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REVIEW

The driving power of the cell cycle: cyclin-dependent kinases, cyclins and their inhibitors

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ABSTRACT
The cell cycle covers cell proliferation and growth and is strictly regulated by cyclin-dependent kinase, cyclins and their inhibitors. Cyclin-dependent kinases are serine/threonine kinases that are activated in certain phases of the cell cycle by regulatory subunits, cyclins, with which they form functional heterodimeric complexes. Under physiological conditions, the activation of cyclin-dependent kinases and cyclins is strictly controlled. The formation of these complexes is inhibited, as needed, either specifically or non-specifically, by cyclin-dependent kinase inhibitors. Progression through the cell cycle is a critical process that drives many aspects of cellular function. The cell cycle is a series of events that occurs in a repeating pattern. Each cell cycle consists of two phases, interphase and mitotic phase. Their dysregulation leads to disruption of cell cycle coordination and uncontrollable cell proliferation, which is the main feature of tumorigenesis *(Fig. 1, Ref. 69)*. Text in PDF *www.elis.sk*
KEY WORDS: cell cycle, regulation, cyclin-dependent kinases, cyclins, inhibitors.

Introduction

In the last two decades, multiple lines of evidence have suggested that dysregulation of cyclin-dependent kinases (CDKs), cyclins and their inhibitors may play a role in carcinogenesis. The cell cycle is regulated by multiple signaling pathways to ensure the cell passes through the individual phases. Regulation of this process requires environmental stimuli that lead to the activation of CDKs (1). CDKs are activated by cyclins with which they form complexes, while different cyclins are required at different stages of the cell cycle (2). CDK activity is downregulated by CDK inhibitors (CKIs) upon their binding to either CDK alone or the CDK-cyclin complex. This review focuses on the role of alternations in genes coding proteins included in G1/S transition in cell cycle and their association with cancer risk.

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Cell cycle

The cell cycle is an organized event where cells go through specific phases, during which the cell doubles in volume and divides into two daughter cells. The process of the cell cycle is tightly regulated in order to retain the quality of genetic information (3). The cell cycle consists of two main parts, interphase and mitosis (M phase). The interphase consists of G1 ("gap 1"), S and G2 ("gap 2") phase. Cells can enter G1 phase either from the quiescent G0 phase or in case they proliferate, after completion of cytokinesis (4). The majority of differentiated cells in adult tissues remain in the G0 phase, which is either temporary or permanent. Signals marked as mitogenic factors from cell surroundings can stimulate cells in G0 phase to re-enter cell cycle (5).

Control of cell cycle

The progression of the cell cycle, alternation of S and M phases, and coordination of cell growth and division are regulated by the so-called checkpoints at which the cycle is stopped and checked. Three major cell cycle checkpoints are known, the G1/S checkpoint, G2/M checkpoint and spindle assembly checkpoint (SAC). The G1 checkpoint controls the entry into phase S and decides whether: (a) the cells are large enough for DNA synthesis to occur; (b) any DNA damage is repaired; and (c) there are favorable external conditions for mitotic cell division. The G2/M checkpoint is checked to see if the DNA is completely replicated and undamaged, and the cell is large enough to divide (6). If the DNA damage is irreparable, cells may initiate senescence or cell death (7).

The SAC provides assurance that chromosome segregation is proceeding correctly and is activated at the metaphase-to-anaphase transition in mitosis, in reaction to microtubule defects or defective kinetochore attachment. Cells also arrest in SAC when they enter mitosis with damaged DNA. SAC inactivation can lead to chromosome mis-segregation and aneuploidy (8).

Cyclins

Cyclins are proteins in size ranging from 30 to 65 kDa. The name cyclin is derived from the periodic change of their concentration (from minimum to maximum) depending on the stage of the cell cycle. They serve diverse functions owing to their sequence heterogeneity. Cyclins are characterized by the presence of a specific amino acid sequence, which serves as a binding place for CDKs, known as the cyclin box (9). Cyclins have a characteristic ability to oscillate activity during the cell cycle. The alphabetical arrangement of cyclins (A, B, C, D and E) represents the order of their discovery; however the order of their activity during the cell cycle is different. First, cyclins C and D control the cell cycle exit from the quiescent G0 phase and progression through the G1 phase; subsequently, cyclin E plays a role in entering the S phase; cyclin A plays a role in DNA replication and G2 phase progression, and cyclin B is one of the major regulators of mitotic onset and chromosome segregation (10); particularly CDKs, because of their key role in cell cycle regulation. Despite the favorable results obtained in preclinical trials, clinical trials did not continue due to the cytotoxic effects of first- and second-generations of CDK inhibitors on healthy cells. However, the third generation of CDK inhibitors (palbociclib, ribociclib and abemaciclib) with a selective CDK4/6 inhibitory effect is an approved drug in the United States for the treatment of breast cancer patients (11).

