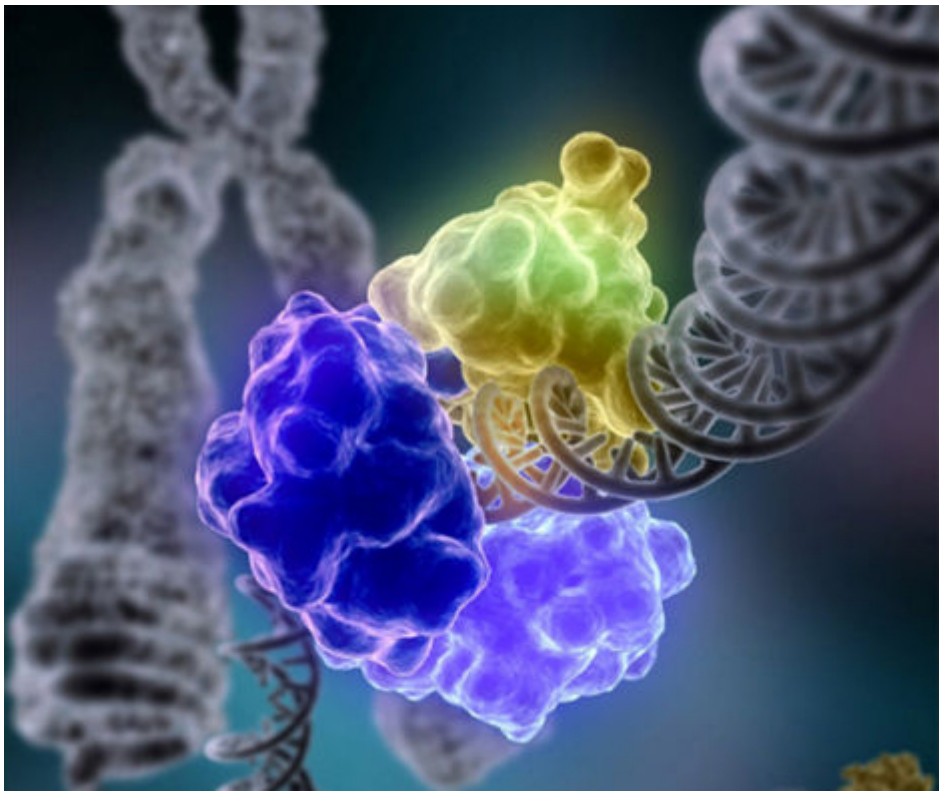
Cell Cycle and Cell Division, P53 Genes, and Mutated Genes

See online here

Cell cycle refers to the process of division marked by cell growth, DNA replication, distribution of replicated chromosomes to daughter cells, followed by cell division that a cell undergoes proliferation. It consists of different phases, regulated by the cell cycle checkpoints. There are a group of enzymes and proteins that regulate and ensure the replication of DNA and cell division linking to the extracellular signals to control cell proliferation. Any defective DNA is immediately repaired, and, if unrepairable, it leads to programmed cell death (apoptosis). These proteins are, in turn, controlled by proto-oncogenes and oncogenes, whose mutation leads to cancer.



Introduction

The cell cycle, or cell division, is a **sequence of events that occurs in a eukaryotic cell, including its physical division, DNA replication, and equal distribution of chromosomes in two daughter cells**. Cell division is enhanced by mitosis and meiosis. Mitosis is a type of cell division characterized by the production of two daughter cells with the same number of chromosomes in each nucleus, whereas meiosis is characterized by the production of four cells with half the total number (haploid) of chromosomes in their

nuclei.

The cell cycle is a vital process that leads to the **formation of a fully developed organism** from a single fertilized egg. It also plays a significant role in the further regeneration of new cells in a fully grown organism.

Stages of the Cell Cycle

The cell cycle has two main phases, which can be further subdivided into distinct stages:

Interphase

- G_1 phase
- S phase (synthesis)
- G_2 phase

Mitotic (M) phase

- Karyokinesis
- Cytokinesis

The G phase is the resting period of a cell after exiting the cell cycle. This exit from the cell cycle is temporary and reversible. It is a dormant phase in which the cell remains metabolically active but does not grow, proliferate, or divide. It also has reduced rates of protein synthesis.

A sequence of events takes place during these phases (see table below):

Phase	Events
G_1 (gap 1)	The cell prepares for DNA replication and grows
S (synthesis)	DNA replication occurs
G_2 (gap 2)	The cell grows and prepares for final cell division
M (mitosis)	The cell divides into two daughter cells

The duration of phases of the cell cycle varies in different kinds of cells. Each phase is dependent on another phase for successful completion of the cell cycle by activation and regulation processes. This restriction is managed and controlled by cell cycle checkpoints present at different phases of a cycle.

