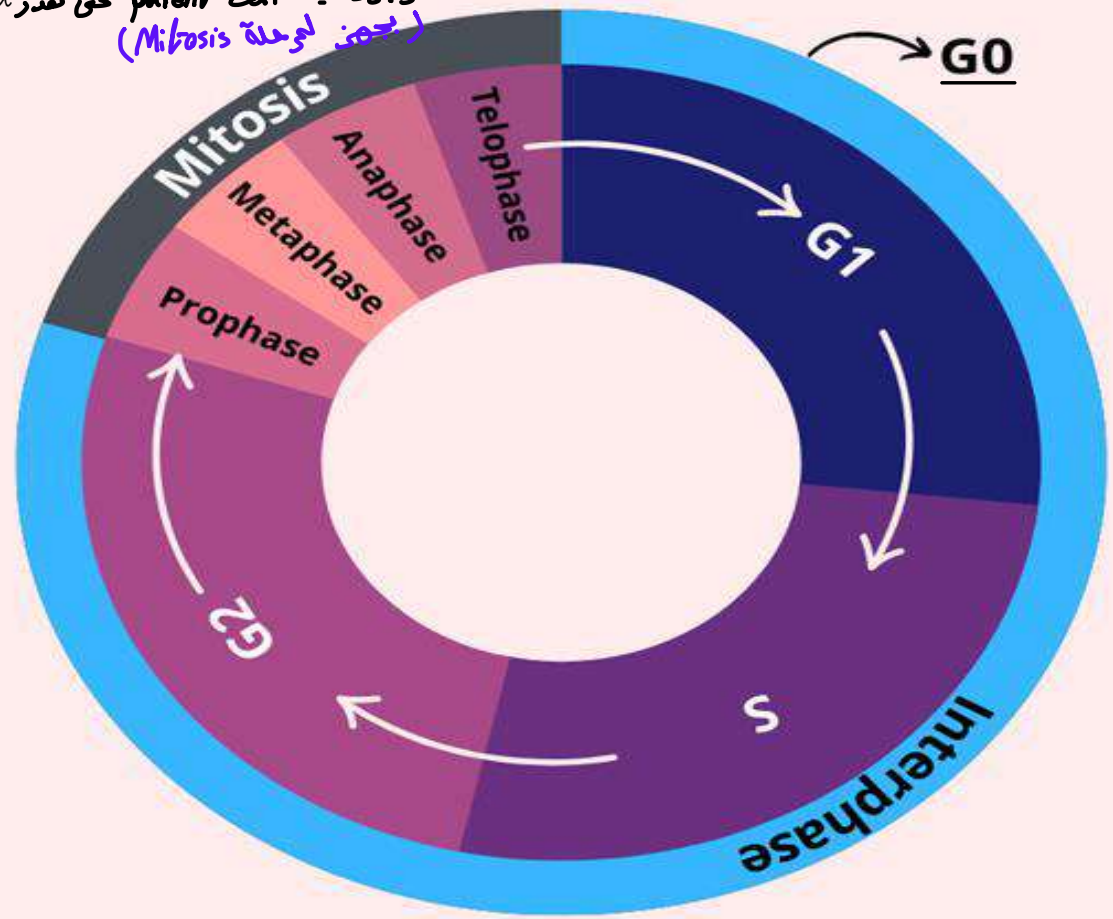
The cell divides its DNA and cytoplasm, forming two new cells

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

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

لا يحدث في هذه المرحلة أنقسام ،يحدث النمو وتكوين ل DNA

لأنه بختلج لإنتاج خلية أخرى material حيث انه لا يمكن الاعتماد على material الموجودة فيه parent cell لحين تقدر Division (يحصل لمرحلة Mitosis)



في هذه المرحلة يحدث growth تختلف عن G1 في أنه فيه التكون DNA ل S phase.

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.

variability في phase اكتر

Cell Cycle Phases

Cancer cells hemato chromatic cells

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

مش كل الخلايا تنقسم في نفس التوقيت
(يوجد خلايا مثل liver cells تأخذ من 6 إلى 12 شهر
حتى يصيرلها division)

❖Events for each phase:

➢**G1 phase**: → The longest phase

- The duration of this phase is about **6-12 hours**.
- During this phase, RNA and proteins needed for cell division are synthesized. → To prepare for mitosis

تجهز الخلية لحتى تحتوي على materials كافية لعمل mitosis

G1 مهمة في regulation حيث ان البروتينات التي تم إنتاجها في هذه المرحلة مهمة في regulation, function

- Active RNA & protein synthesis.

Cell Cycle Phases

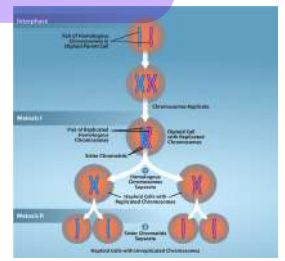
The second longest phase

➢ **S phase**:

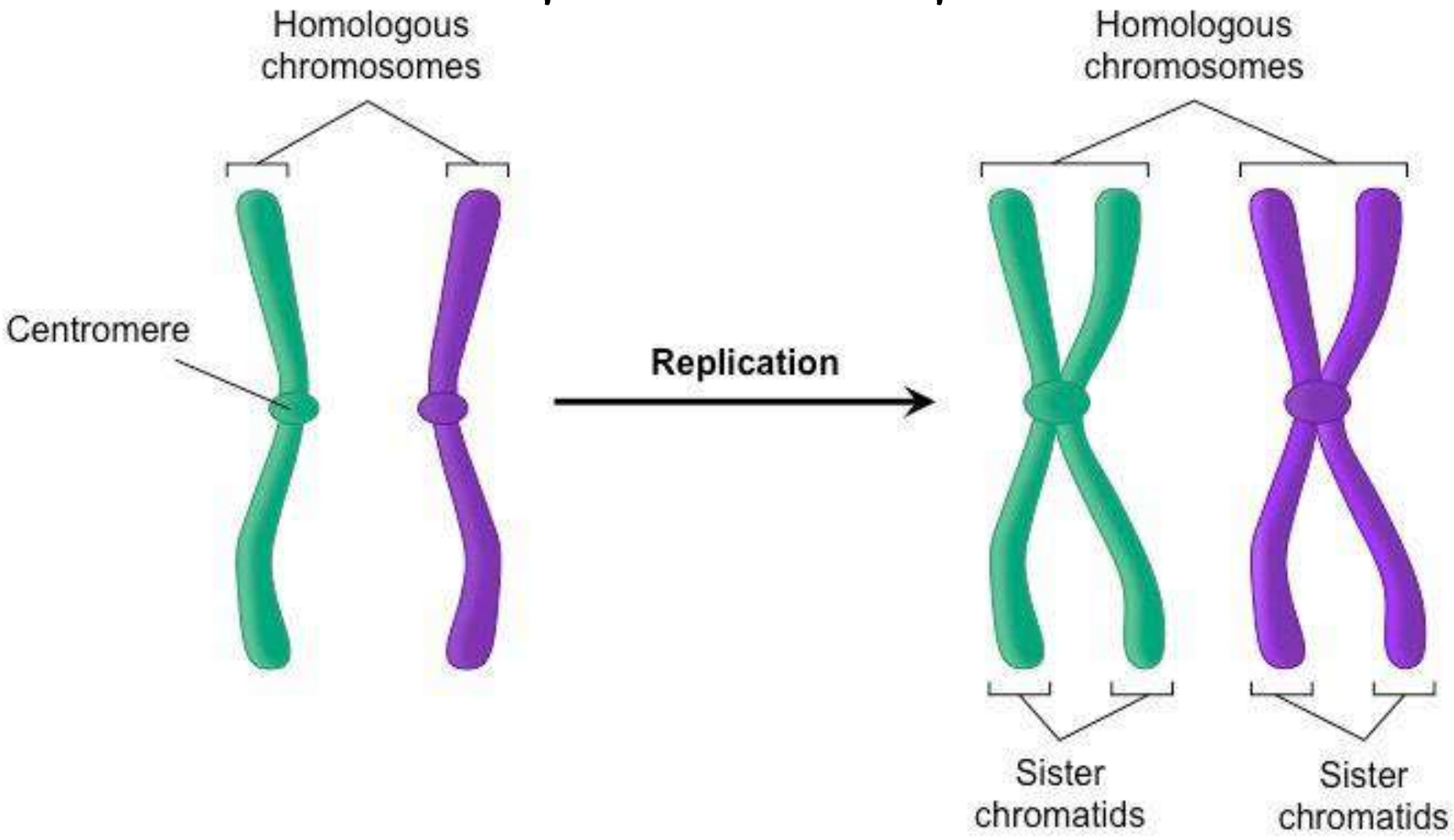
- The duration of this phase lasts about **6 to 8 hours**.
- DNA is replicated (chromosomes are duplicated to become tetraploid).
- These events result in the formation of two sister chromatids attached at the centromere.