Cyclin E1

Of the broad family of cyclins, cyclin E1 (CCNE1) plays an important role in the regulation of the transcription factor E2F through its interaction with CDK2 and in the cell cycle during the transition from G1 to S phase (12). Under physiological conditions, cyclin E/CDK2 complex activity is associated with DNA replication (13). An increase in the expression of cyclin E during the S or G2 phase may affect centrosome duplication as well as the DNA replication cycle (14, 15). Altered expression of cyclin E results in the development of resistant tumor cells. To date, only one study by Amininia et al (2018), was investigating the effect of insertion-deletion variant of CCNE1 on the risk of breast cancer in women of Iranian population. The results did not confirm a significant association of this polymorphism with the risk of breast cancer. In contrast, a study by Han et al (2012) found a significant association between other CCNE1 polymorphisms (rs3218035, rs3218038, rs3218042) with the risk of breast cancer. According to a meta-analysis performed by Zhao et al (2018), patients with increased CCNE1 gene expression have a worse prognosis for gastric cancer (19) and breast cancer (20).

Cyclin D1

The levels of cyclin D (CCND) oscillate during the G1 phase, they increase at the beginning of the G1 phase and accumulate up to their rapid decrease during the transition to the S phase. Cyclin D, together with CDK4/6, regulates the passage through the G1/S phase through the phosphorylation of pRB (21). Cyclin D directly inhibits DNA synthesis after binding to proliferative cell nuclear antigen and CDK2. Early studies indicated that changes in CCND1 levels depend on T286 phosphorylation and are regulated by ubiquitin-dependent proteosomal degradation (22, 23). Phosphorylation of cyclin D1 is increased upon binding to CDK4, and a mutation leading to the substitution of T286 for alanine leads to a significantly higher stability of this cyclin. At the same time, it was proved that CDK4 is not necessary for the phosphorylation of CCND, which indicates the presence of another kinase. Glycogen synthase kinase 3β was identified, which, in addition to T286 phosphorylation, also ensures its translocation from the nucleus to the cytoplasm during the S phase. This transport of cyclin D1 is essential for its degradation, and phosphorylation of T286 affects the association of cyclin D1 with the protein chromosomal maintenance 1 or exportin 1, which facilitates its export from the nucleus (24). Degradation of CCND1 occurs in the late G1 phase and in S phase (25). However, some studies point to their degradation at the G2/M phase transition (26). Cyclin D1 is also involved in the regulation of transcription, both dependently and independently of CDK. In the case of CDK-independent regulation, it is associated with transcriptional regulators, including the chromatin-modifying enzymes P300/CBP-associated factor or K acetyltransferase 2B, NcoA/steroid receptor coactivator 1a, amplified in breast cancer 1, glutamate receptor-interacting protein 1,transcription factor II D and TBP-associated factor 250 kDa. Cyclin D1 also interacts with sequence-specific proteins such as estrogen and androgen receptors and dentin matrix acidic phosphoprotein 1. Such an interaction is generally associated with transcriptional repression (27).

Cyclin-dependent kinases and cell cycle

Cyclin-dependent kinases form a family of heterodimeric kinases that play a key role in cell cycle regulation. In monomeric form, they are inactive. Regulatory subunits, cyclins, with which they form functional heterodimeric complexes, are responsible for their activation at a given stage of the cell cycle (28). In addition to cell cycle regulation, CDKs are also involved in gene transcription (29), DNA repair (13), metabolism (increased glycogen synthesis by overexpression of CDK5), and epigenetic regulation (30). CDKs are serine / threonine kinases belonging to the CMGC family consisting of cyclin-dependent kinases, mitogen-activated kinases, glycogen synthase-3 and CDK-like kinases, with 20 CDKs identified to date (31). The CDK family consists of proteins varying in sizes, from proteins composed of 250 amino acids, with only a catalytic serine/threonine kinase domain, to proteins composed of 1,500 amino acids (AA). All CDKs have a tertiary structure formed by two lobes. The small N-terminal lobe (AA 1-96) contains b-folded leaves, and the large C-terminal lobe is rich in a-helixes.

