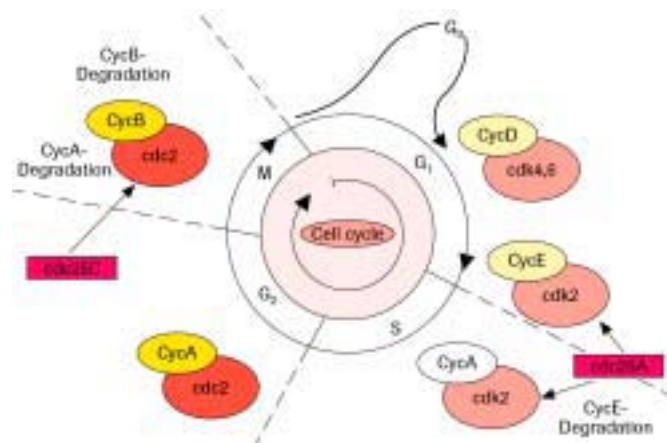


1.2 Cell Cycle

In an organism, the rate of cell division is a tightly regulated process that is intimately associated with growth, differentiation and tissue turnover. Generally, cells do not undergo division unless they receive signals that instruct them to enter the active segments of the cell cycle. Resting cells are said to be in the G_0 phase (quiescence) of the cell cycle (Figure 51). The signals that induce cells to divide are diverse and trigger a large number of signal transduction cascades.

A thorough discussion of the types of signals and the variety of responses they can elicit are beyond the scope of this guide (Table 13). Generally, signals that direct cells to enter the cell cycle are called growth factors, cytokines, or mitogens.



▲ Figure 51: Cell cycle: A schematic overview.

Abbreviation	Description	Reference
RTK	Receptor Tyrosine Kinase	Marshall, (1995) Specificity of receptor tyrosine kinase signaling: transient versus sustained extracellular signal-regulated kinase activation. <i>Cell</i> 80 : 179–185.
RAS	GTP exchange protein	White, M. A. et al. (1995) Multiple Ras functions can contribute to mammalian cell transformation. <i>Cell</i> 80 : 533–541.
RAF	MAP kinase kinase kinase	Avruch, J. et al. (1994) Raf meets Ras-Completing the framework of a signal transduction pathway. <i>Trends Biochem. Sci.</i> 19 : 279–283.
MEK	MAP kinase kinase or MAPK/Erk kinase	Marshall, C. J. (1994) MAP kinase kinase kinase, MAP kinase kinase, and MAP kinase. <i>Curr. Opin. Genet. Dev.</i> 4 : 82–89.
MAPK	Mitogen activated protein kinase or Erk	Marshall, C. J. (1994) MAP kinase kinase kinase, MAP kinase kinase, and MAP kinase. <i>Curr. Opin. Genet. Dev.</i> 4 : 82–89.
PKC	Protein Kinase C	Blobe, G. et al. (1996) Protein Kinase C isoenzymes: regulation and function. <i>Cancer Surveys</i> 27 : 213–248.
JAK	Just Another Kinase or Janus Kinase	Ihle, J. N. et al. (1994) Signaling by the cytokine receptor superfamily: Jaks and STATs. <i>TIBS</i> 19 : 222–227.
STAT	Signal Transducers and Activators of Transcription	Ihle, J. N. et al. (1994) Signaling by the cytokine receptor superfamily: Jaks and STATs. <i>TIBS</i> 19 : 222–227.
Cyclins		Marx, J. (1994) How cells cycle toward cancer. <i>Science</i> 263 : 319–321.
CDK	Cyclin Dependent Kinase	MacLachlan, T. K., Sang, N., and Giordano, A. (1995) Cyclins, cyclin-dependent kinases and cdk inhibitors: implications in cell cycle control and cancer. <i>Crit. Rev. Eukaryot. Gene Expr.</i> 5 : 127–156.
CDC2	Cell division cycle mutant	MacLachlan, T. K., Sang, N., and Giordano, A. (1995) Cyclins, cyclin-dependent kinases and cdk inhibitors: implications in cell cycle control and cancer. <i>Crit. Rev. Eukaryot. Gene Expr.</i> 5 : 127–156.
CAK	CDK Activating Kinase	Morgan, D. O. (1995) Principles of CDK Regulation. <i>Nature</i> 374 : 131–134.

