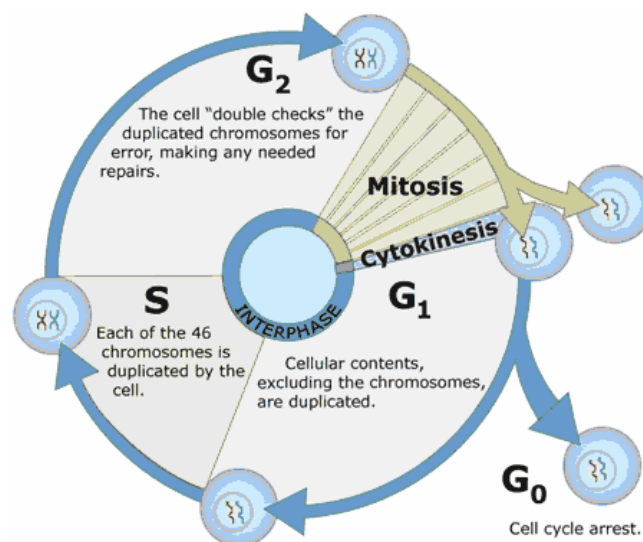


The Cell Cycle.

The cell cycle, or cell-division cycle, is the series of events that take place in a eukaryotic cell leading to its replication. These events can be divided in two brief periods:

- interphase—during which the cell grows, accumulating nutrients needed for mitosis and duplicating its DNA
- mitotic (M) phase, during which the cell splits itself into two distinct cells, often called "daughter cells".

The cell-division cycle is a vital process by which a single-celled fertilized egg develops into a mature organism, as well as the process by which hair, skin, blood cells, and some internal organs are renewed.



The cell cycle consists of four distinct phases: G₁ phase, S phase, G₂ phase (collectively known as interphase) and M phase. M phase is itself composed of two tightly coupled processes: mitosis, in which the cell's chromosomes are divided between the two daughter cells, and cytokinesis, in which the cell's cytoplasm divides forming distinct cells. Activation of each phase is dependent on the proper progression and completion of the previous one. Cells that have temporarily or reversibly stopped dividing are said to have entered a state of quiescence called G₀ phase.

M phase - The relatively brief M phase consists of nuclear division (karyokinesis) and cytoplasmic division (cytokinesis).

Interphase - After M phase, the daughter cells each begin interphase of a new cycle. Although the various stages of interphase are not usually morphologically distinguishable, each phase of the cell cycle has a distinct set of specialized biochemical processes that prepare the cell for initiation of cell division.

G₁ phase - The first phase within interphase, from the end of the previous M phase till the beginning of DNA synthesis is called G₁ (G indicating *gap* or *growth*). During this phase the biosynthetic activities of the cell, which had been considerably slowed down during M phase, resume at a high rate. This phase is marked by synthesis of various enzymes that are required in S phase, mainly those needed for DNA replication. Duration of G₁ is highly variable, even among different cells of the same species.

S phase - The ensuing S phase starts when DNA synthesis commences; when it is complete, all of the chromosomes have been replicated, i.e., each chromosome has two (sister) chromatids. Thus, during this phase, the amount of DNA in the cell has effectively doubled, though the ploidy of the cell remains the same. Rates of RNA transcription and protein synthesis are usually very low during this phase. The duration of S phase is relatively constant among cells of the same species.

G₂ phase - The cell then enters the G₂ phase, which lasts until the cell enters mitosis. Again, significant protein synthesis occurs during this phase, mainly involving the production of microtubules, which are required during the process of mitosis. Inhibition of protein synthesis during G₂ phase prevents the cell from undergoing mitosis.

G₀ phase - The term "post-mitotic" is sometimes used to refer to both quiescent and senescent cells. Nonproliferative cells in multicellular eukaryotes generally enter the quiescent G₀ state from G₁ and may remain quiescent for long periods of time, possibly indefinitely (as is often the case for neurons). This is very common for cells that are fully differentiated. Cellular senescence is a state that occurs in response to DNA damage or degradation that would make a cell's progeny nonviable; it is often a biochemical alternative to the self-destruction of such a

damaged cell by apoptosis. Some cell types in mature organisms, such as parenchymal cells of the liver and kidney, enter the G₀ phase semi-permanently and can only be induced to begin dividing again under very specific circumstances; other types, such as epithelial cells, continue to divide throughout an organism's life.

Regulation.

Regulation of the cell cycle involves steps crucial to the cell, including detecting and repairing genetic damage, and provision of various checks to prevent uncontrolled cell division. The molecular events that control the cell cycle are ordered and directional; that is, each process occurs in a sequential fashion and it is impossible to "reverse" the cycle.

Two key classes of regulatory molecules, cyclins and cyclin-dependent kinases (CDKs), determine a cell's progress through the cell cycle. Many of the genes encoding cyclins and CDKs are conserved among all eukaryotes, but in general more complex organisms have more elaborate cell cycle control systems that incorporate more individual components. Many of the relevant genes were first identified by studying yeast, especially *Saccharomyces cerevisiae*; genetic nomenclature in yeast dubs many of these genes *cdc* (for "cell division cycle") followed by an identifying number, e.g., *cdc25*.

Cell cycle inhibitors

Two families of genes, the *cip/kip* family and the INK4a/ARF (*Inhibitor of Kinase 4/Alternative Reading Frame*) prevent the progression of the cell cycle. Because these genes are instrumental in prevention of tumor formation, they are known as tumor suppressors.

The *cip/kip* family includes the genes p21, p27 and p57. They halt cell cycle in G₁ phase, by binding to, and inactivating, cyclin-CDK complexes. p21 is activated by p53 (which, in turn, is triggered by DNA damage eg. due to radiation). p27 is activated by Transforming Growth Factor β (TGF β), a growth inhibitor.

Cell cycle checkpoints are used by the cell to monitor and regulate the progress of the cell cycle. Checkpoints prevent cell cycle progression at specific points, allowing verification of necessary phase processes and repair of DNA damage. The cell cannot proceed to the next phase until checkpoint requirements have been met. Several checkpoints are designed to ensure that damaged or incomplete DNA is not passed on to daughter cells. Two main checkpoints exist: the G1/S checkpoint and the G2/M checkpoint. G1/S transition is a rate-limiting step in the cell cycle and is also known as restriction point. An alternative model of the cell cycle response to DNA damage has also been proposed, known as the post-replication checkpoint. p53 plays an important role in triggering the control mechanisms at both G1/S and G2/M checkpoints.

A dysregulation of the cell cycle components may lead to tumor formation. As mentioned above, some genes like the cell cycle inhibitors, RB, p53 etc., when they mutate, may cause the cell to multiply uncontrollably, forming a tumor. Although the duration of cell cycle in tumor cells is equal to or longer than that of normal cell cycle, the proportion of cells that are in active cell division (versus quiescent cells in G0 phase) in tumor cells are much more compared to that in normal cells. Thus there is a net increase in cell number as the number of cells that die by apoptosis or senescence remains the same.

The cells which are actively undergoing cell cycle are targeted in cancer therapy as the DNA is relatively exposed during cell division and hence susceptible to damage by drugs or radiation. This fact is made use of in cancer treatment; by a process known as debulking, a significant mass of the tumor is removed which pushes a significant number of the remaining tumor cells from G0 to G1 phase (due to increased availability of nutrients, oxygen, growth factors etc.). Radiation or chemotherapy following the debulking procedure kills these cells which have newly entered the cell cycle.