➢ **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).



Take place in S phase



Cell Cycle Phases

➢ **M phase**:

One chromosome (two chromatids) ---two chromosomes

S phase في تكونوا 2 sister chromatids
2 chromosomes ويعملوا بعض عن ينفصلوا

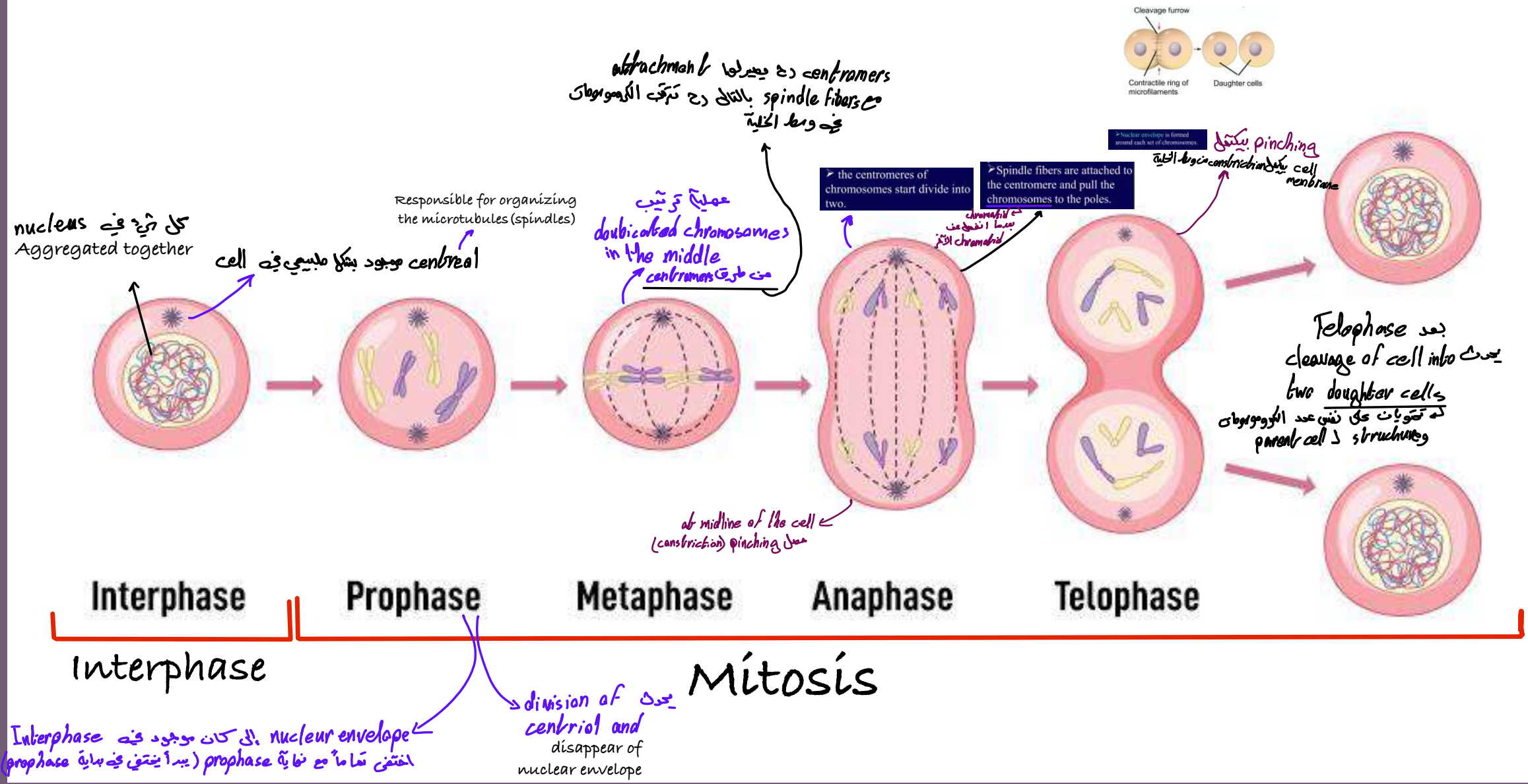
- It is the shortest phase taking about **one hour**.
- During this phase, the **2 sister chromatids segregate** and move to the opposite poles of the mitotic spindle i.e. segregating one of the two sister chromatids to each daughter cell.

دي بتحرك كل واحد إلى أبعد نقطة في الـ cell

كل chromatid دي بقى كروموسوم في خلية لوحده.

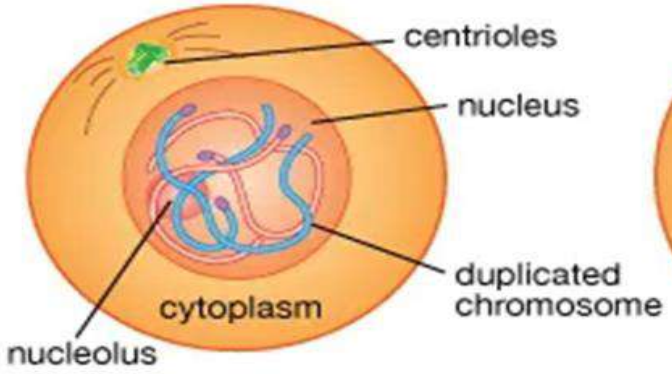
daughter cells اللي نتجت من mitosis

- 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.

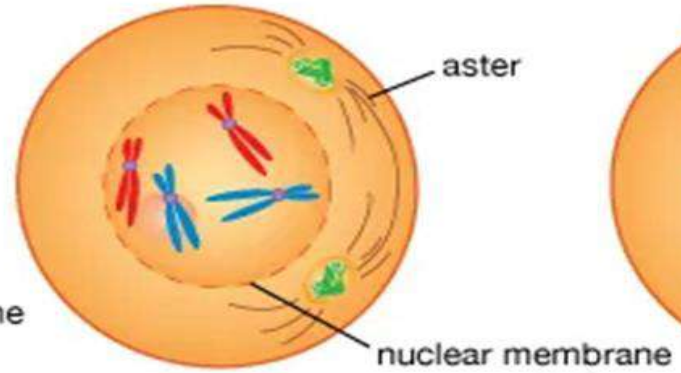

Cleavage furrow
Contractile ring of microfilaments
Daughter cells
Nuclear envelope is formed around each set of chromosomes.
Spindle fibers are attached to the centromere and pull the chromosomes to the poles.
the centromeres of chromosomes start divide into two.
Responsible for organizing the microtubules (spindles)
nucleus
Aggregated together
cell
centreal
doubicolted chromosomes in the middle
centromers
at midline of the cell
(constriction) pinching
pinching
cell membrane
Telophase
cleavage of cell into two doughter cells
Interphase
Prophase
Metaphase
Anaphase
Telophase
Interphase
Mitosis
Interphase
nucleur envelope
prophase
prophase
division of
centriol and
disappear of
nuclear envelope

ما قرأت هذا السلايد
قالت انه نفس الي حكته فوق

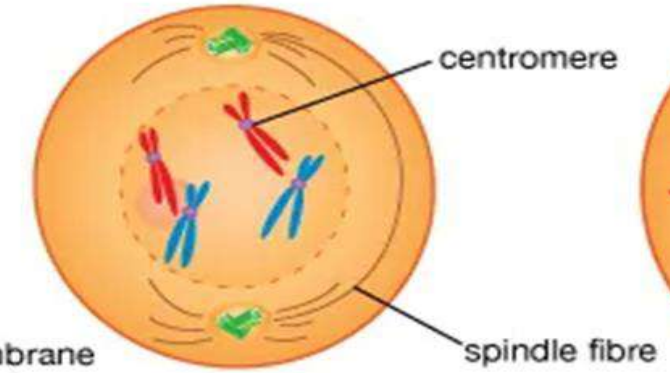
Mitosis, or somatic cell division



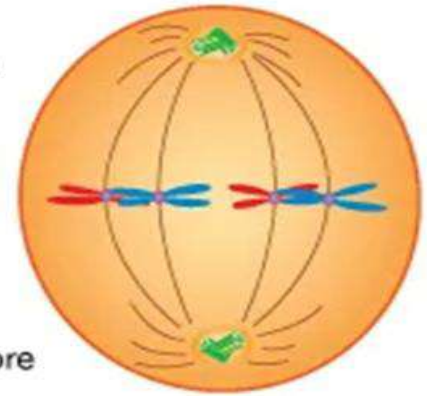
Prior to mitosis, each chromosome makes an exact duplicate of itself. The chromosomes then thicken and coil.



