Cell cycle

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The succession of events that culminates in the asexual reproduction of a cell; also known as cell division cycle. In a typical cell cycle, the parent cell doubles its volume, mass, and complement of chromosomes, then sorts its doubled contents to opposite sides of the cell, and finally divides in half to yield two genetically identical offspring. Implicit in the term cycle is the idea that division brings the double-sized parent cell back to its original size and chromosome number, and ready to begin another cell cycle. This idea fits well with the behavior of many unicellular organisms, but for multicellular organisms the daughter cells may differ from their parent cell and from each other in terms of size, shape, and differentiation state.

The time required for completion of a eukaryotic cell cycle varies enormously from cell to cell. Embryonic cells that do not need to grow between divisions can complete a cell cycle in as little as 8 min, whereas cycling times of 10–24 h are typical of the most rapidly dividing somatic cells. Many somatic cells divide much less frequently; liver cells divide about once a year, and mature neurons never divide. Such cells may be thought of as temporarily or permanently withdrawing from the cell cycle.

Eukaryotic phases

The cell cycle is divided into two main parts: interphase and mitosis (**Fig. 1**). During interphase, the cell grows and replicates its chromosomes. Interphase accounts for all but an hour or two of a 24-h cell cycle, and is subdivided into three phases: gap phase 1 (G1), synthesis (S), and gap phase 2 (G2). Interphase is followed by mitosis (nuclear division), and cytokinesis (cell division). This relatively brief part of the cell cycle includes some of the most dramatic events in cell biology. *See also:* **Mitosis (/content/mitosis/428300)**

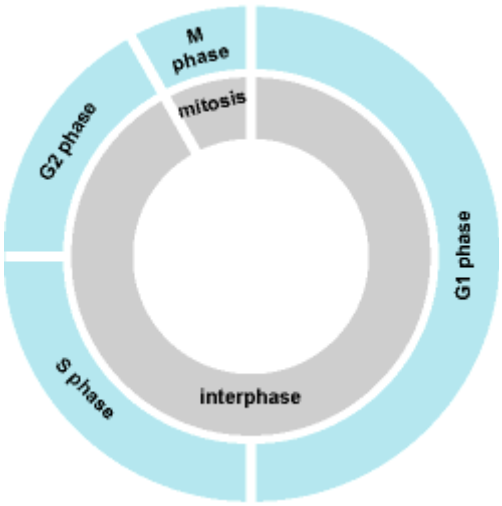

Fig. 1 Phases of the eukaryotic cell cycle.

G1 phase

Gap phase 1 begins at the completion of mitosis and cytokinesis and lasts until the beginning of S phase. This phase is generally the longest of the four cell cycle phases and is quite variable in length. During this phase, the cell chooses either to replicate its deoxyribonucleic acid (DNA) or to exit the cell cycle and enter a quiescent state (the G0 phase). Late in the G1 phase, the cell becomes committed to replicating its DNA. In mammalian cells, the time at which this commitment occurs is called the restriction point.

S phase

Replication of the chromosomes is restricted to one specific portion of interphase, called S phase (DNA synthesis phase), which typically lasts about 6 h. In mammalian cells, the start of S phase—the actual initiation of DNA synthesis—takes place several hours after the cell has committed to carrying out DNA synthesis. During S phase, each chromosome replicates exactly once to form a pair of physically linked sister chromatids. In animal cells, a pair of centrioles is also duplicated during S phase. *See also:* **Chromosome (/content/chromosome/134900)**; **Genetics (/content/genetics/285300)**

G2 phase

The portion of interphase that follows S phase is called gap phase 2. Some cells can exit the cell cycle from G2 phase, just as they can from G1 phase.