Cell Cycle Checkpoints

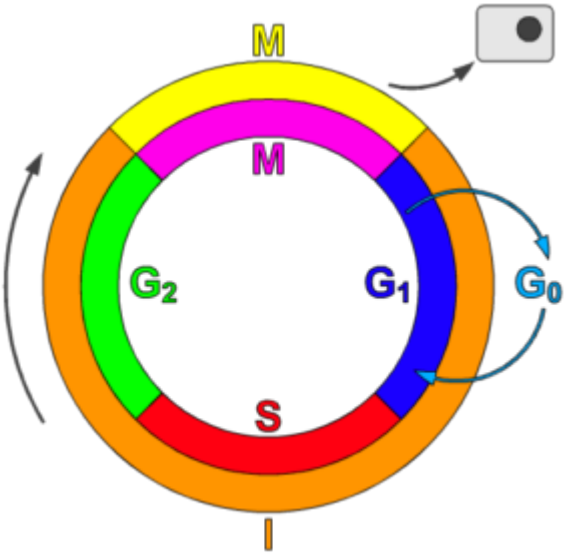


Image: Schematic of the cell cycle. Outer ring: I = interphase, M = mitosis; inner ring: M = mitosis; G1 = gap phase 1; S = synthesis; G2 = gap phase 2. The duration of mitosis in relation to the other phases has been exaggerated in this diagram. By: Zephyris. License: CC BY-SA 3.0

The cell cycle is monitored and controlled by **regulatory proteins** called cell cycle checkpoints. These checkpoints are present at certain critical areas of the cycle to ensure that the previous phase has completed without errors, or that no repairs are needed. Once all necessary repairs in the previous phase have been completed, these checkpoints allow the cell to proceed to the next phase (see image).

There are 3 checkpoints in each cell cycle:

1. G_1/S
2. G_2/M
3. Metaphase

G_1/S Checkpoint

The G_1/S checkpoint, also called the **restriction point**, is the first integral checkpoint of the cell cycle, located between the G_1 and S phase. This checkpoint ensures that **the cell has all the essential nutrients to undergo DNA replication**. It also decides whether the cell should remain in the G1 phase, enter the G phase, or proceed to the S phase.

This decision is based on both **internal and external factors**. A cell with any deficiency or defect that may hinder the DNA replication will not be allowed to move beyond this stage into the S phase.

G_2/M Checkpoint

After the cell undergoes successful DNA replication in the S phase and is growing in the G_2 phase, this checkpoint assesses:

- **If the DNA replication was successful** and if there is any need to repair defective replicated DNA
- Whether **adequate amounts of cytoplasm and phospholipids** are present for the cell to undergo complete division into two daughter cells
- If it is the right time for the cell to **proceed to mitosis phase** for the final

division

The G_2/M checkpoint is regulated by the maturation-promoting factor, which comprises a group of enzymes and proteins called the cyclin-dependent kinase (CNK) complex (see image).

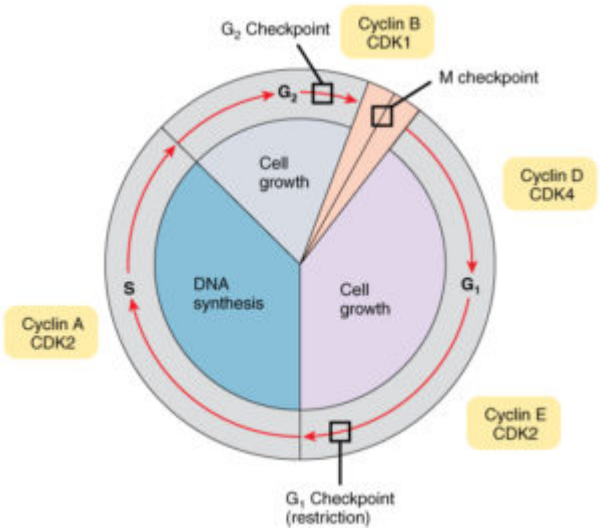


Image: 0332 cell cycle with cyclins and checkpoints. By: OpenStax. License: CC BY 4.0

Metaphase Checkpoint (Spindle Checkpoint)

Once the cell is in metaphase, this checkpoint ensures that:

- The mitotic spindle has formed
- The chromosomes have aligned themselves at the mitotic plate and adequate tension exists in the spindles

The presence of tension in the spindles ensures that there is no inhibition of anaphase-promoting complex (APC) so that the cell can enter the next stage, anaphase (see image).