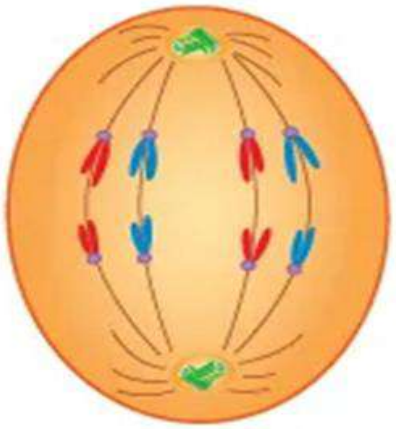
In early prophase the centrioles, which have divided, form asters and move apart. The nuclear membrane begins to disintegrate.



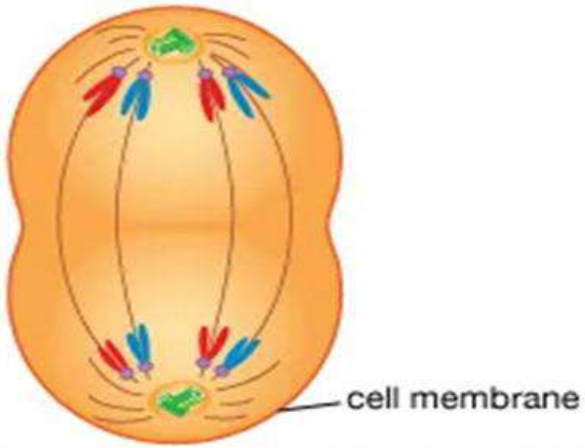
In late prophase the centrioles and asters are at opposite poles. The nucleolus and nuclear membrane have almost completely disappeared.



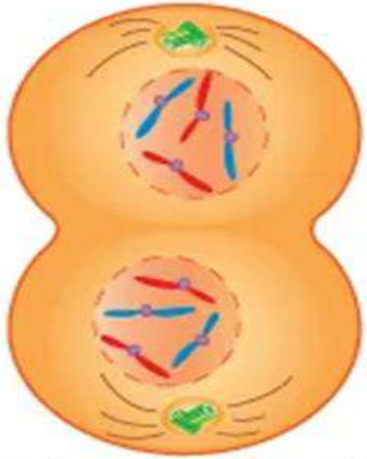
The doubled chromosomes—their centromeres attached to the spindle fibres—line up at mid-cell in metaphase.



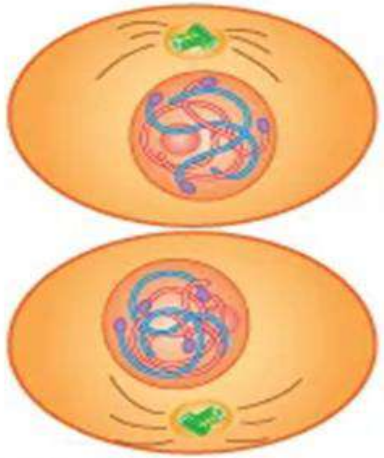
In early anaphase the centromeres split. Half the chromosomes move to one pole, half to the other pole.



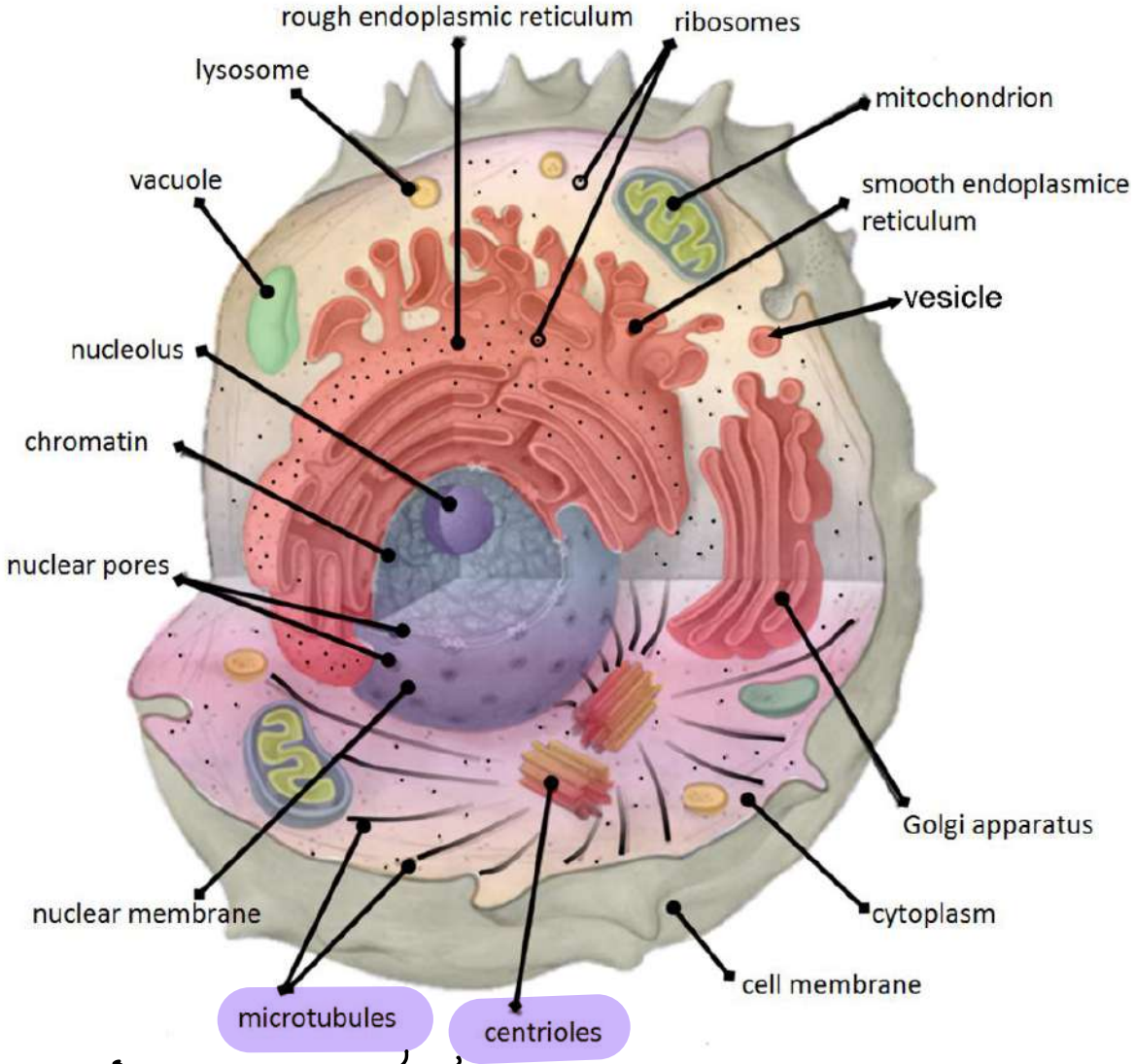
In late anaphase the chromosomes have almost reached their respective poles. The cell membrane begins to pinch at the centre.



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.



موجودين في الخلية (لم يأتوا من الفراغ)

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

regulate the cell cycle.

