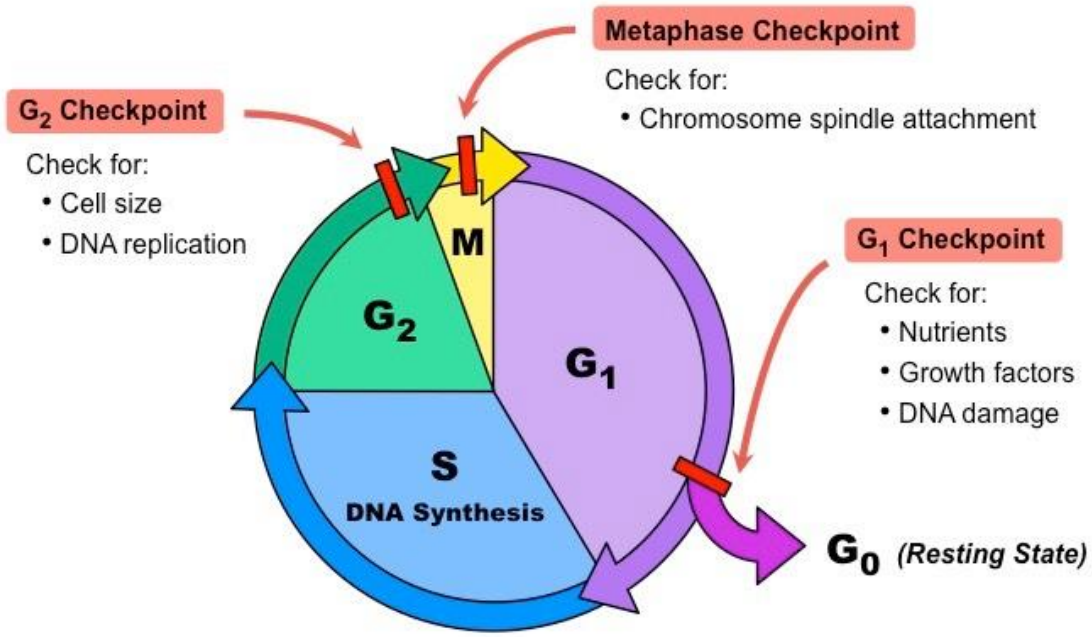
The cell cycle represents a self-regulated sequence of events that controls cell growth and cell division.

The cell cycle incorporates two principal phases:

1. **Interphase**, representing continuous growth of the cell. It is subdivide to three other phases, **G1 (gap1) phase**, **S (synthesis) phase**, and **G2 (gap2) phase**
2. **M phase (mitosis or meiosis)**, characterized by the partition of the genome.



Rapidly renewing populations of human cells progress through the full cell cycle in about 24 hours. Throughout the cycle, several internal quality-control mechanisms or **checkpoints** represented by biochemical pathways control transition between cell-cycle stages. The cell cycle stops at several checkpoints and can only proceed if certain conditions are met—for example, if the cell has reached a certain size. Checkpoints monitor and modulate the progression of cells through the cell cycle in response to intracellular or environmental signals.

- **G1 phase is usually the longest and the most variable phase of the cell cycle and it begins at the end of M phase.**

During the **G1 phase**, the cell gathers nutrients, synthesizes RNA and proteins necessary for DNA synthesis and chromosome replication. The cell's progress through this phase is monitored by two checkpoints:

(1) **Restriction point (or "point of no return")**, which is sensitive to the size of the cell, the state of the cell's physiologic processes, and its interactions with extracellular matrix

(2) **G1 DNA-damage checkpoint**, which monitors the integrity of newly replicated DNA.

For instance, if the DNA has irreparable damage, the **G1 DNA-damage checkpoint** detects this damage and it does not allow the cell to enter the S phase. The cell will then most likely undergo programmed cell death (apoptosis).

The **restriction point** is the most important checkpoint in the cell cycle. At this checkpoint, the cell self-evaluates its own replicative potential before deciding to either enter the S phase and the next round of cell division or to retire and leave the cell cycle. A cell that leaves the cycle in the G1 phase usually begins terminal differentiation by entering the **GO phase** ("O" stands for "outside" the cycle). Thus, the G1 phase may last for only a few hours (average 9 to 12 hours) in a rapidly dividing cell, or it may last a lifetime in a non dividing cell.

- **S phase, in this phase DNA is replicated.**

Initiation of DNA synthesis marks the beginning of the **S phase**, which is about 7.5 to 10 hours in duration. The DNA of the cell is doubled during the S phase. Chromosome replication is initiated at many different sites called **replicons** along the chromosomal DNA. Each replicon has a specifically assigned time frame for replication during S phase.

Presence of the **S DNA-damage checkpoint** in this phase monitors quality of replicating DNA.

- **G2 phase, in this phase the cell prepares for cell division.**

During this phase, the cell examines its replicated DNA in preparation for cell division. This is a period of cell growth and reorganization of cytoplasmic organelles before entering the mitotic cycle. The **G2 phase** may be as short as 1 hour in rapidly dividing

cells or of nearly indefinite duration in some polyploid cells and in cells such as the primary oocyte that are arrested in G2 for extended periods.

Two checkpoints monitor DNA quality:

(1) **G2 DNA-damage checkpoint**

(2) **Unreplicated-DNA checkpoint**. The latter checkpoint prevents the progression of the cell into the M phase before DNA synthesis is complete.

- **M phase, Mitosis or meiosis occurs in this phase.** (Cell division takes place in several stages described in more detail in next lecture).

Cell division nearly always includes both **karyokinesis** (division of the nucleus) and **cytokinesis** (division of the cell). Mitosis lasts about 1 hour. Separation of two identical daughter cells concludes the **M phase**.

The M phase possesses two checkpoints:

(1) **Spindle-assembly checkpoint**, which prevents premature entry into anaphase.

(2) **Chromosome-segregation checkpoint**, which prevents the process of cytokinesis until all of the chromosomes have been correctly separated.

The mitotic catastrophe caused by malfunction of cell cycle checkpoints may lead to cell death and tumor cell development.

Malfunction of any of the three DNA-damage checkpoints at the G1, S, and G2 phases of the cell cycle and the spindle assembly checkpoint at M phase may lead to a **mitotic catastrophe**. **Mitotic catastrophe is defined as the failure to arrest the cell cycle before or at mitosis, resulting in aberrant chromosome segregation**. Under normal conditions, death in these cells will occur by activation of the apoptotic cycle.

Cells that fail to execute the apoptotic cycle in response to DNA or mitotic spindle damage are likely to divide asymmetrically in the next round of cell division. This leads to the generation of aneuploid cells (cells containing abnormal chromosome numbers). Thus, a mitotic catastrophe may be regarded as one of the mechanisms contributing to oncogenesis (tumor cell development).

Malfunction of the **restriction checkpoint at the G1** phase may also result in malignant transformation of cells. Malignant cells lose contact inhibition, a normal process in which cells inhibit their division when they contact other cells.

This mechanism of carcinogenesis occurs in mesothelioma (cancer of the lining epithelium of the pleural cavities in the thorax), osteosarcoma (a type of bone cancer), and ependymoma (a type of childhood brain tumor).