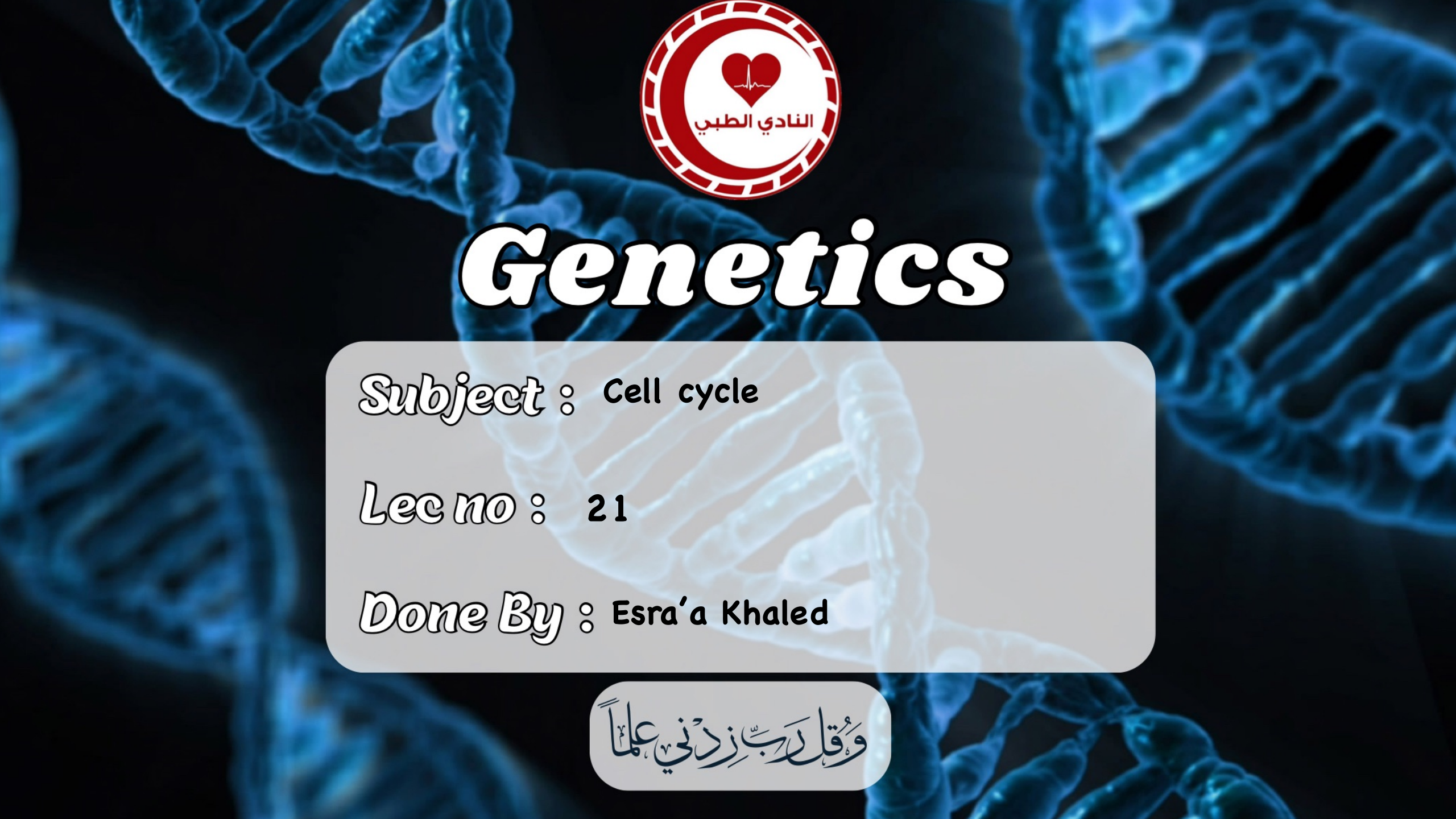


Genetics

Subject : Cell cycle

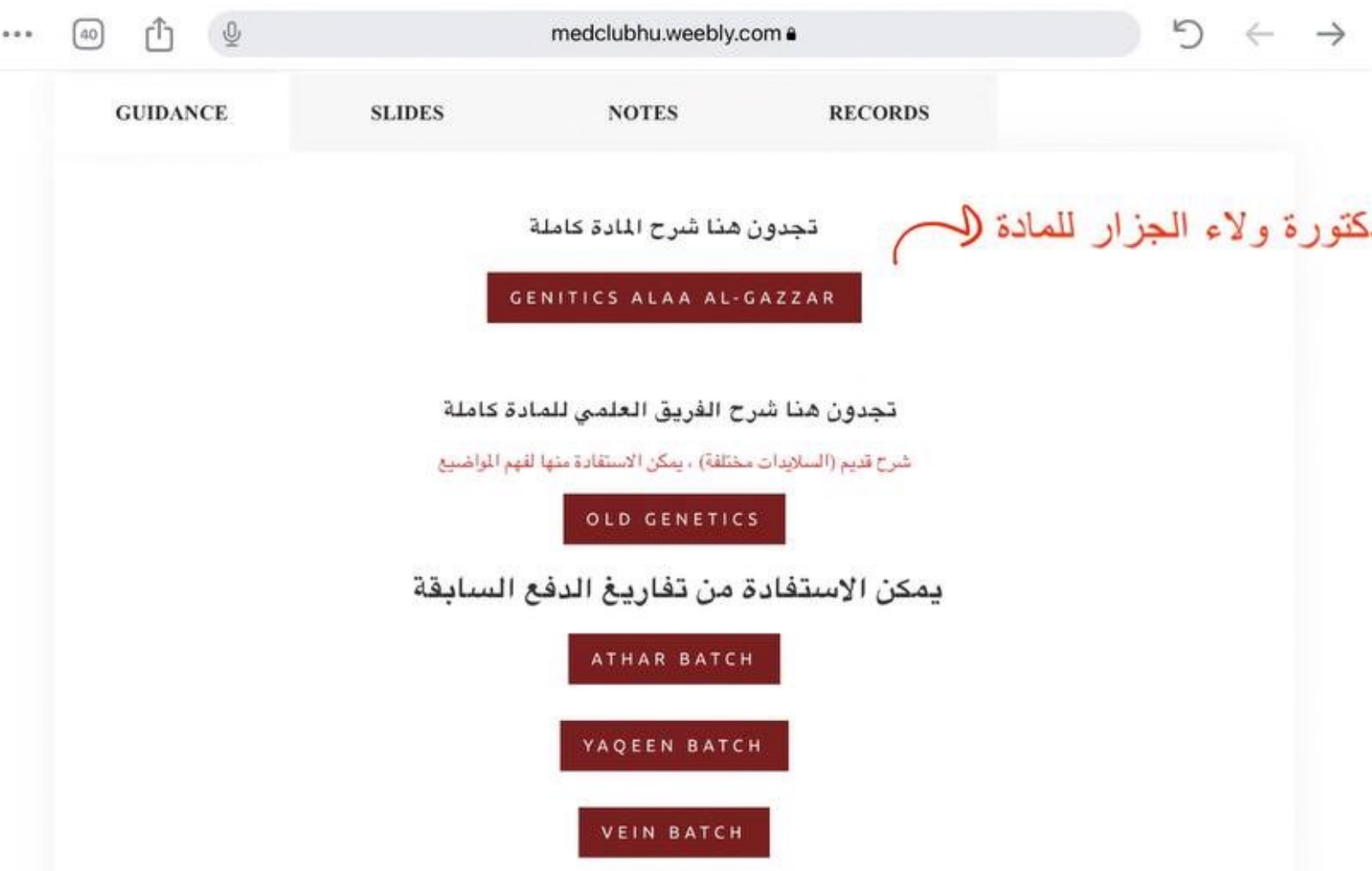
Lec no : 21

Done By : Esra'a Khaled

وَقُل رَّبِّ زِدْنِي عِلْمًا

تجدون في guidance مادة الجينتكس على موقع النادي

للوصول الى guidance الباثو و تفاريغ المادة كاملة :



شرح الدكتورة ولاء الجزار للمادة

كل اعمال الفريق العلمي تنشر على قناة التيليغرام

Cell cycle

Dr. Walaa Bayoumie El Gazzar

Nebras Melhem

ليش ال cell cycle مهمة ؟
لأنه لو صار damage أو injury معين و ماتت الخلايا رح نحتاج خلايا جديدة فبتيجي عن طريق ال cell cycle

Cell Cycle

إكمال / انهاء

- 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.**

هي المرحلة الي ما قبل ال interphase

- **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.