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

to another

concentration of cyclins differ from phase

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

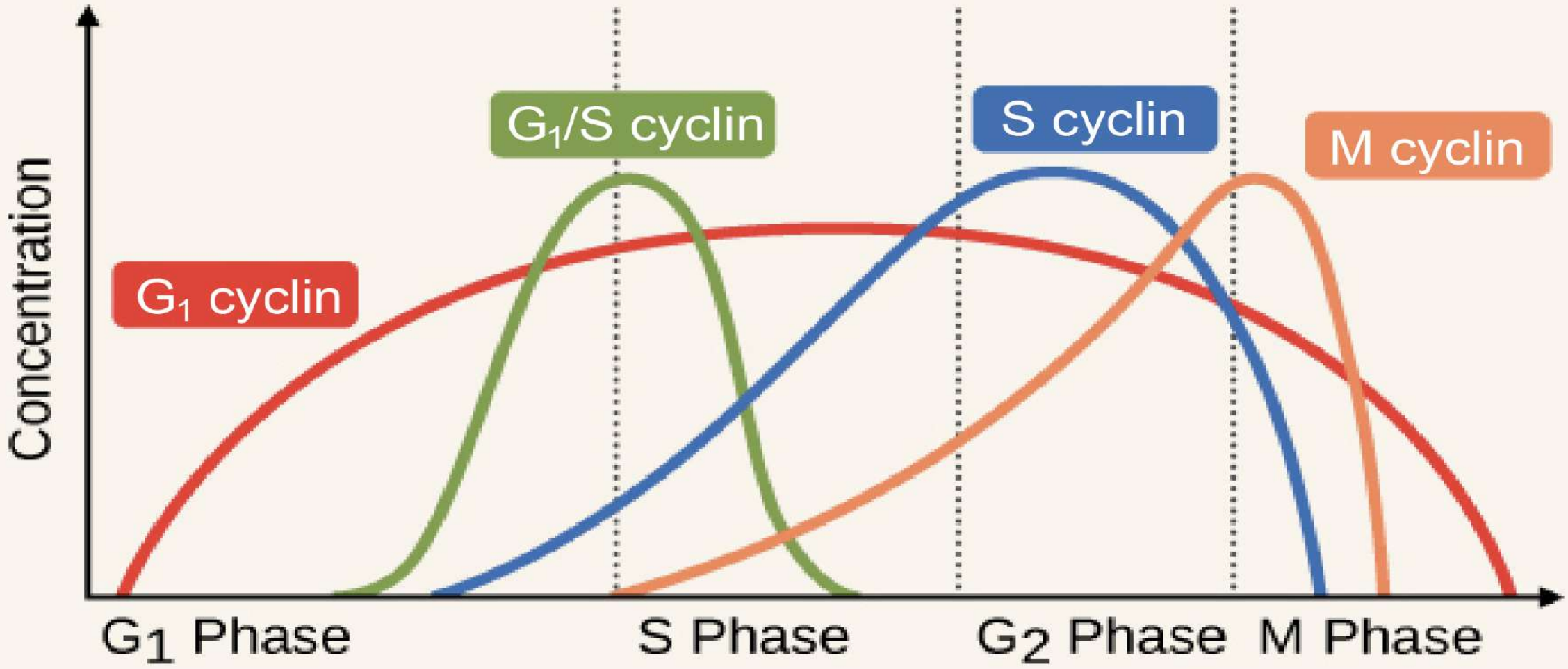
بيختلف تركيزهم فيه cycle حسب كل phase

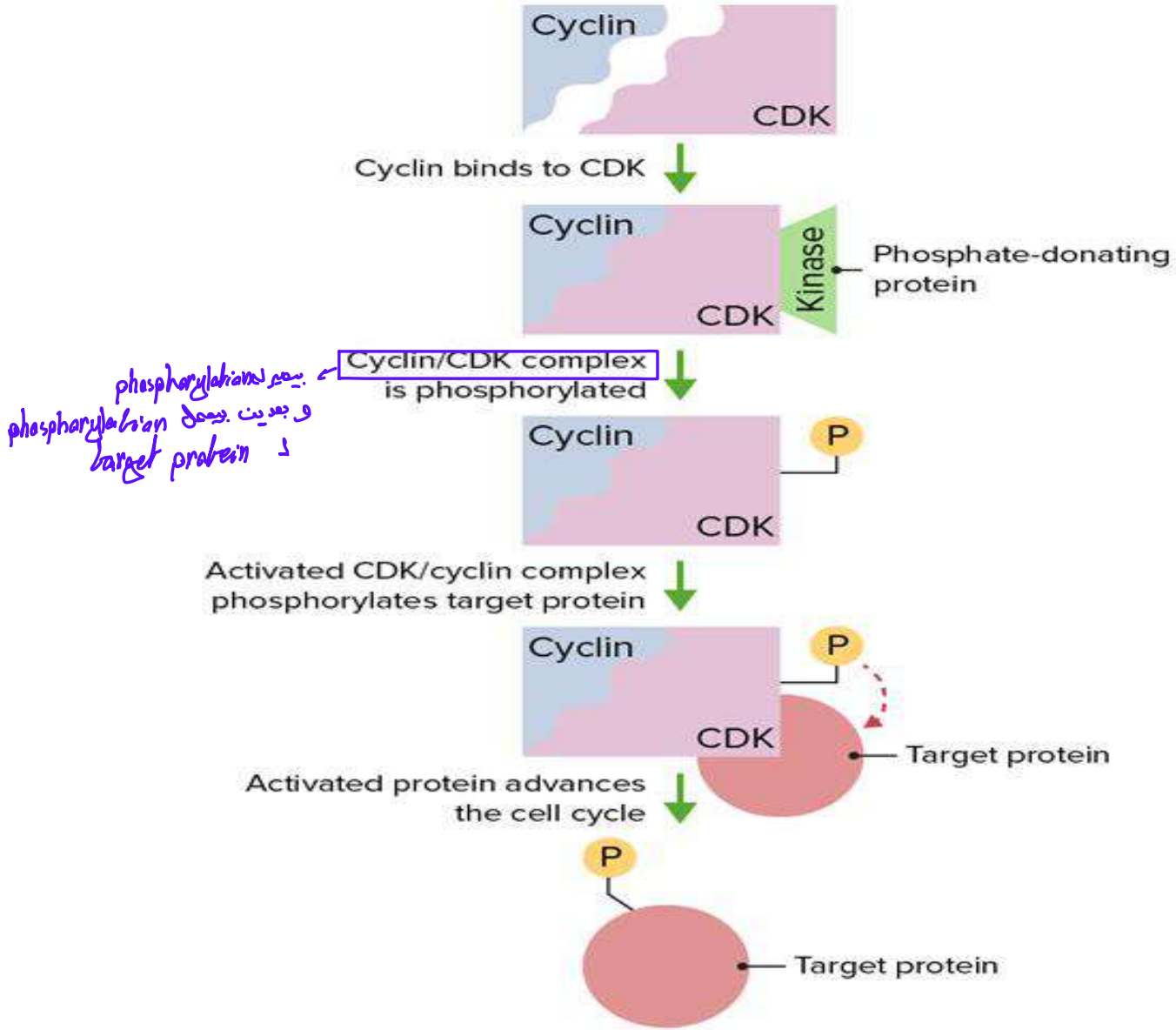
Cyclins —activate→ CDK → تعمل phosphorylation لـ other substanses ← active فيصيروا. يساعدوا على الانتقال من phase لأخرى.

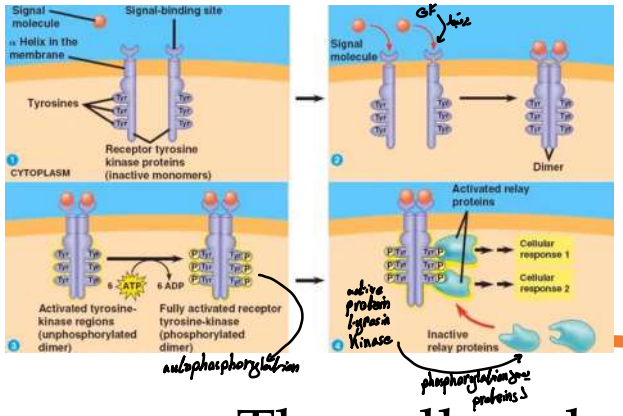
- The cyclins act by **activating** certain **cyclin-dependent protein kinases** (CDKs) that **phosphorylate** substrates essential for the passage of the cell from one phase to another.

