Cell Cycle and Its Regulation

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A decisive characteristic of life is the reproductive capacity of cells, which it does through a collection of highly complex and ordered regulatory process commonly known as the cell cycle. The cell cycle combines DNA replication with chromosomal segregation in an oscillatory manner. In this way, the cell cycle coordinates the precise replication of the genome through specific events to ensure that the duplicated genetic material is distributed equally to each daughter cell. The repetition of this process leads to the exponential proliferation of cells. This process is classically described as interphase and mitosis (M) phase. Most of the cell cycle is in interphase, which encompasses Gap 1 (G1), synthesis (S), and Gap 2 (G2) phases. During the interphase, the cell grows, replicates genetic materials, and repairs DNA damage and replication errors. M phase, a relatively short period, consists of prophase, metaphase, anaphase, and telophase, which completes the equal distribution of genome and cytoplasmic components. Following interphase, most nondividing cells exit the cell cycle at G1 into G0 phase (quiescence). G0 was originally used to describe cells that are not in the cell cycle but with the potential for division. The rate of cell cycling varies with the developmental stage and cell type. In general, the cell cycle is most active during development, as cells in early embryos can proliferate and differentiate to form tissues and organs. The cell cycle involves numerous life processes, and it is closely related to the growth and proliferation of eukaryotic cells, development of organisms, regulation of DNA damage repair, and occurrence of diseases.

cell-cycle regulation CDKs cyclins CKIs UPS E3 ubiquitin ligases DUBs

1. Cyclin–CDK Complexes Regulation

Studies in the past few decades have revealed that the cell cycle is tightly regulated by complexes containing cyclin-dependent kinases (CDKs) and cyclin proteins. CDKs belong to a highly conserved family of serine/threonine protein kinases whose activity relies on a regulatory subunit, a cyclin. The original member of the CDKs family, CDK1 (also known as CDC2), was discovered in genetic screens for *Schizosaccharomyces pombe* and *Saccharomyces cerevisiae* [1]. The proteins of cyclin family are classified by the existence of a CDK-binding domain called the cyclin-box, which vary with cell-cycle progression [2][3]. Cyclins were first identified by Tim Hunt in developing sea urchin eggs, and they were synthesized during interphase and then rapidly destroyed at each cleavage division [4]. Up to now, studies showed that fungi contain 6–8 CDKs and 9–15 cyclins, flies and Echinodermata include 11 CDKs and 14 cyclins, and human cells have 20 CDKs and 29 cyclins [5]. Many of these 29 cyclins lack known CDK partners, and not all cyclins are involved in cell-cycle control, such as cyclin I [6].

Different stages of the cell cycle require different cyclins. CDK4 and CDK6 are frequently regarded together as promoters of G1 progression. Initially, mitogenic signaling induces synthesis and assembly of the D-type cyclins,

the proper folding and transport of CDK4 and/or CDK6 to the nucleus [7]. CDK4 or CDK6 is activated after binding to D-type cyclins (D1, D2, and D3). Active complexes of CDK4/6 and D-type cyclins phosphorylate members of the retinoblastoma protein (pRb) family, which includes Rb/p105, p107, and Rb2/p130. Rb protein is a tumor suppressor, which plays a key role in the negative regulation of cell cycle and tumor progression. It has been demonstrated that pRb is responsible for preventing S phase entry and cell growth. Phosphorylation of Rb protein leads to their functional inactivation [8]. CDK2 associates with cyclin E during late G1 phase and subsequently binds to cyclin A during early S phase for DNA synthesis and replication [9]. Therefore, both the D- and E-type cyclins and their associated kinases are considered to be pivotal for entry into G1 and G1/S phase transition. As the cell cycle progresses, Cyclin A subsequently interacts with and activates CDK1 in late G2 phase to facilitate the onset of M phase. At last, CDK1 becomes activated by B-type cyclins, trigger chromosome condensation, and mitotic entry after nuclear lamina breakdown [1].

2. CKIs Regulation

The activity of each CDK is not only controlled by the availability of its cyclin partner, but it is also negatively regulated by the expression of a specific CDK inhibitor (CKI). CKIs bind to free CDKs or cyclin–CDK complexes to regulate CDK activity. CKIs are classified into two families according to their structures and CDK targets: the CIP/KIP proteins, including $p21^{CIP1}$, $p27^{KIP1}$, and $p57^{KIP2}$, extensively influence the activity of cyclin D-, cyclin E-, and cyclin A-dependent kinase complexes; and the INK4 proteins, $P16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$, and $p19^{INK4d}$, specifically target CDK4 and CDK6 [10][11][12]. The lack of these proteins leads to loss of function in growth control, DNA replication, cell apoptosis, and wound repair. Therefore, CKIs are considered as a potential target for cancer treatment.

3. The Restriction Point and Checkpoints

In fact, Arthur Pardee discovered as early as 1974 that a normal cell needs exogenous mitogenic stimulation only during the first two-thirds of the G1 phase. After undergoing continuous mitogenic stimuli during this period, the cell could decide to continue and complete its cell cycle in the absence of mitogenic signals. This phenomenon suggests the existence of a key point at the mid/late G1 phase, which Pardee termed the “restriction point” (R point) [13][14]. Therefore, the R point is the time after which the cell is committed to entering the cell cycle. The R point is considered to be regulated largely by pRb [15].

Furthermore, these regulatory roles of cyclin–CDK complexes allow for checkpoints during the cell cycle, which are inhibitory pathways. Cell-cycle checkpoints have been defined as “biochemical pathways that ensure dependence of one process upon another process that is otherwise biochemically unrelated.” Checkpoints can control cell-cycle progression and ensure high-fidelity completion of crucial events such as DNA replication and chromosome segregation [16]. Regulatory checkpoints include the DNA damage and DNA replication checkpoints and spindle assembly checkpoint. The DNA damage checkpoint is responsible for detecting damaged DNA and generating arrest in G1, S, and G2 phase of the cell cycle. The G1 arrest provides time for DNA repair before replication, while

the block in G2 allows repair before chromosome separation in M phase. Cells can also be arrested in S phase, slowing down DNA synthesis [17]. The DNA replication checkpoint ensures that mitosis does not take place until DNA replication is complete, otherwise cells face the risk of chromosome mutation [18]. The spindle assembly checkpoint is one of the critical mechanisms to ensure the correct and even distribution of genetic material into two daughter cells. It monitors the binding of chromosomes and spindle microtubules. It monitors the combination of chromosomes and spindle microtubules [19]. Recently, there is a growing body of evidence to suggest that checkpoint dysfunctions result in genomic instability, and they have been related to cancer.

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