BIOCHEMISTRY OF CELL PROLIFERATION AND CELL DEATH

Possible cell fates:

1) Growth and division (cell proliferation)
2) No division but differentiation
3) Elimination by natural death

Cell proliferation under normal conditions:

a. Replacement of daily loss:

- Occurs in almost all tissues
- Most intensive in bone marrow, intestinal epithelia, basal layer of the skin

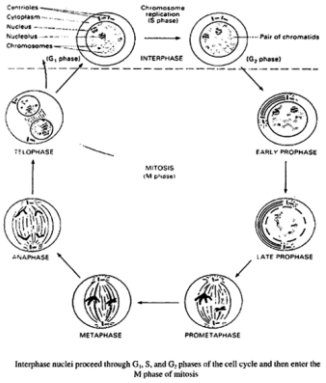
b. To meet increased demand:

- Loss of blood, wound healing
- Cell proliferation regulation:
  - Paracrine regulation
  - Autocrine regulation

Phase	Description	Part of Interphase
G1	Gap between mitosis and DNA replication; cell growth	Yes
S	DNA synthesis; chromosome duplication	Yes
G2	Gap between DNA synthesis and mitosis; cell growth	Yes
M	Mitosis; chromosome condensation and segregation	No
G0	Quiescent state; non-proliferating; can reenter cycle	N/A

N/A stands for "Not Applicable." In this context, it means that the G0 phase does not fall under the category of being part of interphase or not, as it is a separate quiescent state outside of the typical cell cycle progression.

CELLULAR EVENTS IN MITOSIS



Interphase nuclei proceed through G_1, S, and G_2 phases of the cell cycle and then enter the M phase of mitosis

1-Prophase

-Centrosome separation and migration
-Chromatin condensation: H1 histone phosphorylation
-Chromosomes are kept together by cohesin complexes.
-Fragmentation of the nuclear membrane: lamin phosphorylation (late prophase)

2-Prometaphase

- Binding of chromosomes to microtubules

3-Metaphase

- Chromatin migration- mitotic spindle
- Formation of the metaphase plate

4-Anaphase: Sister chromatids are separated: cohesin degradation, mitotic spindle elongation

5-Telophase

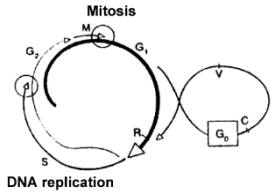
- Nuclear membrane is formed: lamin dephosphorylation.
- De-condensation of chromosomes: H1 histone dephosphorylation

6-Cytokinesis : Division of the cytoplasm and separation of daughter cells (actomyosin ring)

THE FUNCTIONAL CELL CYCLE

- Conventional cell cycle: G1, S, G2, and M phases
- G1 activities may begin during the previous cycle, overlapping with G2 and mitotic events
- Early preparation for mitosis (G2) may overlap with S phase
- Cells can exit from G1 into the G0 quiescent state and re-enter the cycle

Critical points in the cell cycle:

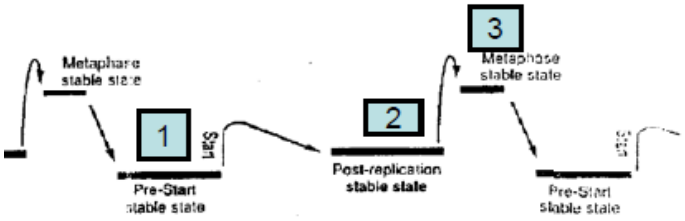


- C: competence
- V: end of entry
- R: restriction point, end of progression

SIMPLIFIED PRESENTATION OFTHE SOMATIC CELL CYCLE

Three stable states:

- pre-start stable state,
- post-replication stable state
- metaphase-stable state



A stable state refers to a phase or condition during which the cell is relatively constant, well-balanced, and not undergoing significant change or progression.

In these stable states, cellular processes and molecular activities maintain a steady level, **allowing the cell to perform specific tasks or prepare for the next stage in the cell cycle.**

Once the necessary conditions are met, the cell transitions from one stable state to another as it moves through the different phases of the cell cycle.

In synchronized cell cultures highly **increased protein kinase activity** was observed after the **pre-start state and following replication**.

The observation of a **cyclic increase in cyclin** levels paralleling **increased protein kinase activity** in synchronized cell cultures suggests that cyclins and their associated CDKs work together to ensure the correct timing and coordination of events within the cell cycle.