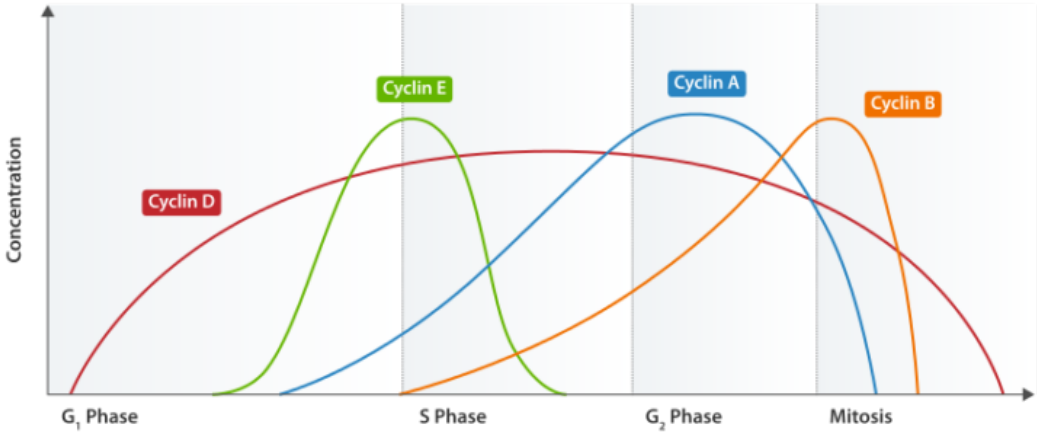


Image: Cyclin expression. By: WikiMiMa. License: Public Domain

Checkpoints: A Cyclically Activated Protein Kinase System

The cell cycle checkpoints **consist of a group of protein kinases called cyclin-dependent kinases**. The activity of these CDKs is controlled by an array of enzymes and proteins collectively referred to as cyclins. This cyclin-CDK complex is the basis of the checkpoints that regulate the cell cycle.

The **activity of CDKs oscillates throughout the cell cycle**, leading to the cyclic phosphorylation of proteins that initiate, regulate, or inhibit the events of the cell cycle.

Eukaryotic cells require three of the four classes of cyclins to bind to CDKs:

- G_1/S cyclins (bind to CDKs at the end of the G_1 phase and let the cell decide on DNA replication)
- S cyclins (bind CDKs during the S phase and initiate DNA replication)
- M cyclins (regulate and promote the events of mitosis)

Cyclin-CDK complexes at play during different phases and checkpoints of the cell cycle are outlined in the table below.

Phase	Cyclin	CDK
G_1	D, E	2, 4, 6
S	A, E	2
G_2	A	1, 2
M	B	1

Checkpoints and their Cyclin-CDK Complexes

The G_1/S Checkpoint and CDKs

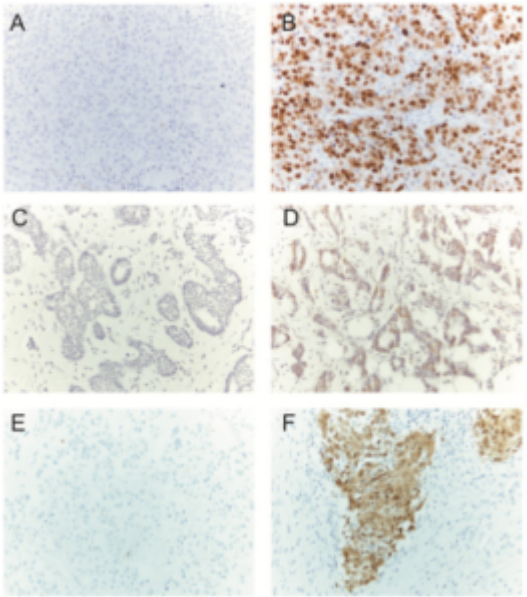


Image: Cyclin D1, CDK4, and p16 expression in invasive ductal breast carcinomas analyzed by immunohistochemistry. (B) High nuclear cyclin D1 expression. (D) High nuclear CDK4 expression. (F) High

p16 expression. (A), (C). and (E) are negative controls for (B), (D). and (F), respectively. Py Peurala E, et al., 2013). License: CC BY 2.0

A rise in cyclin D stimulates its binding to CDK4 and CDK6, and this complex results in the **phosphorylation of proteins**. At the same time, the accumulation of cyclin E induces the formation of a complex with CDK2 that stimulates the cell to **enter an irreversible stage of DNA replication**.

The G_2/M Checkpoint and CDKs

At this checkpoint, cyclin B binds to CDK1, which, in turn, **regulates the events and generates the activation of subsequent proteins** and the entry of the cell into the mitotic phase.

During this stage, **DNA damage is also assessed** and, in the case of defective or incomplete DNA replication, activation of CDK1 and CDK2, along with p53, occurs to halt the cell cycle and prevent it from entering mitosis.

