

CELL CYCLE AND ITS REGULATION

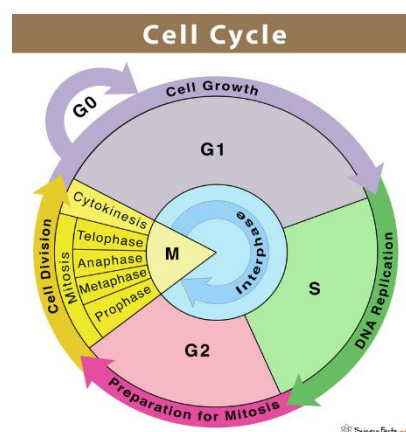
The cell cycle is a series of events that occur in a cell, leading to its division and duplication. Regulation of the cell cycle ensures that cells divide only when necessary and prevents abnormal growth. The cell cycle can be divided into interphase, mitosis, and cytokinesis.

1. **INTERPHASE:** It involves three sub-phases: G₁, S, and G₂. During G₁, the cell grows and prepares for DNA replication. The S phase involves DNA replication, while G₂ is a phase of growth and preparation for mitosis.

2. **MITOSIS:** It is the phase of cell division where the duplicated DNA is divided into two daughter cells. The two daughter cells are identical to each other and to the parent cell. Mitosis can be divided into four stages: prophase, metaphase, anaphase, and telophase, each with specific events that ensure successful division.

G₀ PHASE: This is a stage outside of the normal cell cycle where cells remain in a quiescent state with limited metabolic activity.

Cells in the G₀ phase may re-enter the cell cycle and enter the G₁ phase, or they may continue to remain in G₀ permanently.



MOLECULAR MECHANISM OF REGULATION OF CELL CYCLE

The cell cycle is regulated by a series of checkpoints that ensure proper progression and prevent errors. These checkpoints are controlled by various proteins and signalling pathways, including cyclins and cyclin-dependent kinases.

Cyclin is a regulatory component, whereas CDK is catalytic and acts as a protein kinase. During the cell cycle, cyclins bind to CDKs to activate them, allowing for the phosphorylation of target proteins involved in cell cycle progression. Dysregulation of these checkpoints can lead to diseases such as cancer.

Some examples of cyclins and CDKs of vertebrates are given below

Cyclin	Peak expression in the cell cycle	CDKs
G₁-Cyclin: Cyclin D	G ₁	CDK 4, CDK 6
G₁/S Cyclin: Cyclin E	G ₁ /S	CDK 2
S cyclin: Cyclin A	S/G ₂	CDK 2
M cyclin: Cyclin B	M	CDK 1

❖ Functions played by the Cyclin-CDK complex

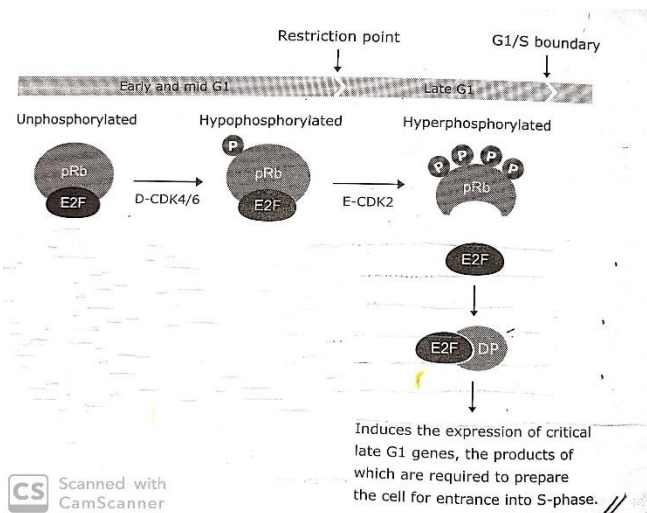
1. The Cyclin D/CDK4/6 complex regulates the G1 to S phase transition in the cell cycle by phosphorylating the retinoblastoma protein, allowing for the activation of E2F family transcription factors.
2. The Cyclin E/CDK2 complex is involved in the initiation of DNA replication and the G1/S transition by promoting the expression of genes needed for S phase entry. Dysregulation of the Cyclin E/CDK2 complex can lead to uncontrolled cell proliferation and cancer.
3. The Cyclin A/CDK2 complex is critical for DNA synthesis and checkpoint control during the S phase, and its malfunction can result in genomic instability and cancer development.
4. The Cyclin B/CDK1 complex is involved in the transition from G2 to M phase and promotes mitotic spindle formation and chromosome segregation.

❖ ROLE OF 'Rb' PROTEIN IN CELL CYCLE REGULATION

The RB1 (retinoblastoma 1) gene codes for a protein called pRb, which plays a vital role in regulating the cell cycle and preventing the development of tumors (RB1 genes are tumour suppressor genes i.e., its activity stops the formation of tumor). Mutations in the RB1 gene can lead to the development of retinoblastoma, a rare type of eye cancer.

