The **cell cycle** is the series of events that take place in a **cell** leading to its **division** and duplication of its DNA (DNA replication) to produce two daughter **cells** identical to those of the parental cell.

* The only way to make a new cell is to duplicate a cell that already exists
* A cell reproduces by performing an orderly sequence of events in which it duplicates its contents and then divides in two. This cycle of duplication and division, known as the cell cycle
* It is the essential mechanism by which all living things reproduce
* In unicellular species, such as bacteria and yeasts, each cell division produces a complete new organism
* In multicellular species, long and complex sequences of cell divisions are required to produce a functioning organism
* In the adult body, cell division is usually needed to replace cells that die (*Epithelial cells of human intestine are continuously renewed every 4–5 days through a process of cell division*)
* Each of us must manufacture many millions of cells every second simply to survive
* If all cell division were stopped—by exposure to a very large dose of x-rays, for example—we would die within a few days.
* The details of the cell cycle vary from organism to organism and at different times in an organism’s life.
* However certain characteristics, are universal.
* At a minimum, the cell must accomplish its most fundamental task: the passing on of its genetic information to the next generation of cells.
* There are three major stages in the cell cycle

Interphase, Mitosis and Cytokinesis. 1) Interphase encompasses the phases of G1 (Growth 1), S (DNA Synthesis) and G2 (Growth 2) phase. 2) Mitosis encompasses the phases of prophase, prometaphase, metaphase, anaphase and telophase. 3) Cytokinesis (cytoplasm divides)

The cell cycle is a set of biochemical events driven by a control system that tells cells whether they can enter the next phase of the cell cycle.

 In most eukaryotic cells, the cell-cycle control system governs cell-cycle progression at three major regulatory transitions

1. **Restriction point** in late G1, Once cells have passed RESTRICTION/START point, they are committed to entering S phase and undergoing cell division cycle.

2. **G2/M transition**, where the control system triggers the early mitotic events that lead to chromosome alignment on the mitotic spindle in metaphase.

1. **Metaphase-to-anaphase transition,** where the control system stimulates sister-chromatid separation, leading to the completion of mitosis and cytokinesis.
* The control system blocks progression through each of these transitions if it detects problems inside or outside the cell. If appropriate growth factors are not available in G1, progression through the cell cycle stops at the restriction point.
* Central components of the cell-cycle control system are members of a family of protein kinases known as cyclin-dependent kinases (Cdks). The control of cell cycle is based on cyclically activated protein kinases. Cdks are serine, threonine kinases. Physical association with cyclins is required for Cdks activity. Phosphorylation on a regulatory domain called the T-loop leads to optimal Cdk activation. Activating and inhibitory phosphorylation of the CDK subunit regulates CDK activity. CDK inhibitors (CKIs) inhibit CDK activity by binding directly to the cyclin-CDK complex.
* The rise and fall of cyclin levels is the primary determinant of Cdk activity during the cell cycle. There are different cycle-specific cyclins that are present at different stages of the cell cycle.
* The ubiquitin-proteasome system limits presence of a cyclin to the appropriate cell cycle stage.
* Several additional mechanisms, however, help control Cdk activity at specific stages of the cycle.
* Phosphorylation at a pair of amino acids in the roof of the kinase active site by a protein kinase known as Wee1 inhibits the activity of a cyclin–Cdk complex.
* Dephosphorylation of these sites by a phosphatase known as Cdc25 increases Cdk activity
* Binding of Cdk inhibitor proteins (CKIs) inactivates cyclin–Cdk complexes.
* CDKs initiate every aspect of each cell cycle stage by phosphorylating many different target proteins.
* The activities of these kinases rise and fall as the cell progresses through the cycle. Cyclical changes in Cdk activity are controlled by enzymes and proteins.
* The most important of these Cdk regulators are proteins known as cyclins.
* Cyclins undergo a cycle of synthesis and degradation in each cell cycle. The levels of the Cdk proteins, by contrast, are constant.

*The control of cell cycle is based on cyclically activated protein kinases.*

**Cdks’ activity depends on**

1. Physical association with cyclins

• Different cyclins present only in the cell cycle stage they promote activate CDKs at different cell cycle stages.

• The ubiquitin-proteasome system limits presence of a cyclin to the appropriate cell cycle stage.