The Metaphase/Spindle Checkpoint and CDKs

The tension created within the spindles **activates APC**, which degrades cyclin B and, in turn, causes a breakdown of proteins (securing, separase, cohesin) that bind the chromosomes together.

Role of p53 Gene

Damaged DNA formed during a cell cycle stimulates the activation of the tumor suppressor gene called p53. Commonly known as “the guardian of the genome,” **this gene ensures that no cell transfers any damaged DNA** into the daughter cells.

If a damaged DNA is sensed at the G_1/S checkpoint, it halts the cycle by activating CDK inhibitor, which temporarily stops the cell cycle by binding to the CDK complex until the DNA is repaired, thereby **activating the production of DNA-repairing enzymes**. These enzymes repair the damaged DNA. If this process fails, the p53 gene allows the cell to undergo programmed cell death.

In cases of a defective or absence p53 gene, damaged and mutated DNA is passed on to the cells and leads to the development of cancer. The mutated **p53 gene is responsible for a healthy completion of the cell cycle**.

Proto-Oncogenes

These genes **regulate cell growth, differentiation, and proliferation, and tend to inhibit apoptosis**. Any mutation in the genes or over-expression will stimulate them to transform into oncogenes, and eventually result in uncontrolled cell proliferation that progresses to cancer.

Some proto-oncogenes include growth factors, RAS proteins, and Src kinase:

- Growth factors **induce cell proliferation**. Growth factor receptors are increased in cases of breast cancer.
- RAS protein is involved in **signaling a pathway in cell proliferation**. The mutation of RAS protein leads to myeloid leukemia, thyroid tumor, and adenocarcinoma of the pancreas and colon. It is activated by mutation in

20%–30% of all cancers.
- Src kinase **regulates cell proliferation, migration, differentiation, and apoptosis**. Its mutation leads to head and neck cancers, brain cancers, etc. It is activated by a mutation in 2%–5% of all cancers.

Tumor-Suppressor Genes

These genes actively de-accelerate cell division, manage DNA repair, and guide the cell toward apoptosis. **Mutation in this gene will lead to the development of cancer, as damaged DNA accumulates in the cells, preventing apoptosis**.

Tumor-suppressor genes are grouped into **caretaker genes, gatekeeper genes, and landscaper genes**. Common tumor-suppressor genes include **retinoblastoma protein (pRb) and p53** (see image).

The pRb protein is mutated in 40% of all cancers, and p53 is mutated in 50%.

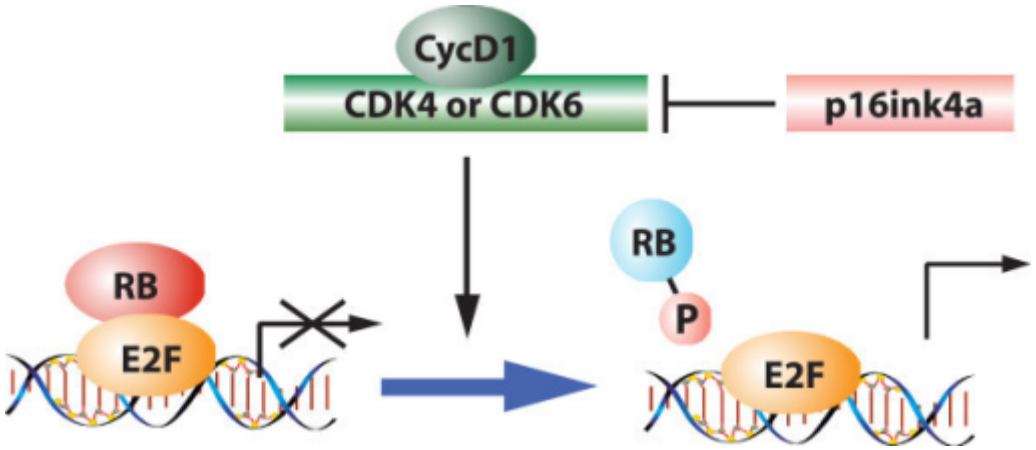


Image: Schematic of the retinoblastoma tumor suppressor pathway. By: Witkiewicz AK, Knudsen ES, 2014.
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The Two-Hit Hypothesis

The two-hit hypothesis was first proposed by A.G. Knudson. This hypothesis states that two mutations should occur in both tumor suppression genes to trigger cancer. If one allele is defective, the other will still produce normal protein, and a cancerous tumor cannot form.

This hypothesis, therefore, indicates that **mutated tumor-suppressor alleles are recessive (deactivated), while mutated oncogene alleles are dominant** (activated) during cancer development.

References

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Paige, A. J. W. Redefining tumour suppressor genes: exceptions to the two-hit hypothesis. *Cellular and Molecular Life Sciences* (2003) 60: 2147. Available at: https://doi.org/10.1007/s00018-003-3027-6

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Notes