▲ Table 13: Published sources that contain more information about cell proliferation.

Signal Transduction Pathways

Three major types of signal transduction pathways are activated in cells in response to growth factors or mitogenic stimuli. The response to these stimuli varies from cell type to cell type and the pathways continue to grow more and more complex. These types of pathways continue to be the focus of a great deal of research and, considering the importance of cell cycle regulation in biology, the pathways will continue to grow in complexity for some time to come.

- The MAP kinase (MAPK) type of pathways are triggered through a cascade of phosphorylation events that begins with a growth factor binding to a tyrosine kinase receptor at the cell surface. This causes dimerization of the receptor and an intermolecular cross-phosphorylation of the two receptor molecules. The phosphorylated receptors then interact with adaptor molecules that trigger downstream events in the cascade. The cascade works through the GTP exchange protein RAS, the protein kinase RAF (MAPKKK), the protein kinase MEK (MAPKK), and MAP kinase (Erk). MAPK then phosphorylates a variety of substrates that control transcription, the cell cycle, or rearrangements of the cytoskeleton.
- The protein kinase C (PKC) pathways consist of a family of phospholipid dependent protein kinases. PKC is regulated by a large variety of metabolic pathways involving phospholipids and calcium levels within a cell. The main regulator of the pathway is diacylglycerol (DAG) which appears to recruit PKC to the plasma membrane and cause its activation. The activity of DAG is mimicked by the phorbol-ester tumor promoters. Once activated, PKC can phosphorylate a wide variety of cellular substrates that regulate cell proliferation and differentiation. Responses to PKC appear to vary with the types of PKCs expressed and the types of substrates available within a cell. Some evidence shows that the PKC pathway may interact with and exert effects through the MAPK pathway.
- The JAK/STAT pathway is activated by cytokine interaction with a family of receptors called the cytokine receptor superfamily. These receptors do not contain a protein kinase domain themselves, but they associate with and activate a family of protein kinases called the JAK (Just Another Kinase or JAnus Kinase) family. JAK family members are recruited to receptor complexes that are formed as a result of ligand binding. The high concentration of JAK in the complex leads to a cross-phosphorylation of JAK and thus activation. JAK then phosphorylates members of another protein family called STAT (signal transducers and activators of transcription). These proteins then translocate to the nucleus and directly modulate transcription.

Control of the Cell Cycle

Once the cell is instructed to divide, it enters the active phase of the cell cycle, which can be broken down into four segments:

- During G_1 (G = gap), the cell prepares to synthesize DNA. In the latter stages of G_1 , the cell passes through a restriction point (R) and is then committed to complete the cycle.
- During S phase the cell undergoes DNA synthesis and replicates its genome.
- During G_2 the cell prepares to undergo division and checks its replication using DNA repair enzymes.
- During M phase, the cell undergoes division by mitosis or meiosis and then re-enters G_1 or G_0 .

B

In most instances, the decision for a cell to undergo division is regulated by the passage of a cell from G_1 to S phase. Progression through the cell cycle is controlled by a group of kinases called cyclin-dependent kinases (CDKs), (see Figure 51). CDKs are thought to phosphorylate cellular substrates, such as the retinoblastoma gene, that are responsible for progression into each of the phases of the cell cycle. CDKs are activated by associating with proteins whose levels of expression change during different phases of the cell cycle. These proteins are called cyclins. Once associated with cyclins, CDKs are activated by phosphorylation via CDK-activating kinase (CAKs) or by dephosphorylation via a phosphatase called CDC25.

D-types cyclins are the primary cyclins that respond to external cellular factors. Their levels start off low during G_1 and increase towards the G_1/S boundary. Cyclin D regulates CDK4 and CDK6. Cyclin E is expressed transiently during the G_1/S transition and is rapidly degraded once the cell enters S. Cyclin E regulates CDK2 and perhaps CDK3. When S phase begins, levels of cyclin A increase and activate CDK2. The cyclin A/CDK2 complex is thought to have a direct role in DNA replication. The progression through mitosis is regulated by the presence of cyclin B. Cyclin B associates with CDC2 and forms the primary kinase present during mitosis (MPF = "M-phase/maturation promoting factor"). During anaphase cyclin B is degraded. This degradation of cyclin B appears to regulate the cell's progression out of mitosis and into G_1 .

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