 **2.** Activating and inhibitory phosphorylation of the CDK subunit

 **3.** CDK inhibitors (CKIs) inhibit CDK activity by binding directly to the cyclin-CDK complex.

Active CDKs initiate every aspect of each cell cycle stage by phosphorylating many different target proteins.

Cdk’s are regulated by Cdk inhibitory proteins as well as by cyclins and phosphorylation

There are 3 classes of cyclins, each defined by the stage of the cell cycle at

which they bind Cdks and function. All eukaryotic cells require three of these

classes

1. G1/S-cyclins activate Cdks in late G1 and thereby help trigger progression

through Start/Restriction, resulting in a commitment to cell-cycle entry. Their levels

fall in S phase.

2. S-cyclins bind Cdks soon after progression through Start/Restriction and help stimulate

chromosome duplication. S-cyclin levels remain elevated until mitosis, and these cyclins also contribute to the control of some early mitotic events.

3. M-cyclins activate Cdks that stimulate entry into mitosis at the G2/M transition. M-cyclin levels fall in mid-mitosis.

In most cells, a fourth class of cyclins, the G1-cyclins, helps govern the activities

of the G1/S-cyclins, which control progression through Start/Restriction in late G1.

In animal cells, progression through the G1 restriction point is controlled by complexes of Cdk4 and Cdk6 with Dtype cyclins. Cdk2/cyclin E complexes are required for the G1 to S transition. Cdk2/cyclin A complexes are then required for progression through S phase and G2. Cdk1/cyclin A and Cdk1/cyclin B complexes drive the G2 to M transition and progressionthrough mitosis.

Growth factors regulate cell cycle progression through the G1 restriction point by inducing synthesis of D-type cyclins via the Ras/Raf/MEK/ERK signaling pathway

When cells are stimulated to divide by mitogens, active G1-Cdk accumulates and phosphorylates Rb family members, reducing their binding to E2F. The liberated E2F proteins then activate expression of their target genes

 Mitogens bind to cell-surface receptors to initiate intracellular signaling pathways.

 One of the major pathways involves activation of the small GTPase Ras, which activates a MAP kinase cascade, leading to increased expression of numerous *immediate early* genes, including the gene encoding the transcription regulatory protein Myc.

 Myc increases the expression of many *delayed-response* genes, including some that lead to increased G1-Cdk activity (cyclin D–Cdk4), which triggers the phosphorylation of members of the Rb family of proteins.

 This inactivates the Rb proteins, freeing the gene regulatory protein E2F to activate the transcription of G1/S genes, including the genes for a G1/S-cyclin (cyclin E) and S-cyclin (cyclin A)

The resulting G1/S-Cdk and S-Cdk activities further enhance Rb protein phosphorylation, forming a positive feedback loop

E2F proteins also stimulate the transcription of their own genes, forming another positive feedback loop.

* Activation of specific cyclin–Cdk complexes drives progression through the Start/Restriction and G2/M transitions by phosphorylation
* Progression through the metaphase-to-anaphase transition is triggered not by protein phosphorylation but by protein destruction, by APC/C leading to the final stages of cell division.
* G1/S-Cdks unleash a wave of S-Cdk activity, which initiates chromosome duplication in S phase and also contributes to some early events of mitosis.
* S-Cdk Initiates DNA replication with the duplication of its chromatin proteins once per cycle.
* The production of chromatin proteins also increases during S phase to provide the raw materials needed to package the newly synthesized DNA.
* *Chromatin packaging helps to control gene expression. In some parts of the chromosome, the chromatin is highly condensed and is called heterochromatin, whereas in other regions it has a more open structure and is called euchromatin*
* At the end of S phase, each replicated chromosome consists of a pair of identical sister chromatids glued together along their length.
* Sister-chromatid cohesion depends on a large protein complex called cohesin,which is deposited at many locations along the length of each sister chromatid as the DNA is replicated in S phase. Two of the subunits of cohesin are members of a large family of proteins called *SMC proteins* (for Structural Maintenance of Chromosomes).
* Cohesin forms giant ringlike structures, and it has been proposed that these surround the two sister chromatids
* M-Cdk activation then triggers progression through the G2/M transition and the events of early mitosis, leading to the alignment of sister-chromatid pairs at the equator of the mitotic spindle.
* When all the chromosomes are aligned properly at the equatorial plate connected bi-orientated by the kinetochor microtubules in the middle of the cell. The APC/C, together with its activator Cdc20 is activated
* Finally, the APC/C, together with its activator Cdc20, triggers the destruction of securin and cyclins, thereby unleashing sister-chromatid separation and segregation and the completion of mitosis.