M phase

M phase includes the overlapping processes of mitosis and cytokinesis. Mitosis is divided into five stages: prophase, prometaphase, metaphase, anaphase, and telophase. During prophase, the chromosomes condense and the football-shaped mitotic spindle begins to form. Prometaphase begins when the nuclear envelope abruptly disappears and the chromosomes begin to migrate toward the spindle's midline. When the chromosomes reach the midline, the cell is said to be in metaphase. Metaphase ends and anaphase begins when the sister chromatids abruptly separate from each other and move toward the spindle poles. During telophase, the nuclear envelope reforms around each set of chromosomes, the chromosomes decondense, and mitosis is completed. Cytokinesis usually begins during anaphase and ends at a point after the completion of mitosis. At the end of cytokinesis, the parent cell has formed its two G1 phase progeny and the cell is ready to repeat the cycle.

Control of cell cycle

The network of proteins that regulate DNA synthesis (G1/S), mitotic entry (G1/M), and mitotic exit (the transition from mitotic metaphase to anaphase and then out of mitosis) appears to be well conserved throughout eukaryotic evolution. At the heart of these cell cycle transitions is the periodic activation and inactivation of cyclin-dependent protein kinases. In addition, in multicellular eukaryotes, pathways regulating entry into and exit from the cell cycle entrain these central cyclin-dependent kinases to extrinsic signals.

Cell cycle entry

In multicellular eukaryotes, most cells spend most of their time in the quiescent G0 state. In response to peptide growth factors, cells initiate a signal transduction cascade that culminates in entry into G1 phase. Components of these mitogenic signaling pathways include receptor tyrosine kinases [such as the epidermal growth factor (EGF) receptor], small G-proteins (such as Ras), and signal-relaying protein kinases (such as MAP kinase). Mitogenic signaling culminates in the activation of at least two waves of gene transcription, leading to the synthesis of a G1 cyclin protein (cyclin D) and neutralization of the retinoblastoma tumor suppressor protein (pRb).

Many components of these mitogenic signaling pathways are capable of causing malignant transformation when overexpressed or inappropiately activated. The cancer-causing forms of these proteins are termed oncoproteins, and their genes are termed oncogenes; the corresponding normal forms from which oncogenes and oncoproteins are derived are termed proto-oncoproteins and proto-oncogenes. Conversely, several tumor suppressor genes (genes that can promote malignant transformation when inactivated) have now been shown to encode proteins that oppose mitogenic signaling proteins (for example, the retinoblastoma protein and the PTEN phosphatase). These discoveries underscore the idea that when the biochemical machinery that controls normal cell growth goes awry, cancer may result. *See also:* **Oncogenes (/content/oncogenes/468950)**

Much less is known about how cells are induced to exit the cell cycle and enter the quiescent G0 state.

Mitotic control

When interphase cells are artificially fused with cells in mitosis, the interphase cells' nuclei rapidly enter mitosis. This discovery indicates that some dominant mitosis-inducing factor is present in M-phase cells. Studies on frog oocytes and eggs, unusually large cells that are naturally arrested in G2 phase (oocytes) or meiotic M phase (eggs), underscore this point: when oocytes are microinjected with cytoplasm from eggs, the oocytes enter M phase, a process termed oocyte maturation. The factor responsible, maturation promoting factor (MPF), is present and active during both meiotic M phase and mitotic M phase, and can be found in M-phase cells from evolutionarily distant organisms. This suggests that MPF is the universal M-phase trigger. The ease of obtaining large quantities of M-phase frog eggs meant that the identification of MPF could be approached biochemically.

Other crucial insights into M-phase control came from studies of growth regulation in the yeast *Schizosaccharomyces pombe*. Mutations in genes that regulate M-phase onset of *S. pombe* give rise to organisms that are too long or too short. Once such a mutant strain is isolated, the gene responsible for its altered size can be identified by molecular genetic methods. Two genes identified through this approach were *cdc2*$^+$ and *cdc13*$^+$. Genes related to *cdc2*$^+$ and *cdc13*$^+$ were found in a variety of other eukaryotes, suggesting that they encoded universal regulators of M-phase onset. *See also:* **Molecular biology (/content/molecular-biology/430300)**; **Mutation (/content/mutation/441200)**

Ultimately it was realized that the biochemical studies of M-phase regulation in frog oocytes and the genetic studies of M-phase regulation in *S. pombe* had succeeded in identifying the same M-phase regulators. MPF proved to be a complex of

the *Xenopus* homologs of *S. pombe cdc2*$^+$ and *cdc13*$^+$ (the Cdc13 protein is more usually called a B-type cyclin, because it rises and falls in abundance during the cell cycle). The fact that two very different approaches and two evolutionarily distant organisms had converged upon the same M-phase regulators underscored the importance and universality of the regulators.