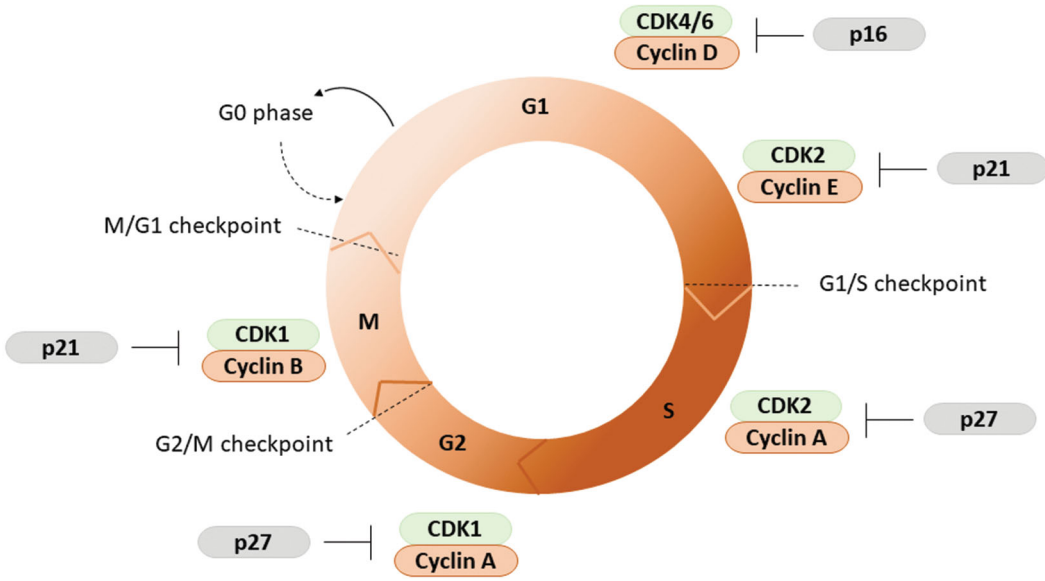

Fig. 1. Individual phases and transitions in the cell cycle regulated by cyclin-dependent kinases (CDK), cyclins and their inhibitors (adjusted according to Peyressatre et al, 2015). CDK1: cyclin-dependent kinase 1; CDK2: cyclin-dependent kinase 2; CDK4: cyclin-dependent kinase 4; CDK6: cyclin-dependent kinase 6.

There is an active site between the N- and C-lobes. These two terminal lobes are joined by a single peptide chain (AA 81-83), which ensures that the lobes rotate relative to each other without disrupting the secondary structure of the CDKs. The ATP binding site is located in the loophole between the lobes (32). The N-lobe contains a glycine-rich (G-loop) inhibitory region and a unique major helix, the C-helix. The C-lobe contains an activation domain and a T-loop, which includes an amino acid residue sensitive to phosphorylation (T160 in CDK2, T172 in CDK4 and T177 in CDK6). In monomeric form, without the bound cyclin, the CDK catalytic site is closed by a T-loop (9). In addition, if CDK is not active, the amino acid side chains at the active site are not properly oriented to the phosphate binding from ATP and kinase reaction. CDK activation therefore requires extensive structural changes in the CDK active site (33).

The transition through different phases of the cell cycle is coordinated by changes in CDK activity, by three different mechanisms (34), cyclin availability (35), regulation of CDK activity by phosphorylation of kinase subunits (36) and CKIs (Fig. 1) (37).