في خلايا بتقضي طول حياتها بمرحلة ال G 0 لأنها ما بتنقسم (زي الخلايا العصبية)
فما في داعي يدخلو في عمليات ال interphase

2 phases :

The Cell Cycle

مرحلة متوسطة ، و ما بصير فيها أي نوع من الانقسام

1) **Interphase**

The cell grows and copies its DNA

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

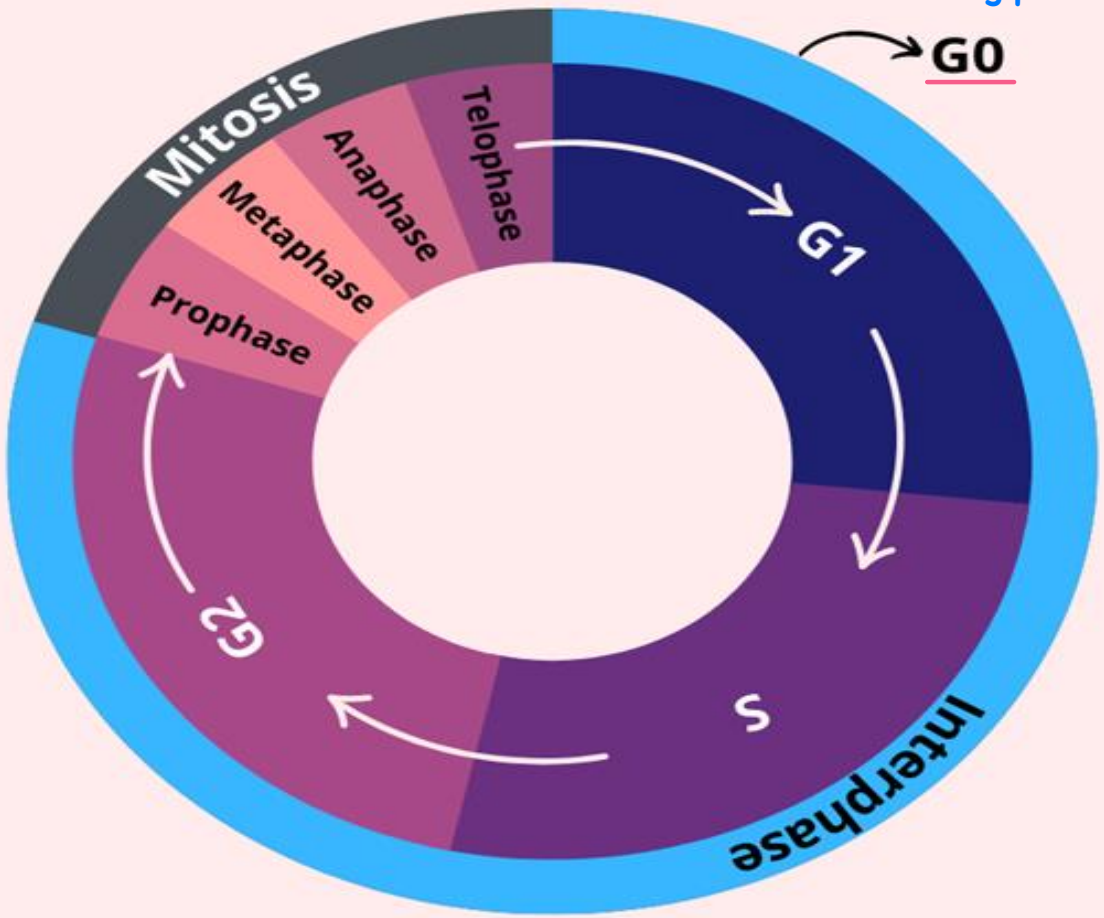
2) **Mitosis** هون بصير في انقسام

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

تعتبر ال resting 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)

* كل phase بتاخد ساعات معينة و اكثر phase فيها اختلافات
هي ال G1 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.

* بالخلايا السرطانية أو بالخلايا المكوّنة للدم ال cell cycle ممكن تاخد فقط 24 ساعة

* في اختلافات بال cell cycle بين الخلايا ، مثلاً خلايا الكبد ممكن تاخد من 6 اشهر ل 12 شهر لحتى تنقسم

❖Events for each phase:

➢**G1 phase**: هي اطول phase

Q : which of the following takes the longest time to complete ? 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.

بننتج ال RNA و ال Proteins عشان نقدر نمشي من phase ل phase لنوصل لل mitosis

+ ال proteins الها دور بال regulation فهي مهمة

Cell Cycle Phases

➢ **S phase**: بهاي المرحلة بتصنّع ال DNA & RNA

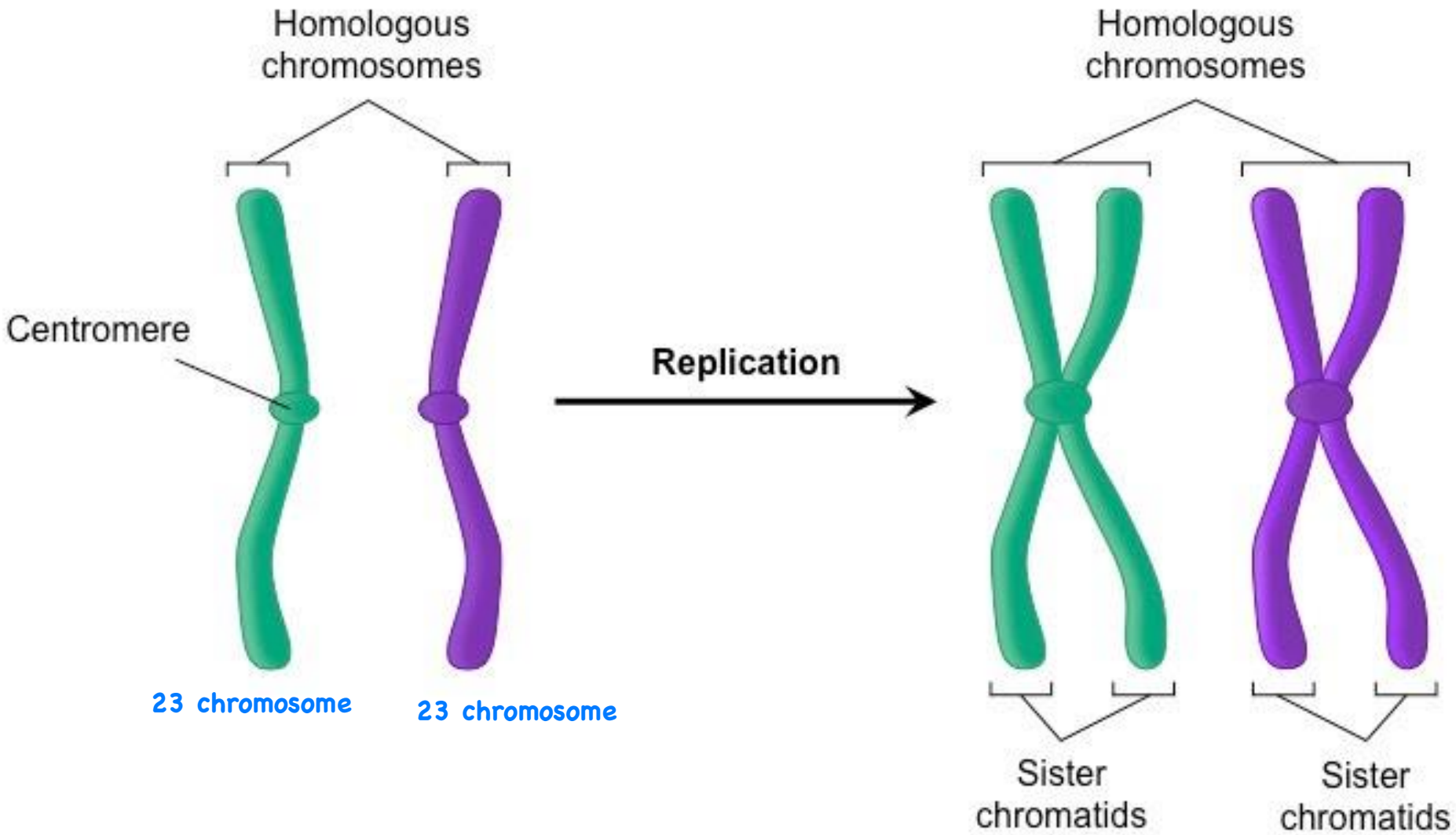
عدد الكروموسومات 46 ، يعني 23 زوج من الكروموسومات و هاد اسمه diploid
لكن بال S phase رح نعمل replication لهدول الكروموسومات فبصير عنا بنسميها tetraploid (23 , 23 , 23 , 23)

- 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**: المرحلة التجهيزية الي ما قبل ال mitosis

- 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).

* هاي العملية بتصير بال S phase



23 chromosome

23 chromosome

2 sister chromatids

Cell Cycle Phases

➢ **M phase**:

اسرع مرحلة

- It is the shortest phase taking about **one hour**.

بهاي المرحلة رح ينفصلو ال 2 sister chromatids

- 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.