* When mitosis is complete, multiple mechanisms collaborate to suppress Cdk activity,resulting in a stable G1 period.
* Mitosis is traditionally divided into five stages—*prophase*, *prometaphase*, *metaphase*, *anaphase*, and *telophase*—defined primarily on the basis of chromosome behavior as seen in a microscope.
* As mitosis is completed, the second major event of M phase—cytokinesis—divides the cell into two halves, each with an identical nucleus.
* From a regulatory point of view, mitosis can be divided into two major parts, each governed by distinct components of the cell-cycle control system.
* First,
* An abrupt increase in M-Cdk activity at the G2/M transition triggers the events of early mitosis (prophase, prometaphase, and metaphase). During this period, M-Cdk and several other mitotic protein kinases phosphorylate a variety of proteins, leading to the assembly of the mitotic spindle and its attachment to the sister-chromatid pairs.
* The second
* Major part of mitosis begins at the metaphase to-anaphase transition, when the APC/C triggers the destruction of securin, liberating a protease that cleaves cohesin and thereby initiates separation of the sister chromatids.The APC/C also promotes the destruction of cyclins, which leads to Cdk inactivation and the dephosphorylation of Cdk targets, which is required for all events of late M phase, including the completion of anaphase, the disassembly of the mitotic spindle, and the division of the cell by cytokinesis.
* In order to prevent, daughter cells get smaller with each division. The cells must be make preparation before begining of the cell division. The preparation of cell divison phase is called interphase

Cell cycle consist of two parts

* İnterphase
* Mitosis

İnterphase includes

* G1: 1st Growth Phase
* S: DNA Synthesis Phase
* G2: 2nd Growth Phase

Before M phase 3 important events take place in interphase

* DNA replication
* In animal cell centrosome replication
* Cell growth

DNA replication is necessary for two new generated cells to get two equal copies of genom from the parental cell

Centrosome replication is necessary for forming two mitotic tubule poles and each of them generate own mitotic spindles which is necessary for cell dividing

Cell growth is necessary to generate two new equal size cells that are equal size of the parental cell

Centrosome duplication take place in interphase Centrosome duplication begins in G1 phase and finishes G2 phase in interphase

**Cdk1 and cyclin B subunits form MPF (M Phase Promoting Factor).**  **MPF activation induce cell to enter mitosis. In S and G2 phases Cdk1 makes complex with cyclin B and MPF is formed.**

**For Cdk1 and therefore MPF activation:**

 **Phosporylation of Cdk1 is needed at position 161 of Theronine sides**

 **Dephosporylations of Cdk1 are nedeed; at position 14 side of Theronine and also at position 15 side of Tyrosine. Then MPF is activated and M phase begins G2→M.**

**The mitotic protein kinases Cdk1, Aurora, and Polo-like kinases are activated in a positive**

**feedback loop at the onset of M phase. They induce multiple nuclear and cytoplasmic**

**changes during mitosis by phosphorylating proteins such as condensins, cohesins,**

**components of the nuclear envelope, Golgi matrix proteins, and proteins associated**

**with centrosomes, kinetochores, and microtubules. MPF activation is controlled by periodically cyclin B synthesis, accumulation and breaks down during the progress of the cell cycle.**

**Cyclin B degradation and phosporilation/dephosporilation of Cdc2 inactivates MPFWhen MPF is deactivated, by ubiquitin proteolyic degragation of cyclin B and mitosis ends.**

* **Chromatin which is found in the nucleus of interphase gets ~ 10 000 times more condense to produce metaphase chromosome**

 **Chromosome condensation results up to a 10000 fold reduction in chromosome length in vertebrates!**

* **Transcription is stopped in these highly condensed metaphase chromosomes**
* **Although the mechanism of condensation is not fully understood yet, cohesin and condensin which are the members of SMC (structurel maintanence of chromosome) family are thought to be important in condensation mechanisms**

**The condensation and resolution of sister chromatids depend, at least in part, on a five-subunit protein complex called condensin. It is not clear how condensin catalyzes the restructuring and compaction of chromosome DNA, but it may form a ring structure that encircles loops of DNA within each sister chromatid**