غير مهمة
فقط يجب ان نعرف انه تركيز cyclins يختلف من phase لأخرى

Cyclin Expression Cycle




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

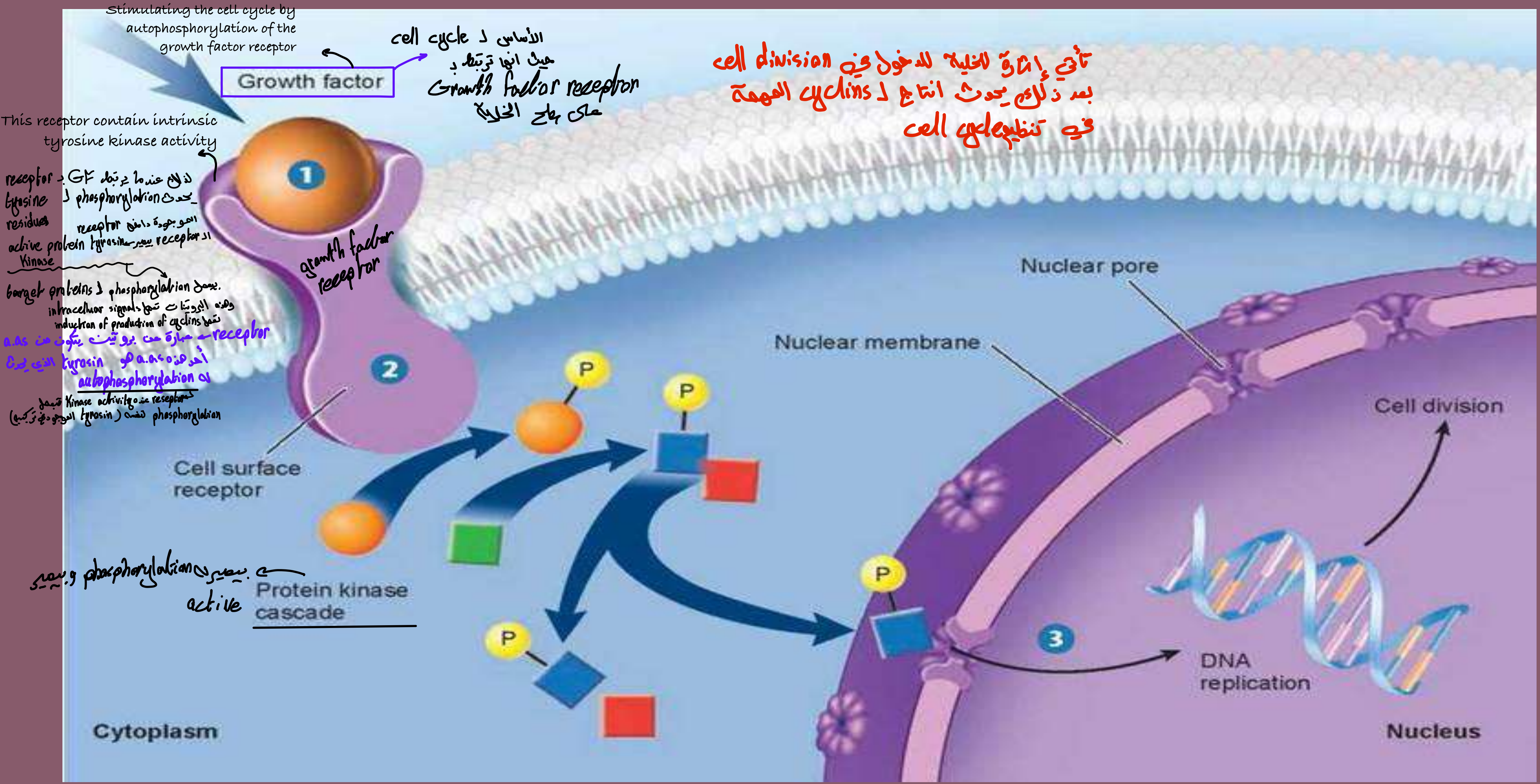


Control of cell cycle

- 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.**


Stimulating the cell cycle by autophosphorylation of the growth factor receptor
Growth factor
This receptor contain intrinsic tyrosine kinase activity
cell cycle الأساس لـ
حيث انها ترتبط بـ Growth factor receptor على سطح الخلايا
تأتي إشارة للخلية للدخول في cell division
بعد ذلك يحدث انتاج لـ cyclins المهمة
في تنظيم cell cycle
growth factor receptor
Nuclear pore
Nuclear membrane
Cell division
Cell surface receptor
Protein kinase cascade
active
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.**

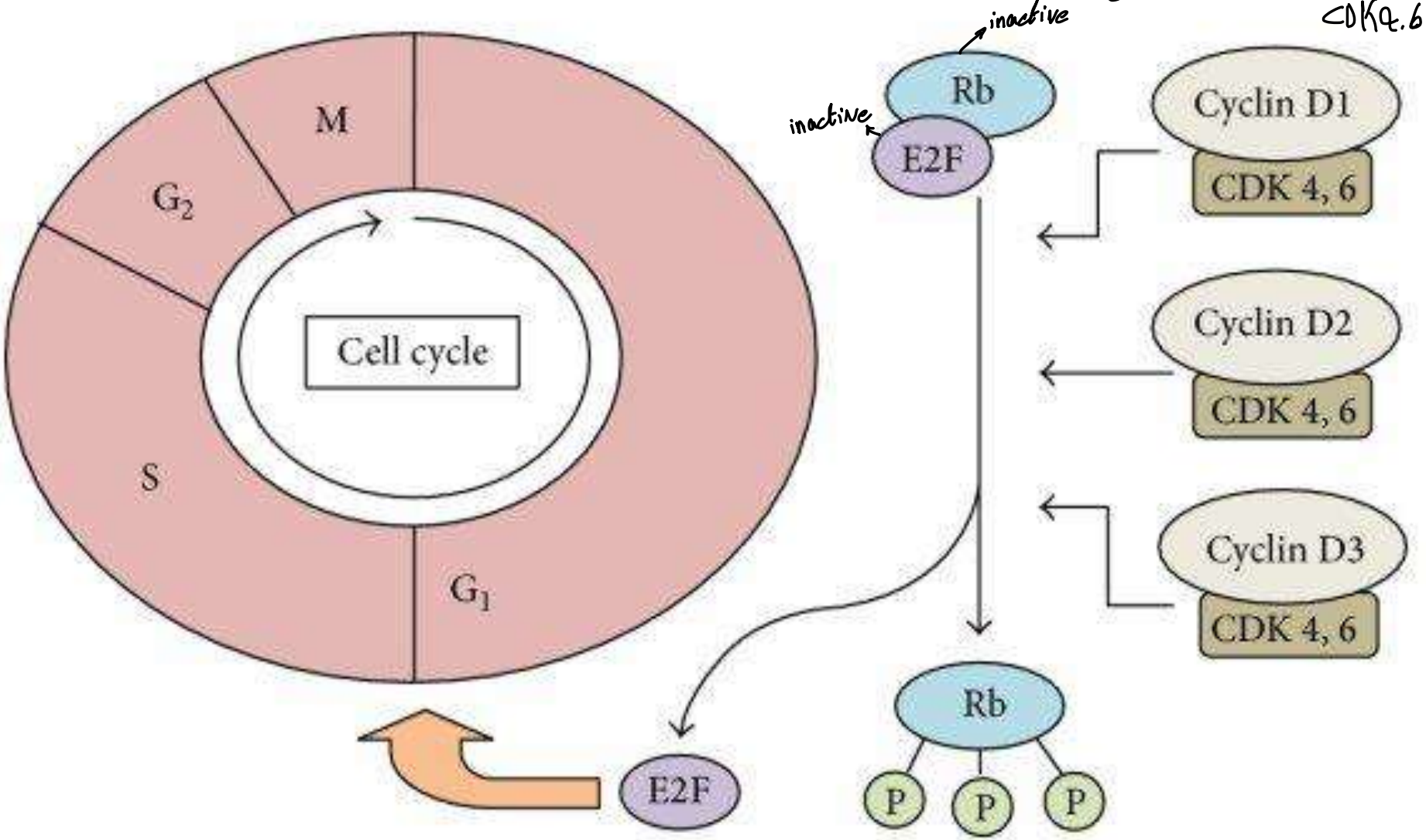
- The **cyclin D-CDK4/CDK6 complex catalyzes phosphorylation of the retinoblastoma (Rb) protein.**

- 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).