و رح يتحركو باتجاه ابعد نقطة بال cell

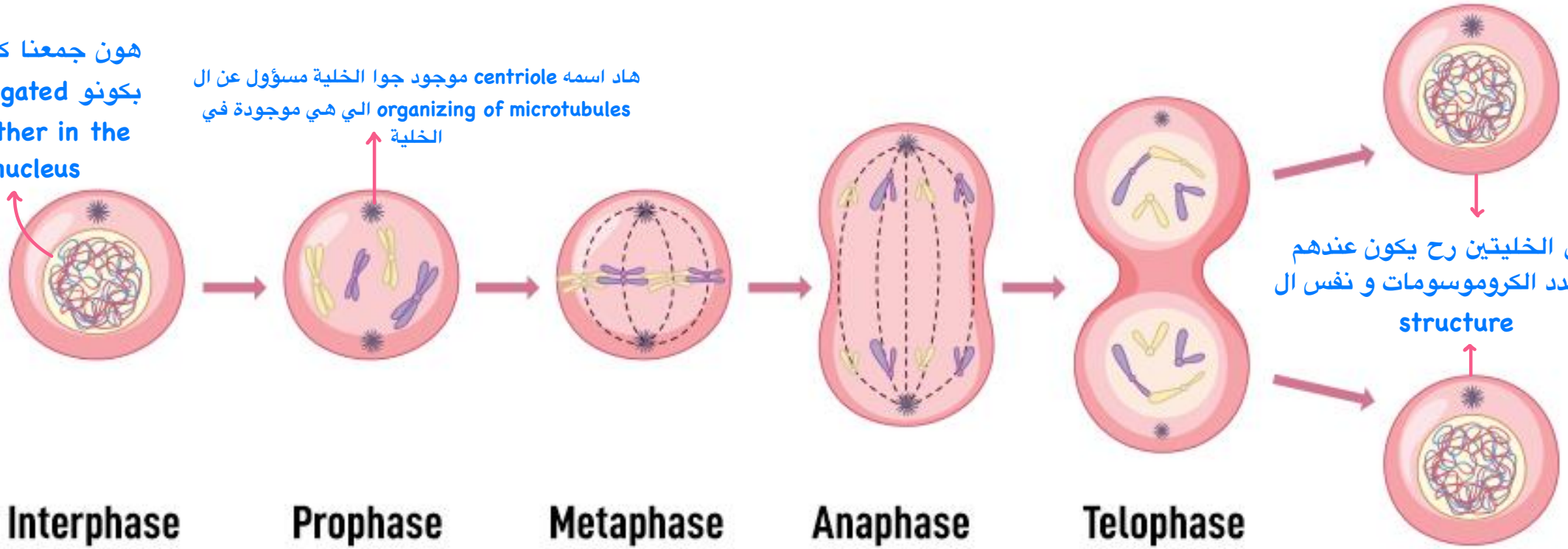
أسماء ال G 0 :

- 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.

يعني الخلايا الي بتنقسم ممكن ترجع تدخل في عملية ال cell cycle أو ممكن تروح عال G0 و تضلها functional و تشتغل شغلها ، لكن مش ضروري تروح عال interphase و يصيرلها division

هون جمعنا كل شي بكونو aggregated together in the nucleus

هاد اسمه centriole موجود جوا الخلية مسؤول عن ال organizing of microtubules الي هي موجودة في الخلية



هدول الخليتين رح يكون عندهم نفس عدد الكروموسومات و نفس ال structure

تعتبر اول مرحلة بال cell cycle لكن مش بال mitosis

هاي اول مرحلة بال mitosis

رح اكتب تفاصيل المراحل هون

١) Prophase : بهاي المرحلة ما رح نتدخل بالكروموسومات بتكون ترتبت بس ، فأول أشي ال centriole رح ينقسم و يصير في 2 centrioles ثاني اشي ال nuclear envelope الي كان موجود بال interphase اختفى بال prophase

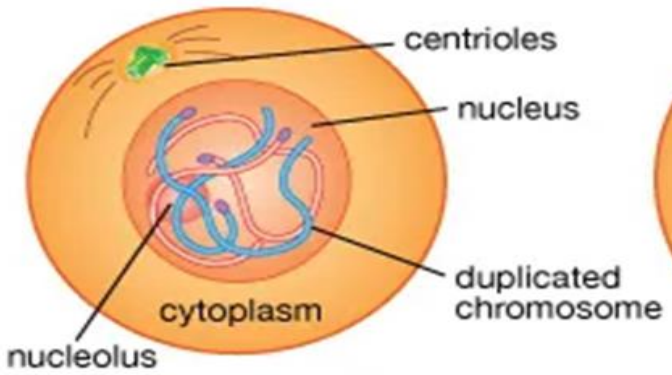
٢) Metaphase : هون الكروموسومات رح تترتب بالوسط عن طريق ال centromeres تبعت الكروموسومات ، بحيث انه هدول ال centromeres بعملو attachment مع ال spindle fibers الي جاية من ال microtubules تبعت ال centrioles ، طبعاً ال centriole الواحد موجود على قطب و التاني على القطب الآخر

٣) Anaphase : كل centriole من هدول الاتنين رح يبلشو يشدو بالكروموسومات باتجاه ال poles (الأقطاب) تبعتهم ، فال centromere الي كانت رابطة الكروموسومات مع بعض رح تفصلهم ، و بتصير الكروموسومات مشدودة باتجاه ال centrioles ، برضه صار في pinching بوسط ال cell

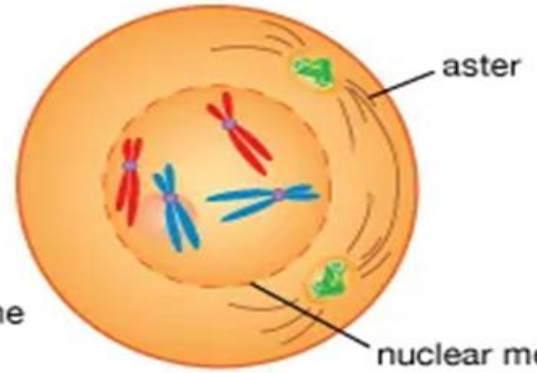
٤) Telophase : هون بصير شغلتين اول وحدة انه ال pinching بكتمل يعني بضل يصير constriction لبين ما ينفصلو عن بعض ثاني شغلة انه ال nuclear envelope الي اختفى بال prophase برجع يبين بهاي المرحلة

* آخر شي بصير mitosis و بنتج خليتين عندهم نفس عدد الكروموسومات و نفس ال structure

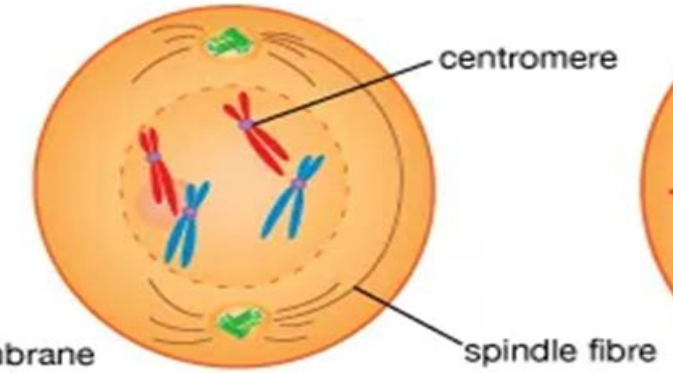
Mitosis, or somatic cell division



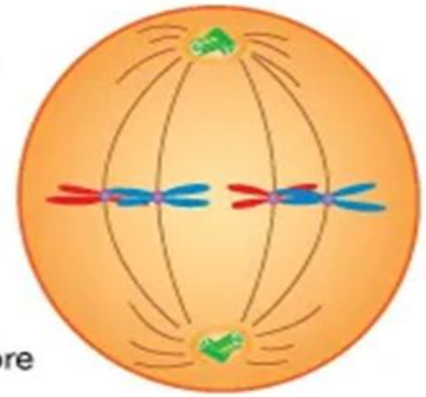
Prior to mitosis, each chromosome makes an exact duplicate of itself. The chromosomes then thicken and coil.



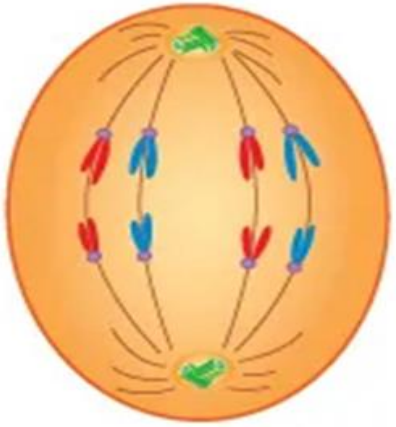
In early prophase the centrioles, which have divided, form asters and move apart. The nuclear membrane begins to disintegrate.