* **Nuclear-envelope breakdown is a complex, multistep process, which is thought to begin when M-Cdk phosphorylates several subunits of the nuclear pore complexes in the nuclear envelope.**
* **This phosphorylation initiates the disassembly of nuclear pore complexes and their dissociation from the envelope.**
* **M-Cdk also phosphorylates components of the nuclear lamina, the structural framework beneath the envelope. The phosphorylation of these lamina components and of several inner-nuclear-envelope proteins leads to disassembly of the nuclear lamina and the breakdown of the envelope membranes into small vesicles. Breakdown of nucear envelope determines the end of prophase. In some unicellular eucaryotic organisms (like yeast), cell division occurs while nuclear envelope integrity is protected during mitosis. This is called closed mitosis**
* **Nuclear breakdown allows the binding of kinetochore microtubules to chromosomes and initiates chromosome migration at prometaphase**
* **Kinetochore proteins contain microtubule motor proteins (CENP-E and cytoplasmic dynein) that direct chromosome movement to the minus end of microtubules connected to centrosome. Plus end directed chromosomes attached by a single kinetochore to one spindle pole move both toward and away from it.**
* **When the second kinetochore attaches to the opposite pole, the chromosome moves toward the metaphase plate by a series of motor proteins and microtubul elongation prevent chromosomes from approaching the poles**
* **Kinetochore also contain non-motor proteins, at least some of which (Mad2, Bub1) are involved in regulating the metaphase-anaphase (M-A) transition**
* **During spindle formation, one kinetochore on a chromosome attached to and oriented towards one spindle pole, while the other becomes attached to and oriented towards the opposing pole.**
* **This state is called kinetochore bi-orientation or chromosome bi-orientation**
* **When all the chromosomes are aligned properly at the equatorial plate, connected bi-orientated by the kinetochor microtubules in the middle of the cell.**
* **The checkpoint mechanism ensures that cells do not enter anaphase until all chromosomes are correctly bi-oriented on the mitotic spindle. When bi-orientation is achieved, the forces pulling the kinetochore toward the spindle pole are resisted by forces pulling the other sister kinetochore toward the opposite pole.**
* **The spindle assembly checkpoint depends on a sensor mechanism that monitors the strength of microtubule attachment at the kinetochore, possibly by sensing tension. Metaphase check point, Spindle assembly check point allow cell to go anaphase.**
* **Any kinetochore that is not properly attached to the spindle sends out a diffusible negative signal that blocks Cdc20–APC/C activation throughout the cell and thus blocks the metaphase-to-anaphase transition. When the last sister-chromatid pair is properly bi-oriented, this block is removed, allowing sister-chromatid separation to occur.**
* **The activation of APC/C by Cdc20 leads to the ubiquitylation and destruction of securin, which normally holds separase in an inactive state. The destruction of securin allows separase to cleave Scc1, a subunit of the cohesin complex holding the sister chromatids together**
* **The pulling forces of the mitotic spindle then pull the sister chromatids apart.**
* **Cdk inactivation in anaphase (resulting from cyclin destruction) also promotes separase activation by allowing its dephosphorylation.**
* **The chromosomes movement by two independent and overlapping processes.**
* **The first, anaphase A; sister-chromatid separation initiates the chromosome movements of anaphase A is the initial poleward movement of the chromosomes, which is accompanied by shortening of the kinetochore microtubules.**
* **The second, anaphase B, is the separation of the spindle poles themselves, which begins after the sister chromatids have separated and the daughter chromosomes have moved some distance apart**
* **By the end of anaphase, the daughter chromosomes have segregated into two equal groups at opposite ends of the cell.**