* لم تتكلم عن D_1, D_2, D_3 ← فقط اي cyclin D

بيكون مرتبط مع CDK4,6



Control of cell cycle

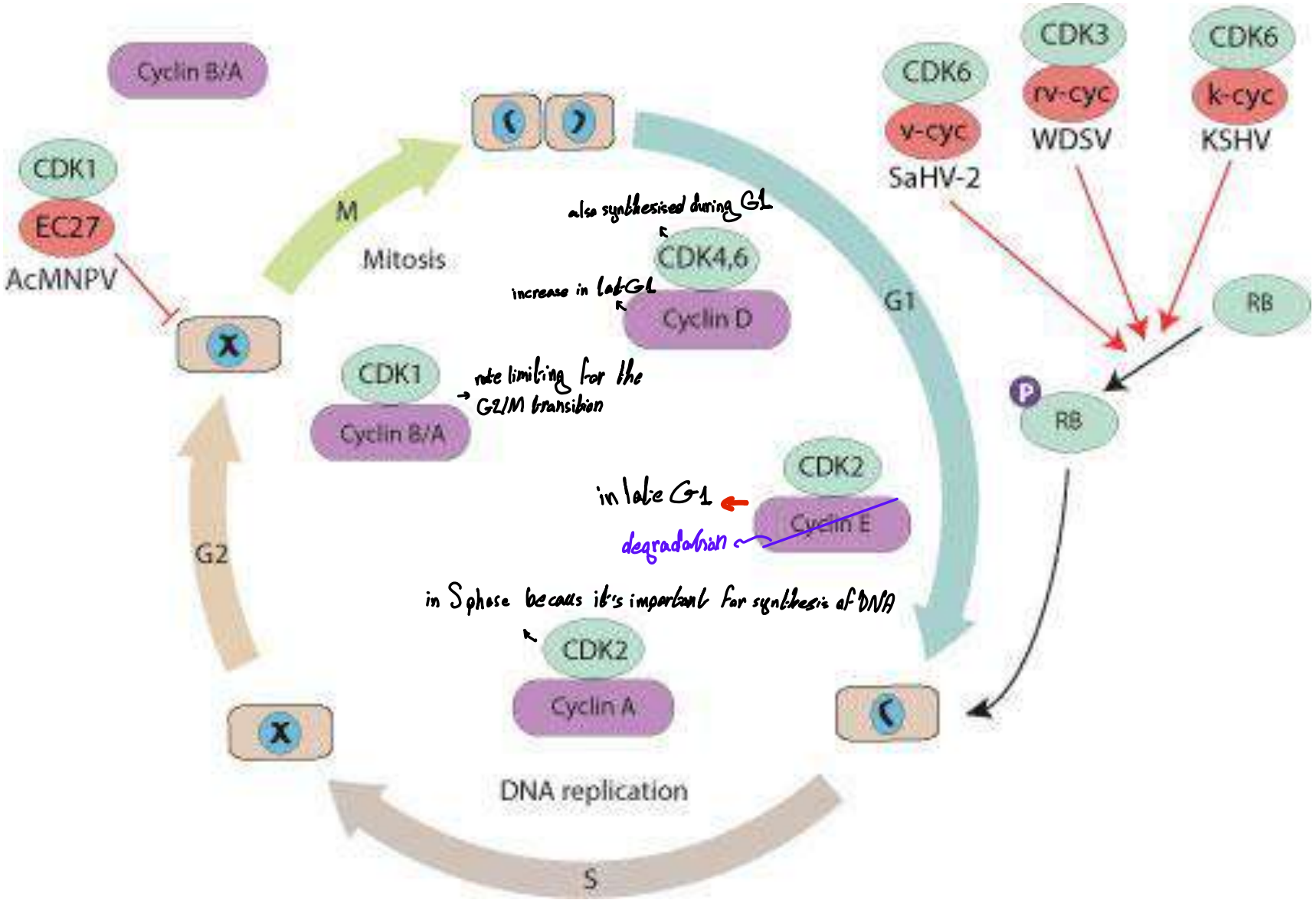
- Other cyclins CDKs are involved in different aspects of cell cycle progression.
- **Cyclin E & CDK2** forms a complex in **late G1**.
- Cyclin E rapidly degraded, and the released **CDK2 then forms a complex with cyclin A.**
- This sequence is **necessary for the initiation of DNA synthesis in S phase.**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

* CDK2 بيكون عامل complex مع cyclin E
← وأنت انا بستناه لشي اخر فـ cyclin E بيصير degradation
وبالتالي CDK2 بيصير release
← وبالتالي CDK2 بيرتبط مع cyclin A

Cyclin A - CDK2 complex necessary for the initiation of DNA synthesis in S phase.

← الانتقال من G2 ← M

← لانه عند الوصول إلى mitosis
لازمكان الخلية (مباشرة تبدأ عملية الانقسام)

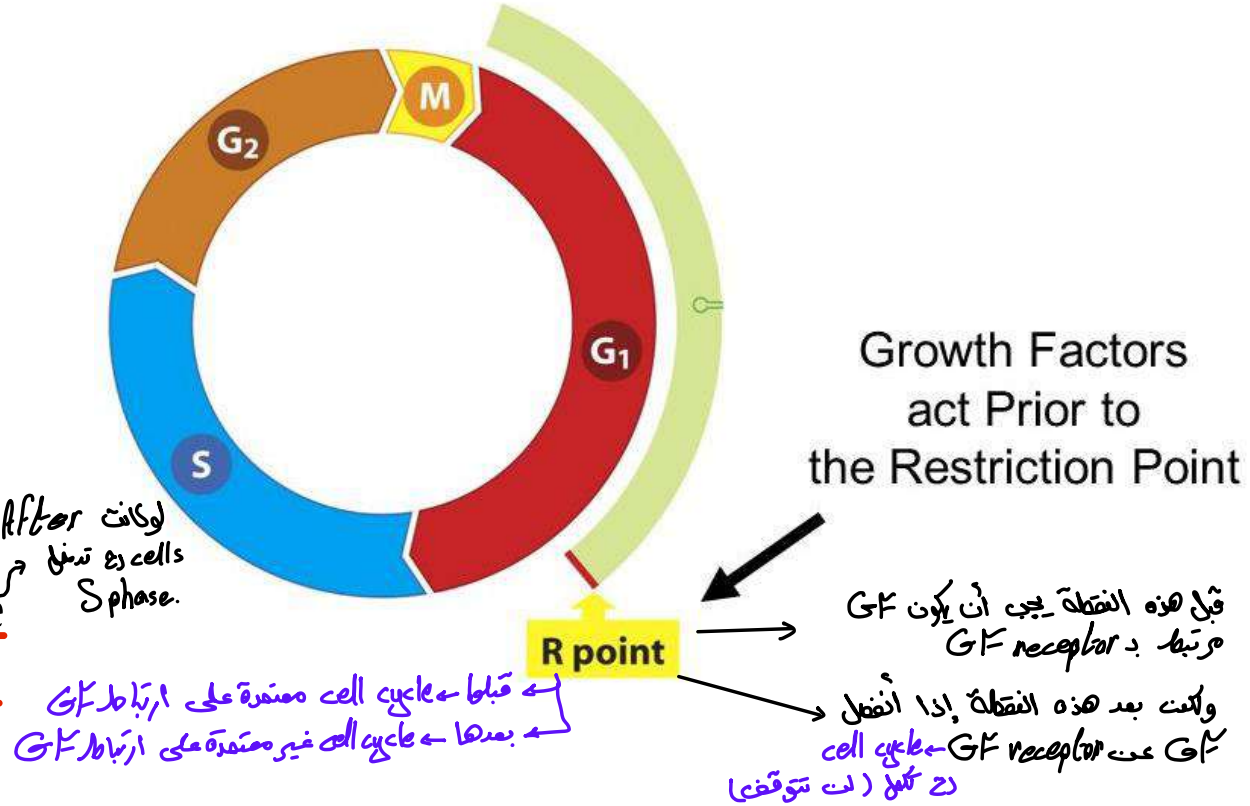

Cyclin B/A
CDK1
EC27
AcMNPV
M
Mitosis
also synthesised during G1
CDK4,6
increase in late G1
Cyclin D
CDK1
Cyclin B/A
rate limiting for the G2/M transition
CDK6
v-cyc
SaHV-2
CDK3
rv-cyc
WDSV
CDK6
k-cyc
KSHV
RB
P
RB
G1
in late G1
CDK2
Cyclin E
degradation
in S phase because it's important for synthesis of DNA
CDK2
Cyclin A
G2
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.