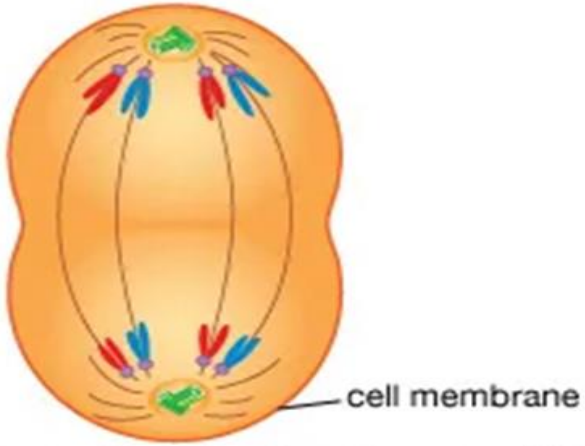
In late prophase the centrioles and asters are at opposite poles. The nucleolus and nuclear membrane have almost completely disappeared.



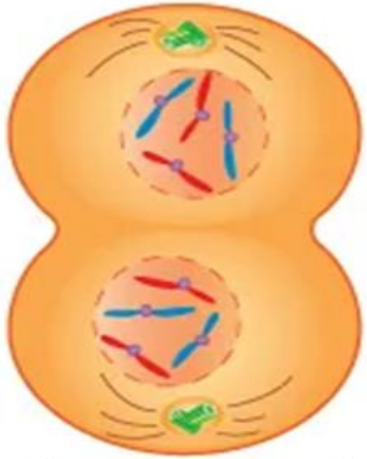
The doubled chromosomes—their centromeres attached to the spindle fibres—line up at mid-cell in metaphase.



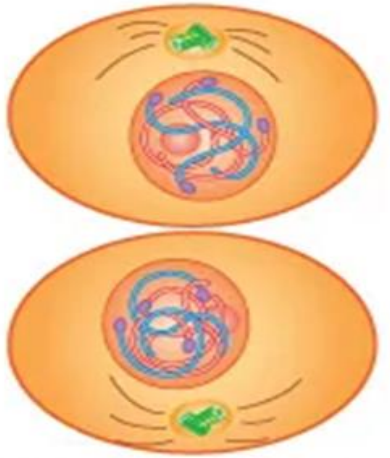
In early anaphase the centromeres split. Half the chromosomes move to one pole, half to the other pole.



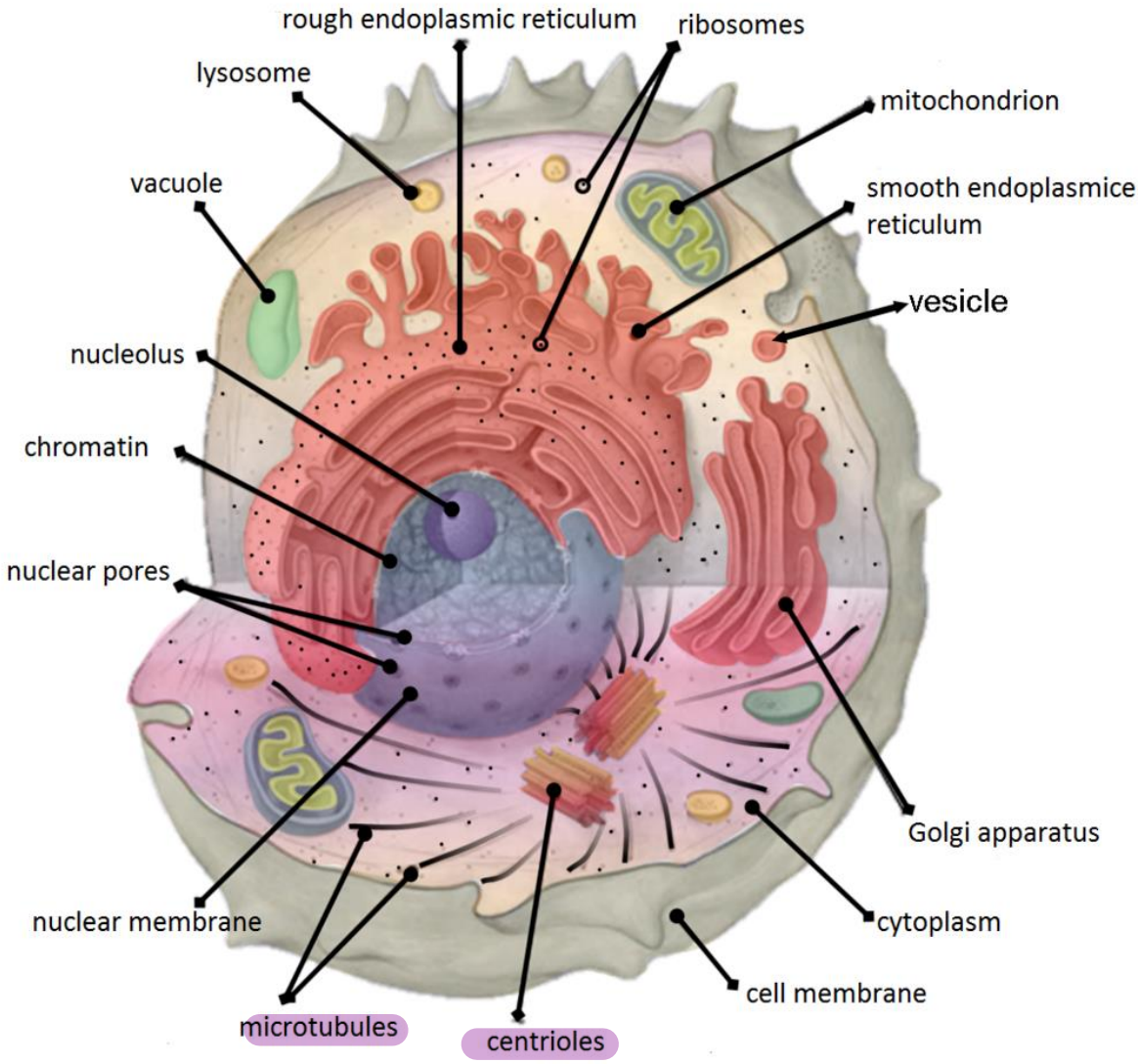
In late anaphase the chromosomes have almost reached their respective poles. The cell membrane begins to pinch at the centre.



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.

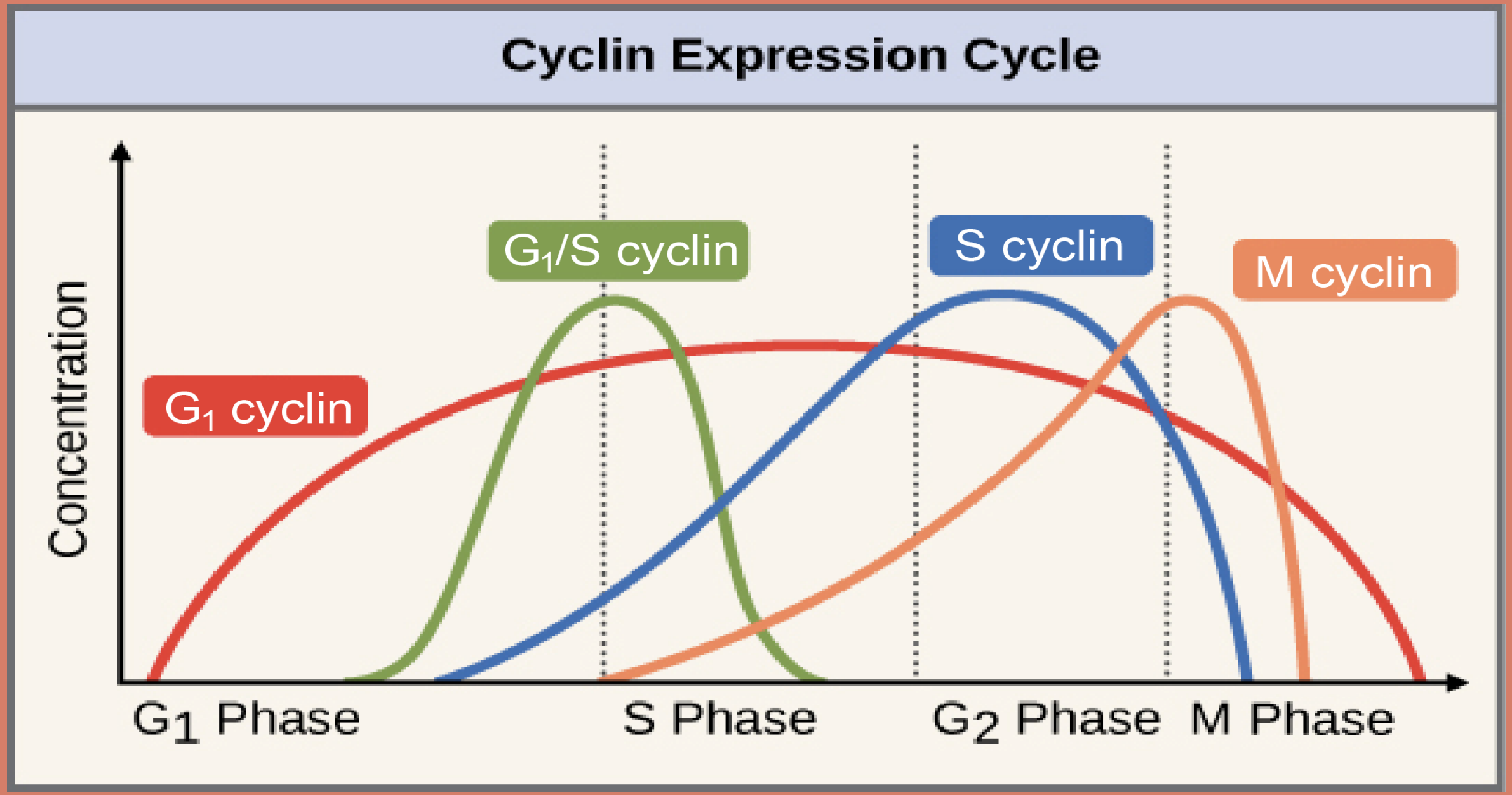
زي ما حكينا في بروتينات بتعمل regulation لل cell cycle هدول ال proteins
اسمهم cyclins بساعدونا نتحرك من نقطة لنقطة