How RB1 protein regulate cell cycle?

- pRb is a negative regulator of cell cycle because they halting the cell cycle.
- pRb act as substrate for CDK/Cyclin D complex in the G1 phase.
- In normal cells, pRb is in its active, unphosphorylated, or hypophosphorylated form. This allows pRb to bind to and inhibit the activity of E2F transcription factors, preventing cell division.
- Phosphorylation of pRb results in its inactivation and release of E2F, which then heterodimerizes with DNA binding proteins (DB) to activate the transcription of G1/S genes, promoting cell division.
- Phosphorylation of pRb is initiated by cyclin D-CDK4/6 and cyclin E-CDK2 in G1.



However, in cancer cells, pRb is often hyperphosphorylated and unable to inhibit E2F, leading to uncontrolled cell proliferation and tumor formation.

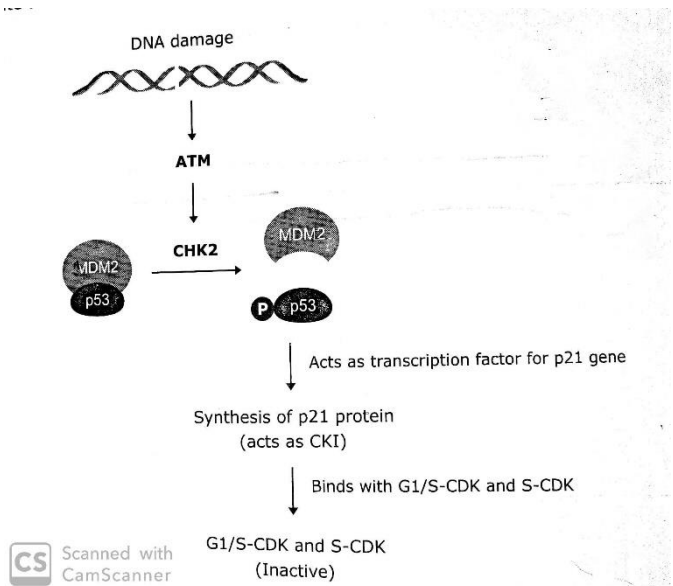
(***Therefore, targeting pRb and E2F signalling has become a promising therapeutic strategy for cancer treatment).

DP are DNA-binding proteins that are essential for E2F activation, as they enable E2F to bind to DNA and initiate transcription.

Transcription is the process by which genetic information is copied from DNA to RNA, ultimately leading to the production of functional proteins within the cell. Without proper regulation of the cell cycle and transcriptional activity, cells may divide uncontrollably, leading to the formation of tumors and cancer.

❖ ROLE OF P53 PROTEIN IN CELL CYCLE REGULATION

- Like the RB1 gene, TP53 is a tumor suppressor gene that codes for the p53 protein.
- P53 is known as the "guardian of the genome" and helps prevent cells with damaged DNA from dividing by inducing cell cycle arrest or triggering apoptosis.
- In normal cells, p53 is inactivated by the MDM2 protein, which binds to p53 and targets it for degradation.
- However, when DNA damage is detected, p53 is stabilised and activated, leading to downstream effects on cell cycle progression.
- The loss of p53 function is a common event in cancer cells and can contribute to their uncontrolled growth and proliferation.
- p53 is phosphorylated by ATM and ATR kinases in response to double strand breaks in DNA. This activation leads to p53 separating from its negative regulator, MDM2, and accumulating in the nucleus to either activate genes involved in DNA repair or induce apoptosis.
- Therefore, p53 plays a critical role in maintaining genomic stability and preventing cancer formation.



Cell cycle checkpoints

Cell cycle checkpoints are critical regulators that ensure the proper progression of the cell cycle. These checkpoints prevent cells with DNA damage or other abnormalities from dividing, ultimately preventing the development of cancer and other diseases.

There are two main types of cell cycle checkpoints: the spindle assembly checkpoint or mitotic checkpoint, and the DNA damage checkpoint.

- The spindle assembly checkpoint ensures proper alignment and attachment of chromosomes during mitosis.
- The DNA damage checkpoint detects DNA damage and activates repair mechanisms before allowing progression into the next phase. This checkpoint is further classified as **G1/S, intra-S, or G2/M** depending on where in the cell cycle it occurs. The G1/S checkpoint evaluates the cell's DNA and determines whether it is ready to enter the S phase and replicate its DNA. The intra-S checkpoint monitors the DNA replication process to ensure that it proceeds without errors, while the G2/M checkpoint checks for any remaining DNA damage before the cell enters the mitosis phase.

References

Kumar, & Mina. (2018). *Life Sciences Fundamentals and Practice I* [English] (Sixth). Pathfinder publication, New Delhi, India. ISBN: 978-81-906427-0-5