Biochemistry II BIOCHEMISTRY OF CELL PROLIFERATION AND CELL DEATH
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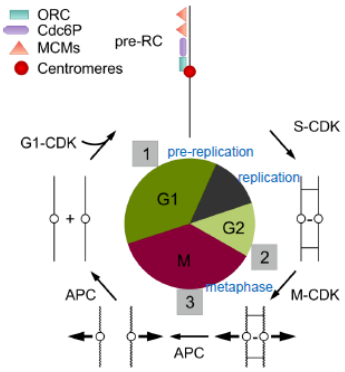
CYCLINS, KINASES, INHIBITOR SAND TRANSITIONS

- **Cyclins:** specific proteins with oscillating concentrations during the cell cycle

Cyclins activate cyclin-dependent kinases (CDKs) at appropriate moments.

- Cyclin oscillations are influenced by transcriptional control of mRNA production and proteolysis via ubiquitin ligases.
- **CDK inhibitors (CKIs)** represent another layer of control.
- Constitutive and inducible CKIs exist, with inducible CKIs responding to special circumstances (e.g., DNA damage)
- Degradation of **CKIs** required for cell cycle progression.

MAJOR TRANSITIONS DURING THE CHROMOSOME CYCLE OF EUKARYOTIC CELLS



1,2, and 3 are the stable states

G1 phase: low CDK activity due to presence of CKIs and lack of cyclin gene transcription, LETS MAKE CDK BY KILLING THE CKI's :)

After this, Initiated cyclin synthesis and CKI proteolysis lead to **G1-CDK** activity.

Synthesis of Cdc6 protein during G1 promotes pre-replication complex **(pre-RC)** assembly at future replication origins. (MCM proteins bind to chromatin and cell assembles Pre-RC)

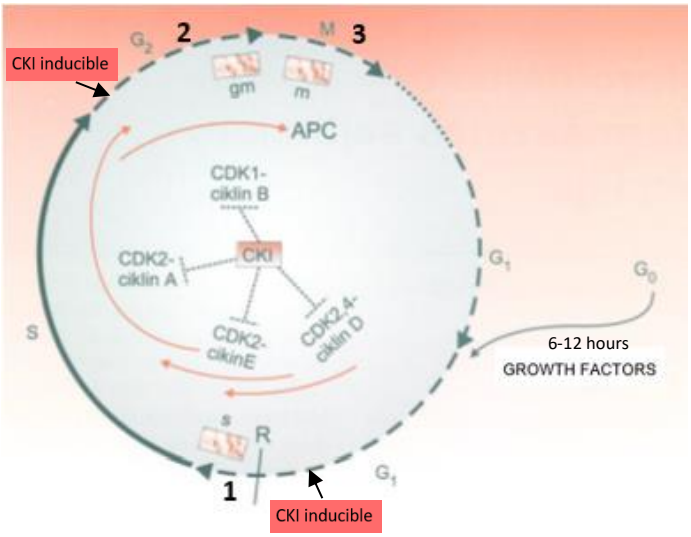
Activation of **S-phase CDKs** triggers firing of origins with pre-RCs, leading to replication and formation of sister chromatids

M-phase CDKs

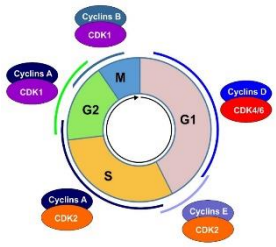
- Promote mitotic spindle formation, allowing sister chromatids to align on the metaphase plate.
- Promote activity of anaphase-promoting complex (APC), leading to loss of sister chromatid cohesion and M-phase cyclin destruction.

APC remains active during subsequent G1 period and is turned off by the accumulation of **G1-CDKs**

Phase	Process/Activity
G1 phase	- Low CDK activity due to presence of CKIs and lack of cyclin gene transcription
	- Initiated cyclin synthesis and CKI proteolysis lead to G1-CDK activity
	- Synthesis of Cdc6 protein, promoting pre-replication complex (pre-RC) assembly at future replication origins
	- MCM proteins bind to chromatin and cell assembles Pre-RC
S-phase	- Activation of S-phase CDKs triggers firing of origins with pre-RCs, leading to replication and formation of sister chromatids
M-phase	- M-phase CDKs promote mitotic spindle formation, allowing sister chromatids to align on the metaphase plate
	- M-phase CDKs also promote activity of anaphase-promoting complex (APC), leading to loss of sister chromatid cohesion and M-phase cyclin destruction
Subsequent G1 period	- APC remains active during the subsequent G1 period and is turned off by the accumulation of G1-CDKs



1,2 and 3 are check point at the "p" (pre-start), "gm" (post-replication) and "m" (metaphase) stable states.



Growth factors can stimulate cell division and proliferation by promoting the formation and activation of CDK's and CKIs

"CKI inducible" refers to the ability of certain Cyclin-dependent kinase Inhibitors (CKIs) to be produced or activated in response to specific signals or conditions. This means that the expression or activity of these CKIs can be regulated and increased when needed, such as in response to DNA damage.

git config--global user.email "iamtierd12@gmail.com"

git config--global user.name "AbdullahDora"