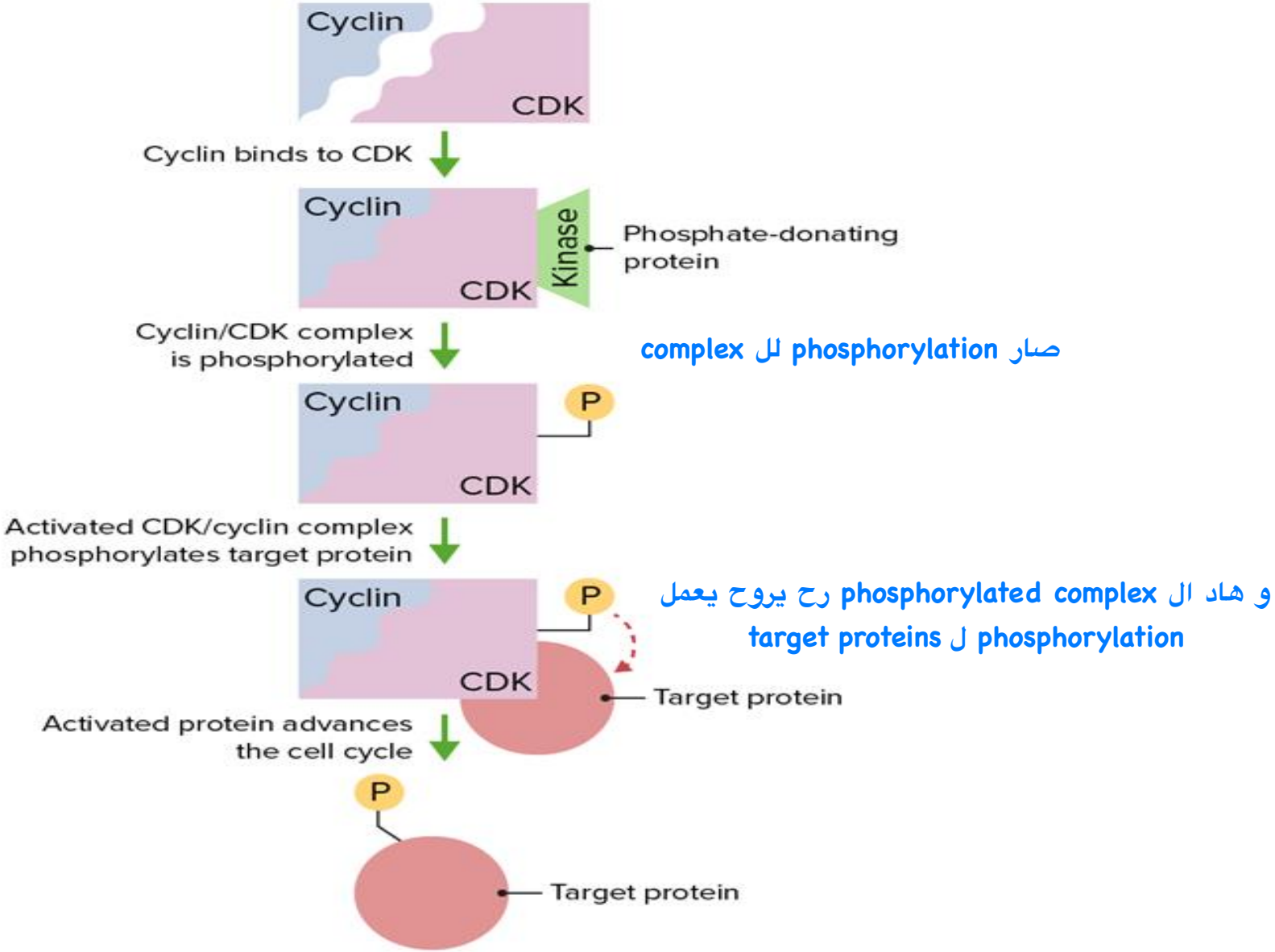
- The concentration of different cyclins **increases & decreases during different phases** of the cell cycle, and hence their name.

بتغير ال concentrations تبعتهم

- 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.

مش حفظ ، بس نشوف اختلاف ال concentrations بين ال phases





صار phosphorylation لل complex

و هاد ال phosphorylated complex رح يروح يعمل phosphorylation ل target proteins

Control of cell cycle

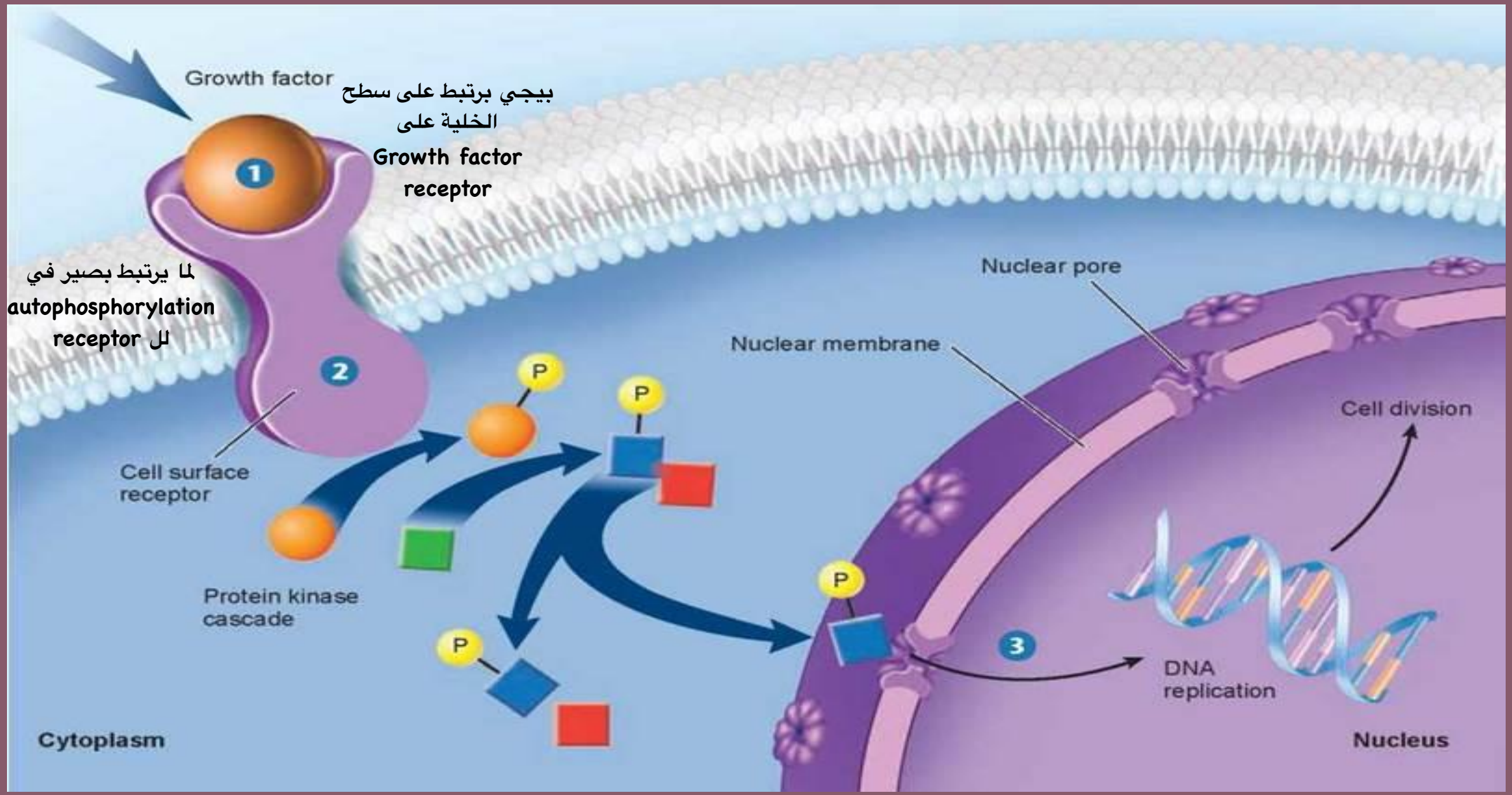
- The cell cycle is initiated by the **binding of a growth factor** to **growth factor receptor** on the plasma membrane of the cell.