Cyclin dependent kinase 2

Cyclin-dependent kinase 2, also known as p33 or DKN2 protein kinase, is one of the most important regulators of the cell cycle, where it plays a role in the G1/S transition, initiation of DNA synthesis and regulation of S phase progression (38). The activation of CDK2 consists of the formation of a heterodimeric complex with a regulatory subunit (cyclin A or cyclin E) and phosphorylation of the Thr160 residue (39). Substitution of a threonine residue with serine has been shown to result in a more efficient phosphorylation and slower dephosphorylation of CDK2 (40). The activation of the cyclin A-CDK2 complex during the S phase supports the phosphorylation of endogenous substrates, DNA replication, and inactivation of the transcription factor E2F, which is necessary to complete the S phase. The presence of the active form of E2F in the absence of the cyclin A-CDK2 complex can lead to cell apoptosis. The inactivation of endogenous inhibitors or inappropriate CDK expression results in various malignancies such as lung cancer, ovarian cancer, and pancreatic cancer (41).

Cyclin-dependent kinases 4 and 6

Cyclin-dependent kinases 4 and 6 have 71 % amino acid homology but differ in subcellular localization (42). CDK6, in human osteosarcoma epithelial cells, is preferentially localized in the cytoplasm (43). In mouse astrocytes, CDK6 is similarly localized mainly in the cytoplasm and CDK4 in the nucleus (44). In T cells, on the other hand, CDK6 was found both in the cytoplasm and in the nucleus, but only the nuclear fraction carries out the pRB kinase function (45). As mentioned above, the cyclin D-associated CDK4 and CDK6 facilitate cell progression from G1 to S phase of the cell cycle through phosphorylation of the RB family of proteins (pRB, p130, and p107) (46). This complex is also directly involved in the regulation of transcription and cell proliferation, which can be shown on an example of the activation of FOXM1-dependent transcription, which increases the expression of genes responsible for regulating the transition between G1/S phases (47).

Inhibitors of cyclin-dependent kinases

Cyclin-dependent kinase activity is negatively regulated by CKIs. Based on the structure and specificity, two groups of CKI

were described. The first group is the INK4 family consisting of $p16^{Ink4a}$, $p15^{Ink4b}$, $p18^{Ink4c}$ and $p19^{Ink4d}$, which specifically bind to and inhibit CDK4 and CDK6, as well as prevent their association with cyclin D (48). The second, Cip / Kip family, consists of $p21^{Cip1 / waf1}$, $p27^{Kip1}$ and $p57^{Kip2}$. They are non-specific for CDKs and bind to the cyclin-CDK complex. These inhibitors contain a KID domain at the N-terminus, which ensures their binding to cyclins and CDKs. Because these inhibitors exert most of their functions in the nucleus, they contain a sequence at the C-terminus that ensures their translocation to the nucleus. Other sequences are inconsistent, thus suggesting their different functions and mode of regulation (49).

Protein p27

The p27 protein acts as an inhibitor of CDKs, thus inhibiting the progression of cell cycle through specific molecular mechanisms. It is also involved in cell proliferation, cell differentiation and apoptosis. A decrease in p27 expression is associated with the aggressive manifestation of many epithelial tumors, including prostate cancer (50). The role of the p27 protein depends on its localization within the cell. In the nucleus, it acts as a tumor suppressor, whereas in the cytoplasm, it behaves as an oncogene. The effect of p27 is prominent in the resting G0 phase and in the early S phase, when it binds and inhibits the cyclin E / CDK2 complex. Upon entering the S phase, cyclin E levels increase, which results in binding to CDK2 and thus in activating it (51). This in turn results in phosphorylation of p27 on Thr187. Subsequently, p27 becomes unstable and is degraded by SCFskp2 ubiquitin ligase, thus resulting in the initiation of DNA replication (52).

So far, 21 single nucleotide polymorphisms have been characterized in the p27 gene, of which 11 have a low allele frequency and 9 occur in the non-coding regions (53). The most studied polymorphism of p27 is V109G (rs2066827), characterized by substitution of T for G at codon 109 leading to valine for glycine exchange. This polymorphism is thought to affect the normal function of the p27 gene through altered transcription. It also affects the levels of the protein itself, which leads to cell cycle dysregulation and induction of tumorigenesis (54). Many studies have investigated the association between the p27 V109G polymorphism and carcinomas, including prostate cancer. The results are contradictory; some of these studies confirm a reduced risk of prostate cancer (55, 56), other studies found an association between the reduction in prostate cancer risk and p27 V109G polymorphism (53, 57).