The Cdc2/cyclin B complex is essential for initiation of all M phases in all organisms. The complex functions as a protein kinase—an enzyme that adds a phosphate group to specific amino acid residues in target proteins. The catalytic subunit of the complex is Cdc2; cyclin B is necessary for the activation of Cdc2 and is responsible for localizing the complex to the nucleus at the onset of M phase. The nuclear lamin proteins are Cdc2 target proteins, which form a scaffolding that supports the nuclear envelope. The Cdc2/cyclin B complex can phosphorylate lamins, causing the lamin network to disassemble. This disassembly allows the nuclear envelope to break down into small vesicles, which will coalesce and reassemble during telophase after cyclin B has been degraded and the lamins have been dephosphorylated. Other likely targets of Cdc2/cyclin B complex include histone proteins, whose phosphorylation may contribute to chromosome condensation, and a number of regulatory proteins.

At the onset of anaphase, a protein complex termed the anaphase-promoting complex (APC) becomes activated, bringing about the proteolytic destruction of several key mitotic regulators. One critical APC target is cyclin B; its destruction is required for mitotic exit. APC also directly or indirectly causes the destruction of other proteins (securins, cohesins) that keep the pairs of sister chromatids attached to each other and keep the cell in metaphase. As was the case with MPF, the rapid progress in the understanding of APC function and the appreciation of its universality were made possible through a combination of genetic studies (in the budding yeast *Saccharomyces cerevisiae*) and biochemical studies (mostly in frog egg extracts).

G1- and S-phase control

The other cell cycle transitions, for example, the commitment to DNA synthesis that occurs in G1 phase, and the initiation of DNA synthesis at the start of S phase, are also triggered by activation of heterodimeric protein kinases consisting of Cdc2-like catalytic subunits (termed Cdks, for cyclin-dependent kinases) and cyclin-like regulatory subunits. At least nine Cdc2-like catalytic subunits (Cdc2/Cdk1 and Cdk2–9) and at least eleven classes of cyclins (cyclins A through J and cyclin T) have now been identified in animal cells. A subset of these proteins have been implicated in cell cycle regulation (Cdc2, Cdk2, Cdk4, Cdk6; cyclins A, B, D, E). Thus, the entire cell cycle may be driven by the sequential activation and inactivation of Cdk/cyclin complexes (**Fig. 2**).

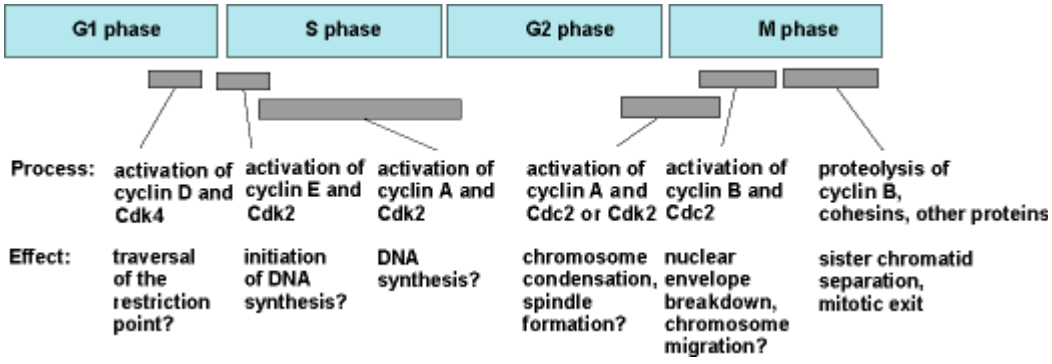

Fig. 2 Behavior of various Cdk/cyclin complexes and their cellular events.

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