- 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.**

بصير عن طريق ال cascade of phosphorylation التابعة لارتباط ال growth factor
بال growth factor receptor

كيف بتبلش ال cell cycle أو شو اساسها ؟ اساسها هو ال growth factor لما يرتبط بعمل activation لل cell cycle



ال cyclins مهمين ، احفظو اسمائهم و بأي phase موجودين

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).

Retinoblastoma

- The **dephosphorylated Rb protein binds to & inactivates a protein called transcription factor E2F.**

هاد ال transcription factor بنحتاجه لحتى نعمل transcription لجينات بتصنع بروتينات بتحولنا من مرحلة ال G1 إلى S

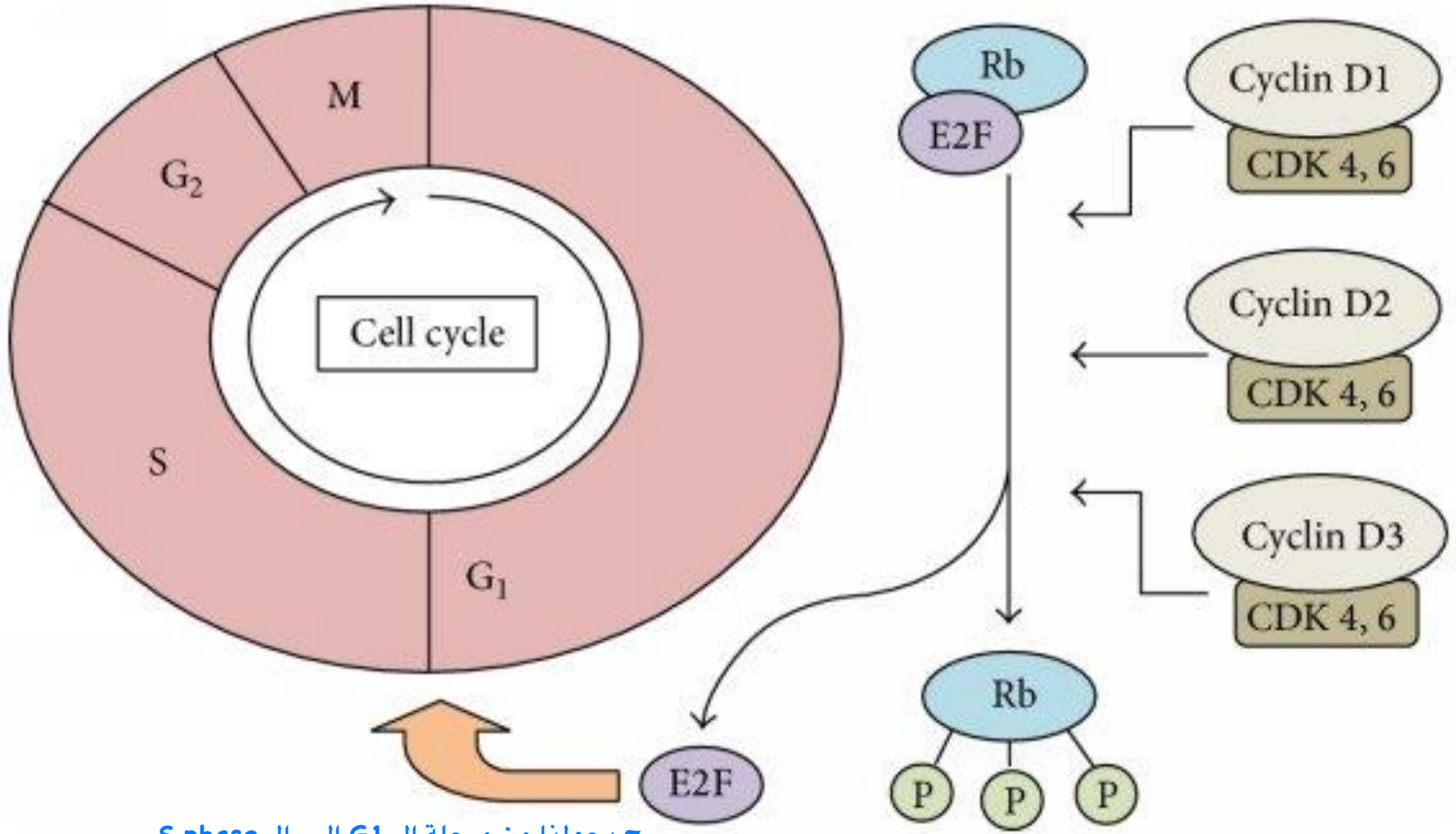
- The **cyclin D-CDK4/CDK6 complex catalyzes phosphorylation of the retinoblastoma (Rb) protein.**

هاد ال Rb مع ال E2F بكون inactive ، فهون بيجي دور ال cyclin D بعمل phosphorylation لل Rb

فبالتالي رح يترك ال E2F و بصير activated

- 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).



رح يحولنا من مرحلة ال G1 الى ال S phase

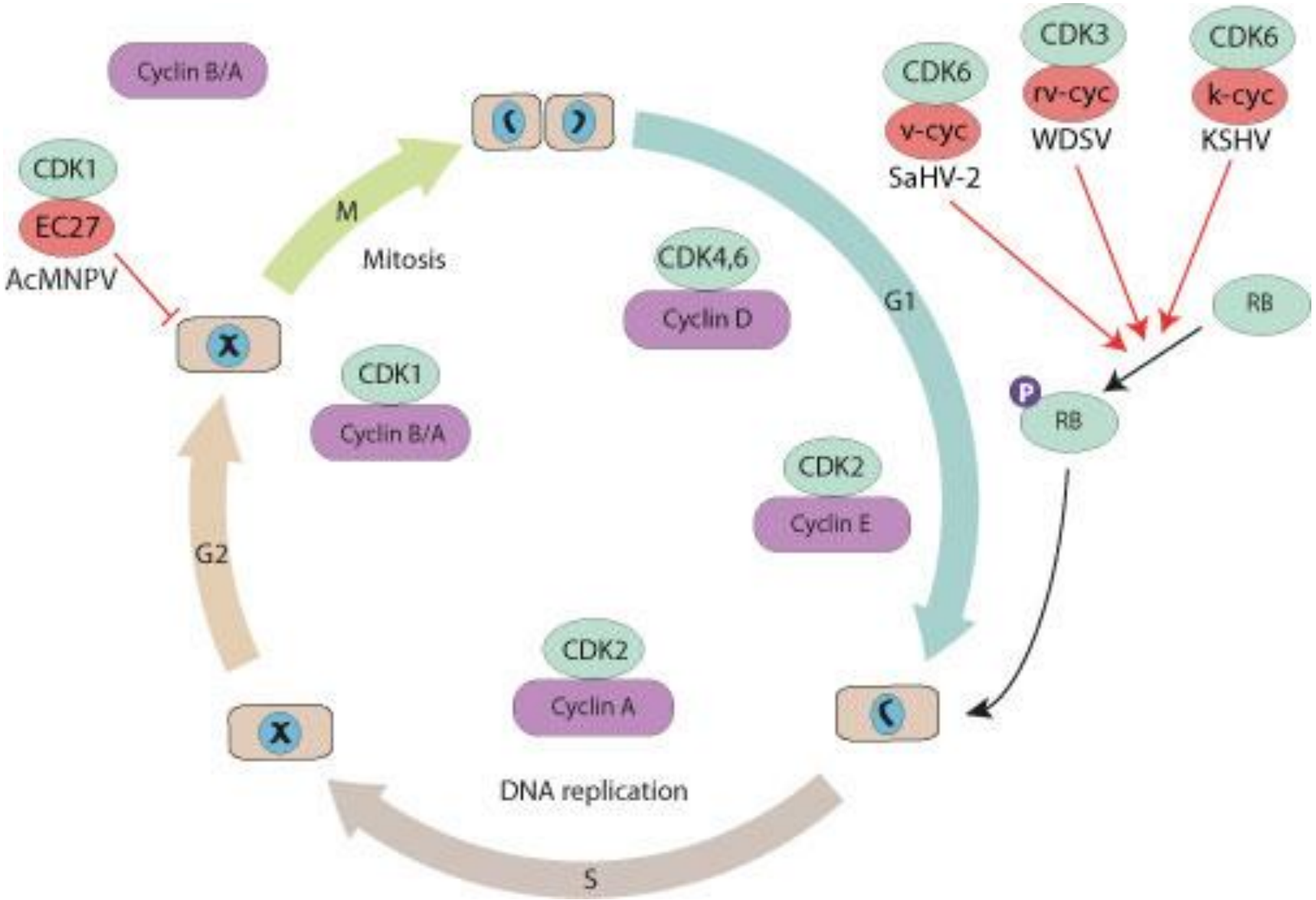
Control of cell cycle

- 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.** ارتباط ال CDK2 مع ال Cyclin A ضروري لحتى نبلش ال DNA synthesis بال 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.**