$p15^{INK4b}$ and $p16^{INK4a}$

The gene encoding $p16^{INK4a}$ (also called MTS1 or CDKN2), CDKN2A, is located in the INK4/ARF tumor suppressor locus on chromosome 9p21.3 (58). CDKN2A encodes two transcripts differing in their transcriptional start site. Both transcripts contain exons 2 and 3, but their translation occurs on different open reading frames, giving rise to two distinct proteins: $p16^{INK4a}$ and ADP ribosylation factor ($p14^{ARF}$ in humans, $p19^{ARF}$ in mice). In addition to CDKN2A, the INK4/ARF locus encodes a third tumor suppressor protein, $p15^{INK4b}$. The $p15^{INK4b}$ and $p16^{INK4a}$ proteins are characterized by 85% amino acid homology and differ only slightly in their biochemical properties (59). The $p16^{INK4a}$ protein acts as an inhibitor of the G1/S phase of the cell cycle. Stress stimuli (e.g., DNA damage, oncogenic signals) stimulate the binding of $p16^{INK4a}$ to CDK4/6, thus preventing the formation of the cyclin D-CDK4/6 complex and phosphorylation of pRB. The RB protein is maintained in the cytosol in a hypophosphorylated state and bound to the transcription factor E2F1. This results in transcriptional repression of E2F1 target genes that are crucial for the G1/S transition of the cell cycle. All four proteins bind *in vitro* to CDK4/6, but only $p16^{INK4a}$ fulfills the role of a tumor suppressor (60). The $p15^{INK4b}$ gene, located on chromosome 9q21, is frequently deleted together with the coding sequence of the $p16^{INK4a}$ and p14ARF genes (61). The expression of $p15^{INK4b}$ is induced by TGF-β (62).

Cell cycle and cancer

Under physiological conditions, CDK and cyclin activation are strictly controlled. Their dysregulation disrupts the cell cycle coordination which leads to uncontrollable cell proliferation characteristic for tumor cells (63). While mutations leading to CDK hyperactivation cause a selective cell growth, mutations causing inactivation of CDK regulators lead to loss of cell cycle inhibition. Studies have confirmed that alternations of cyclins, CDKs, and CKIs occur in most cancers. These changes include chromosomal translocations, point mutations, insertions or deletions, gene overexpression, frame-shift mutations, missense mutations or splicing (64). A multitude of CDK mutations have been described in the COSMIC catalog (catalog of somatic cancer mutations, www.sanger.ac.uk/genetics/CGP/cosmic). The incidence of these mutations is very low and there are few studies showing that these mutations lead to a reduction in the catalytic activity of kinases (65). In most cancers, the CDK4/6-RB pathway is dysregulated through several mechanisms and the cyclin D-CDK4/6 complex is inactivated. Some signaling pathways such as JAK-STAT, PI3K-Akt, and Ras/ Raf/MAPK/ERK induce cyclin D overexpression, while potentiating CDK4/6 activity leading to uncontrollable cell proliferation (66, 67). The CDK4/ 6-RB pathway is associated with the p53 signaling pathway through $p21^{CIP1}$ transcription, which can inhibit cyclin D-CDK4/6 and cyclin E-CDK2 complexes. Mutations in p53 result in inactivation of the G1 checkpoint leading to uncontrolled cell proliferation (68). Deregulation of amplification of genes encoding cyclins or their cellular delocalization leads to impaired CDK activation. One such cyclin is cyclin D, whose deregulation has been observed in 15 % to 40 % of various cancers, including breast, lung, and oral cavity cancers (64). The gene encoding cyclin D1 is activated by various oncogenic signals, including Ras, Src, MAPK and myc. Cyclin D1 is associated with the resistance to chemotherapy and increased incidence of relapse in head and neck tumors. Increased expression of cyclin D1 is generally considered an unfavorable prognostic factor in cancer patients. The overexpression of cyclin D1 is present in many cancers, especially breast cancer, small cell lung cancer and leukemia (69).

Conclusion

The cell cycle is a complex process that involves numerous regulatory proteins that direct the cell through a specific sequence of events ensuring the correct cell division. Central to this process are CDK, which create a complex with the cyclin proteins. The complexity of regulation of the cell cycle is also reflected in various alterations leading to aberrant cell proliferation and development of cancer. Consequently, targeting the cell cycle in general and cyclin-dependent kinases, in particular, presents unique opportunities for drug discovery.

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