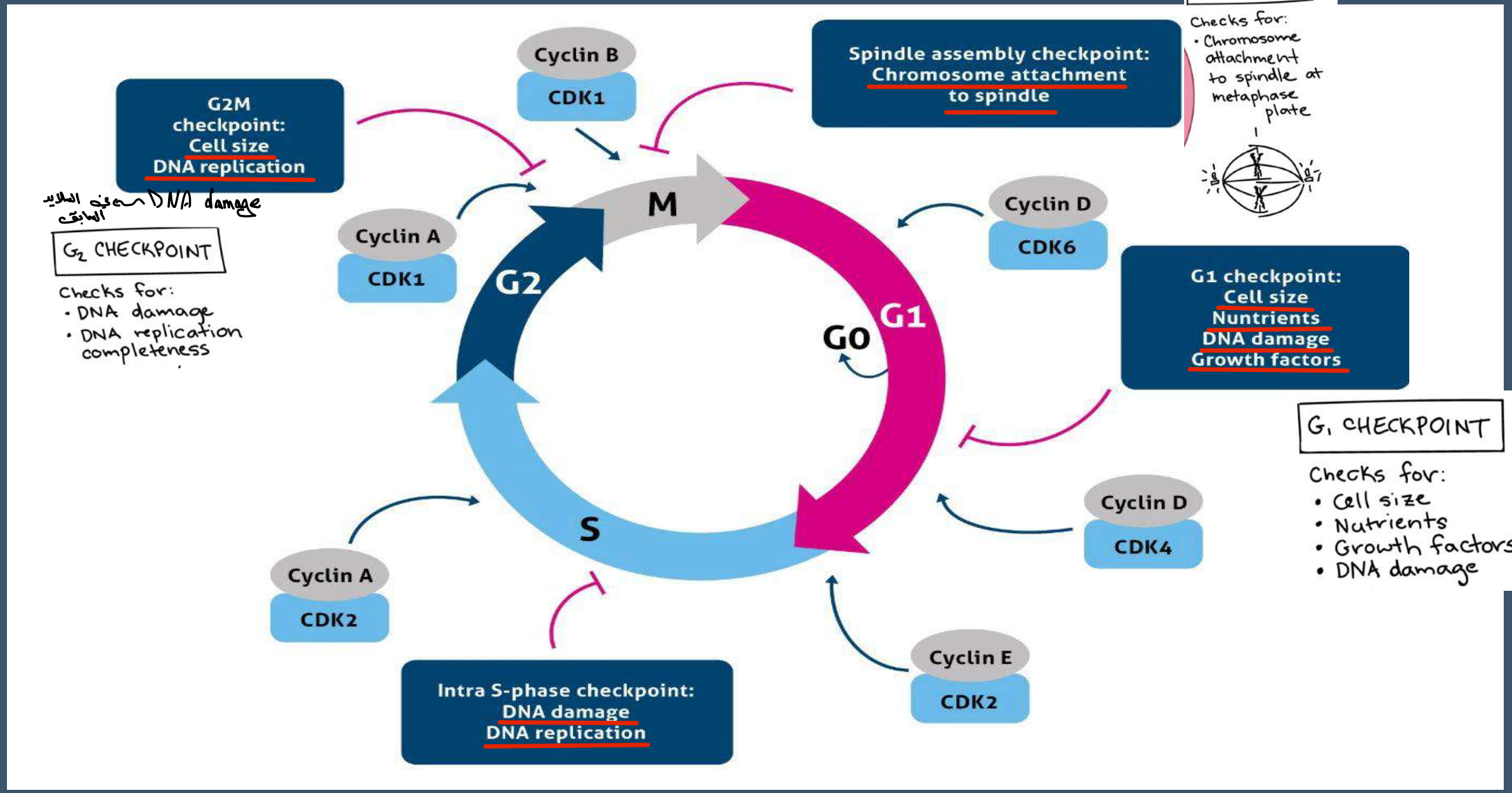
ex:

- 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.



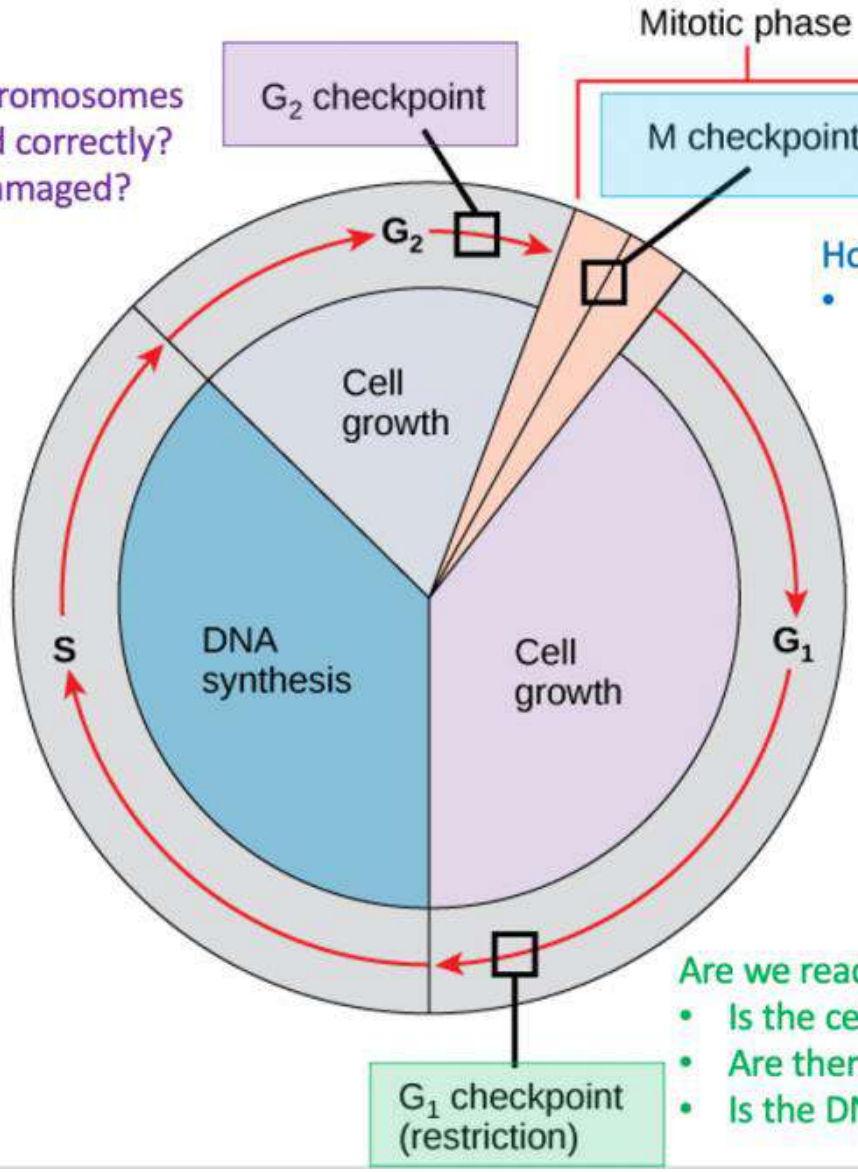
Cell cycle check points

- 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).