تعتبر rate limiting لأنه اول ما نوصل ال mitosis بنبلش انقسام فما رح نقدر نرجع لمراحل ال interphase

ارتباط ال CDK1 مع ال Cyclin B مهم عشان ينقلنا من ال G2 phase إلى ال Mitosis


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

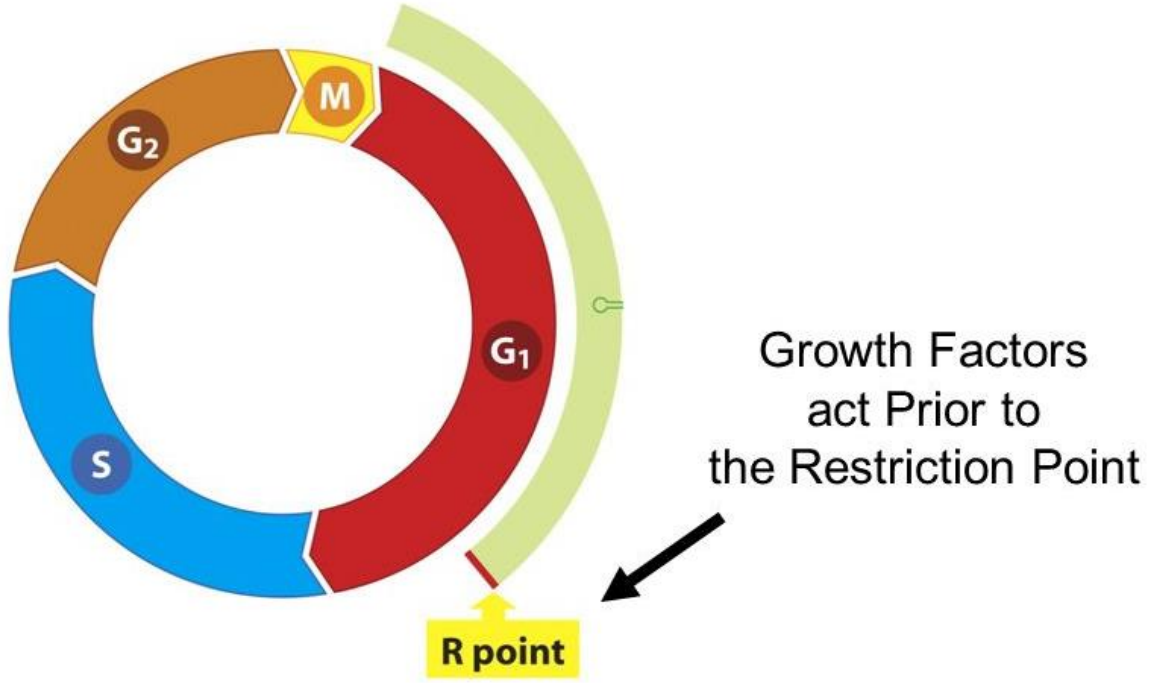
Restriction point

قبل هاي النقطة لازم يكون ال growth factor مرتبط بال receptor تبعه

- 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.

لكن بعد هاي النقطة بتبطل معتمدة على ارتباط ال growth factor بال receptor

- 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.

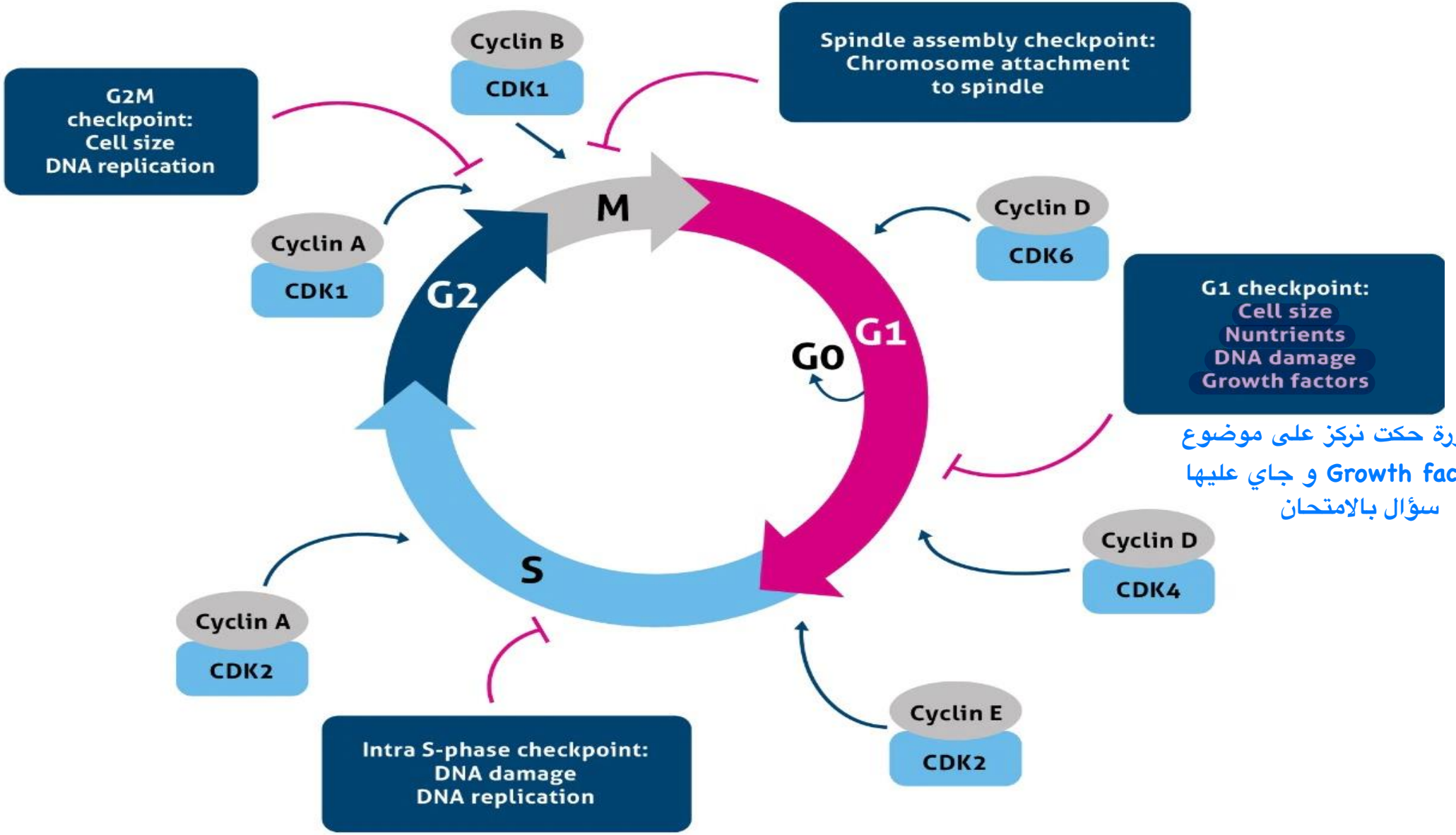


نقاط تفتيش

Cell cycle check points

- DNA, chromosome, chromosome segregation integrity is continuously monitored throughout the cell cycle in **4 check points**. بتشيك إذا كل شي ماشي تمام
- *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. بنتأكد إذا الكروموسومات انقسمت صحيح او لا
- 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).