**In telophase, the final stage of mitosis, the two sets of chromosomes are packaged into a pair of daughter nuclei.**

* **The first major event of telophase is the disassembly of the mitotic spindle**
* **The re-formation of the nuclear envelope. Initially, nuclear membrane fragments associate with the surface of individual chromosomes. These membrane fragments fuse to partly enclose clusters of chromosomes and then coalesce to reform the complete nuclear envelope.**
* **The mitotic chromosomes are reorganized into their interphase state, allowing gene transcription to resume.**
* **A new nucleus has been created, and mitosis is complete.**
* **The phosphorylation of various proteins by M-Cdk promotes spindle assembly, chromosome condensation, and nuclear-envelope breakdown in early mitosis.**
* **The dephosphorylation of these same proteins is required for spindle disassembly and the re-formation of daughter nuclei in telophase.**
* **In principle, these dephosphorylations and the completion of mitosis could be triggered by the inactivation of Cdks, the activation of phosphatases, or both.**
* **The final step in the cell cycle is cytokinesis, the division of the cytoplasm in two.**
* **The first visible change of cytokinesis in an animal cell is the sudden appearance *cleavage furrow*, on the cell surface.**
* **During anaphase, the spindle generates signals that initiate furrow formation at a position midway between the spindle poles, thereby ensuring that division occurs between the two sets of separated chromosomes.**
* **The furrow rapidly deepens and spreads around the cell until it completely divides the cell in two**
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* **The furrow rapidly deepens and spreads around the cell until it completely divides the cell in two**
* ***Dephosphorylation of Cdk targets, which results from Cdk inactivation in anaphase, triggers cytokinesis at the correct time after anaphase.***
* ***After cytokinesis, the cell enters a stable G1 state of low Cdk activity, where it awaits signals to enter a new cell cycle.***

**MEIOSIS**

* **Meiosis reduces the chromosome number by half using many of the same molecular machines and control systems that operate in mitosis.**

**In the first meiotic anaphase, duplicated homologs rather than sister chromatids are pulled apart and segregated into the two daughter nuclei**

* **Only in the second division (meiosis II), which occurs without further DNA replication, are the sister chromatids pulled apart and segregated (as in mitosis) to produce haploid daughter nuclei.**
* **In this way, each diploid nucleus that enters meiosis produces four haploid nuclei, each of which contains either the maternal or paternal copy of each chromosome, but not both**
* **As in the mitotic cell cycle, the cell begins the meiotic program by duplicating its chromosomes in meiotic S phase, resulting in pairs of sister chromatids that are tightly linked along their entire lengths by cohesin complexes.**
* **Unlike mitosis, however, two successive rounds of chromosome segregation then occur**
* **In Meiosis 1:The duplicated paternal and maternal homologs pair up alongside each other and become physically linked by the process of genetic recombination.**
* **These pairs of homologs, each containing a pair of sister chromatids, then line up on the first meiotic spindle**
* **During mitosis in most organisms, homologous chromosomes behave independently of each other.**
* **During meiosis I, however, it is crucial that homologs recognize each other and associate physically in order for the maternal and paternal homologs to be bi-oriented on the first meiotic spindle.**
* **During early prophase I: The homologs begin to associate along their length in a process called pairing, between complementary DNA sequences (called *pairing sites*) in the two homologs.**
* **As prophase progresses, the homologs become more closely juxtaposed, forming a four-chromatid structure called a bivalent**
* **At this stage, the homologs are usually joined by a protein complex called the *synaptonemal complex***
* **Assembly of the synaptonemal complex begins in early zygotene and is complete in pachytene. The complex disassembles in diplotene.**
* **A fundamental difference between meiosis I and mitosis (and meiosis II) is that :**

**1) In meiosis I: Homologs rather than sister chromatids separate and then segregate**

**2) Crossovers generate a strong physical linkage between homologs, allowing their bi-orientation at the equator of the spindle—much like cohesion between sister chromatids is important for their bi-orientation in mitosis**

* **Crossing over takes place during Prophase 1 pachytene stage**
* **It occurs between non-sister chromatids of homologous chromosomes**
* **Crossing-over has two distinct functions in meiosis:**
* **It helps hold homologs together so that they are properly segregated to the two daughter nuclei produced by meiosis I,**
* **It contributes to the genetic diversification of the gametes that are eventually produced.**
* **Crossing-over is highly regulated: the number and location of double-strand breaks along each chromosome is controlled.**
* **Although the double-strand breaks that occur in meiosis I can be located almost anywhere along the chromosome, they are not distributed uniformly: they cluster at “hot spots,” where the DNA is accessible, and occur only rarely in “cold spots,” such as the heterochromatin regions around centromeres and telomeres.**
* **One ensures that at least one crossover forms between the members of each homolog pair, as is necessary for normal homolog segregation in meiosis I.**
* **Activities of Meiosis tahat differ from Mitosis**
* ****