G2M checkpoint:
Cell size
DNA replication
Cyclin B
CDK1
Spindle assembly checkpoint:
Chromosome attachment to spindle
SPINDLE CHECKPOINT
Checks for:
• Chromosome attachment to spindle at metaphase plate
DNA damage في السلايد السابق
G2 CHECKPOINT
Checks for:
• DNA damage
• DNA replication completeness
Cyclin A
CDK1
M
G2
Cyclin D
CDK6
G1 checkpoint:
Cell size
Nuntrients
DNA damage
Growth factors
G0
G1
G1 CHECKPOINT
Checks for:
• Cell size
• Nutrients
• Growth factors
• DNA damage
Cyclin D
CDK4
S
Cyclin A
CDK2
Intra S-phase checkpoint:
DNA damage
DNA replication
Cyclin E
CDK2

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

apoptosis مبرمج جينيا" لانه يحتوي على

- 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

Fas receptor — tumor necrosis factor receptor1

cell membrane على receptor يكون في *

بترتبط مع substrate(ligand) ← receptor فبيصير cell signaling

activation of apoptotic proteins و

It can be induced by several stimuli as follows:

The first method

❖ 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).

The second method

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

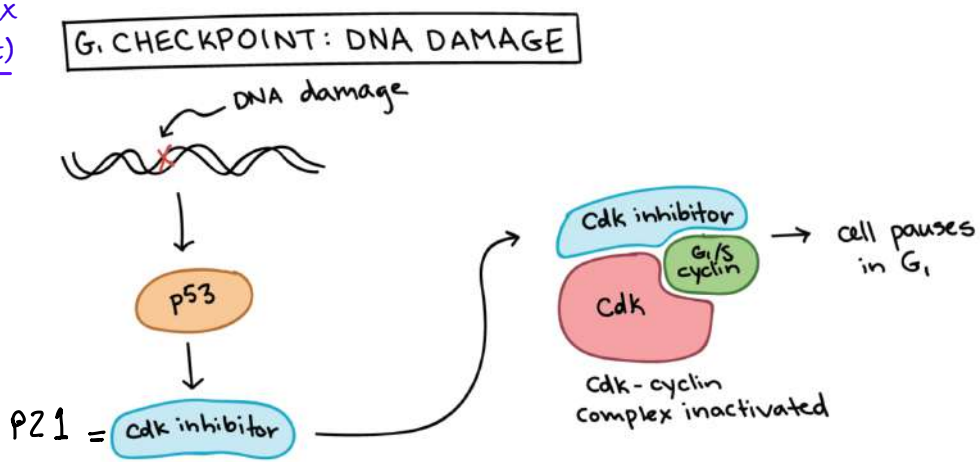
Either repair or apoptosis occurs

- 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**.

Radiation, hypoxia, free radicals and chemical agents as chemotherapy produce DNA damage. → Activation of p53

Activation off p21 (if the damage is small) → Inhibition of CDKs (Important to move from one phase to another) → So the damage can be repaired and then move to the next phase

activate the apoptotic pathway through activation of the apoptotic gene i.e. Bax gene (if the damage is significant)



Apoptosis

damage عالية apoptosis الخلية اللي فيها أقدر أعمل بالتالي ما رح
(Bax غياب بسبب apoptosis عالية وممكن قادر اعمل repair ومش قادر اعمل damage كبير فممكن

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

inactivation ويعمله Bax بيرتبط مع
apoptosis فبالتالي يكون منع

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

Biomarker of cancer

- 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)**.

Induction of apoptosis ⟶ ↑Bax
Inhibition of apoptosis ⟶ ↑Bcl-2

- Mitochondrial membrane becomes more permeable than it was before → Bax creates pores on Mitochondrial membrane
- Is to allow a particular molecule that is normally found within the inter-membrane space allows this molecule to exit the inter-membrane space and enter the cytoplasm, and the name of this molecule is cytochrome c
- Cytochrome C activate, a family of enzymes inside of the cytoplasm called caspases (by an activation cascade that leads to activation of caspases)
- Caspase is a type of enzyme that breaks down proteins

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).

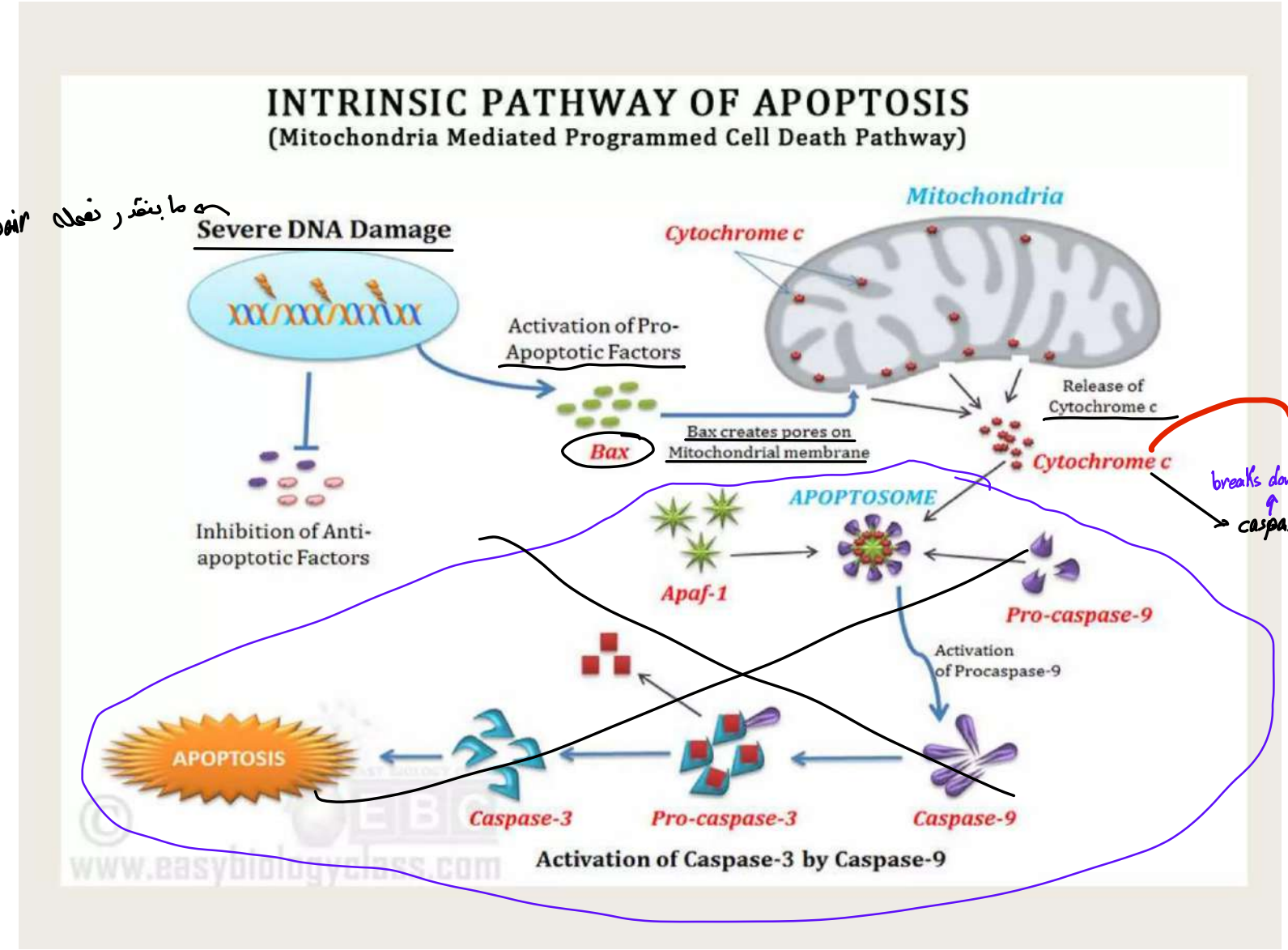
غير مطلوبه

- 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).
   ↳ endonucleases

- 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).
  ↳ رح ناخذه بالمحاضرات القادمة



repair ما بتقدر تعمله

breaks down proteins
caspases
split DNA
endonucleases
Apoptosis