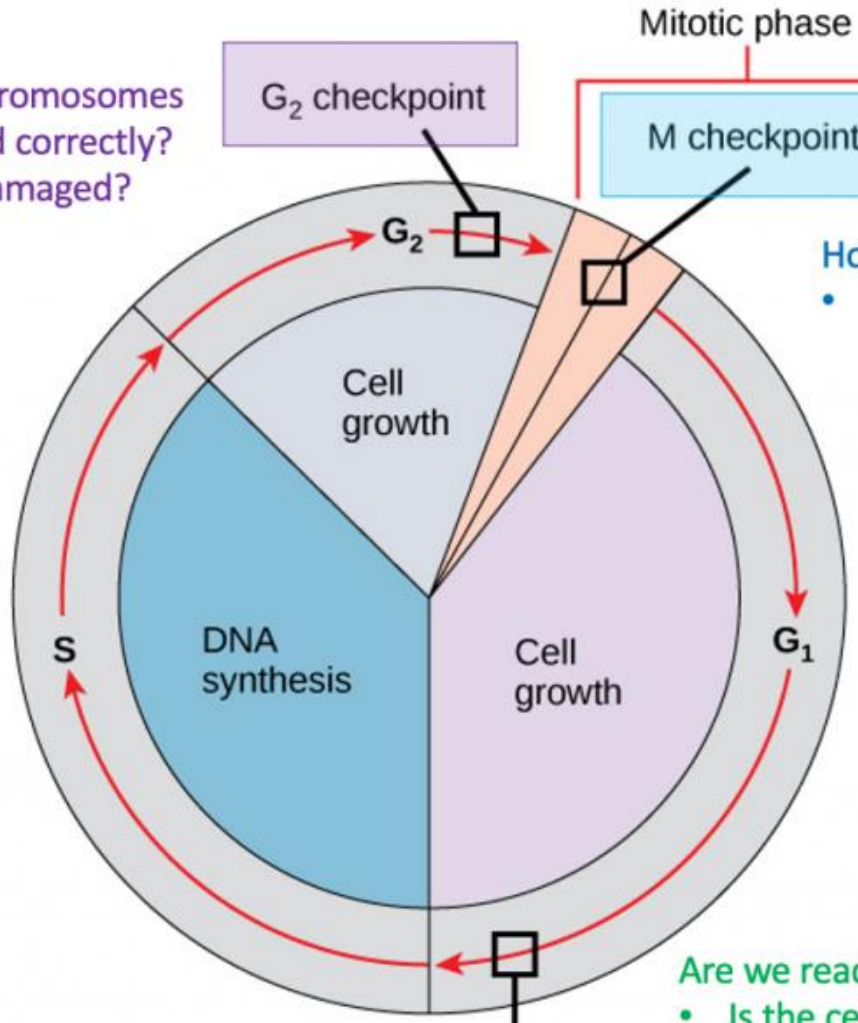
الخلايا ما رح تمشي بال phases إذا كان في أي نوع من المشاكل لازم يصيرله repair و إذا ما صارله repair رح يعمل Apoptosis



* الدكتورة حكت نركز على موضوع ال Growth factors و جاي عليها سؤال بالامتحان

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

يعني مبرمج جينياً انه يحتوي على Apoptosis

- 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).

External things cause DNA damage:

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

بس يصير activation لل P53 رح يعمل activation لبروتين تاني اسمه P21
و ال P21 بعمل arrest لل cell cycle فبعمل inhibition لل CDK

- 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**.

رح نوقف ب phase حسب ال damage مثلاً إذا كان ال damage متوسط بصير في induction ل P21
بعدين بيجي يعمل inhibition لل CDK و بتوقف ال cell cycle ، أما إذا كان ال damage هائل و ما
بتصلح فبتنشط ال Apoptotic pathway عن طريق تنشيط ال BAX gene

و حكينا انه ال CDK ضروريين عشان ننتقل من مرحلة لمرحلة و
لما ما يكون في CDK ال cyclins ما رح يرتبطو بإشي

Apoptosis

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

ال cancer بصير لما الخلية تكون damaged و ال Bax مش موجود و
ما في DNA repair فبتضل الخلية damaged و مستمرة بالانقسام

Apoptosis للـ inhibition بعمل

- **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.

اول شي بصير في فتحة بال mitochondria بتطلع ال cytochrome C و خروجه رح يعمل activation cascade و هاد رح يعمل activation لل Caspases

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

مجموعة انزيمات بتعمل تكسير للبروتينات

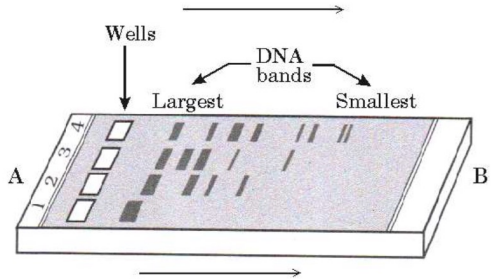
- They derive their name from the "c" from cysteine amino acid present in the catalytic site of the enzyme and **caspase** refers to their unique ability to cleave the substrate after aspartic acid residue.

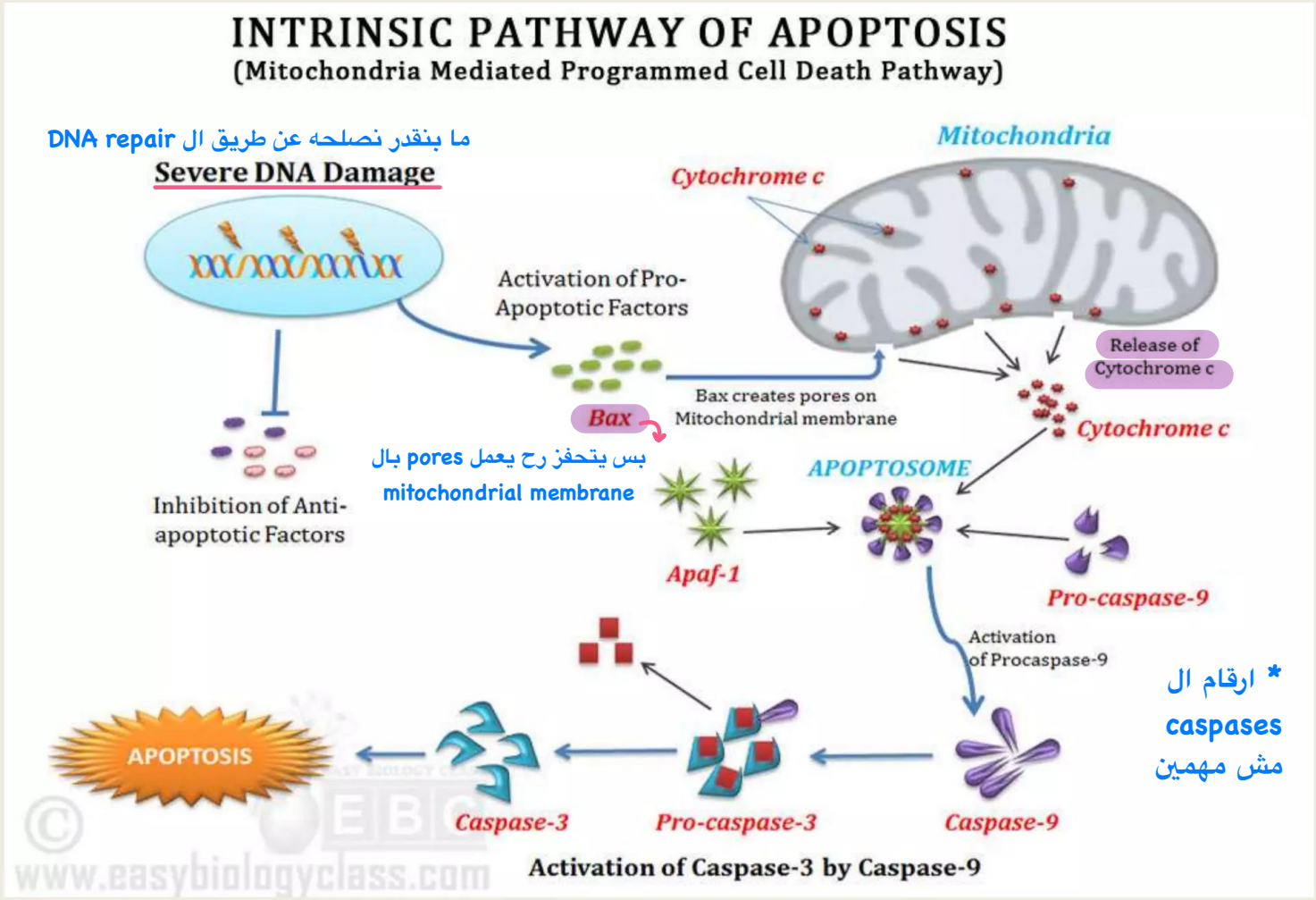
حكت الدكتورة مش مهم كتير نعرف عن التسمية

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 زي السلم appearance on gel electrophoresis (it is a diagnostic test).




INTRINSIC PATHWAY OF APOPTOSIS
(Mitochondria Mediated Programmed Cell Death Pathway)
ما بنقدر نصلحه عن طريق ال DNA repair
Severe DNA Damage
Mitochondria
Cytochrome c
Activation of Pro-Apoptotic Factors
Release of Cytochrome c
Bax creates pores on Mitochondrial membrane
Bax
Cytochrome c
بس يتحفز رح يعمل pores بال mitochondrial membrane
APOPTOSOME
Inhibition of Anti-apoptotic Factors
Apaf-1
Pro-caspase-9
Activation of Procaspase-9
* ارقام ال caspases مش مهمين
APOPTOSIS
Caspase-3
Pro-caspase-3
Caspase-9
Activation of Caspase-3 by Caspase-9
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