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Cyclic Dependent Kinase (CDK): Role in Cancer Pathogenesis and as Drug Target in Cancer Therapeutics

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Abstract

The cell cycle is the process by which mammalian cells regulate proliferation and has S, M, G2 and G1 phase. Loss of these cell-cycle control and increased resistance to apoptosis (programmed cell death) represent major hallmarks of cancer. Cyclic dependent kinases (CDKs), a family of serine/threonine, can control the cell cycle progression and transcription. Besides, they are also involved in regulating mRNA processing, the differentiation of nerve cells and glucose homeostasis. Therefore, CDKs are multiple function proteins. Cellular proliferation, driven by CDKs and their cyclin partners, is decontrolled in cancer; therefore, cancer is considered as a proliferative disorder and targeting the cell cycle, therefore, seems to be a good strategy for new targeted anticancer agents. CDKs activity is closely associated with specific cyclin co-factors and at least 12 separate genetic loci are known to code for the CDKs. Therefore, cyclins are considered to be the gears that are changed to aid the transition between cycle phases. CDKs are generally classified into two major groups, based on whether they control cell cycle progression which includes CDK1 to CDK6 or regulate gene transcription by RNAPII that includes CDK 7, CDK8, CDK9 and CDK19. Increases in level of CDKs are observed in cancer. Inhibition of CDKs, which are the key regulators of the cell-cycle progression and RNA transcription, represents a good strategy for cancer drug discovery and development as well as therapy. This review was briefly described the above-mentioned possible roles of CDKs in the physiological and pathological mechanisms of cancer, further discussing recent advances and challenges in CDKs as a therapeutic target.

Keywords: Cancer; Cell cycle; Cyclic dependent kinase; Therapeutic target; Drug discovery; Cancer therapeutics

Abbreviations: DNA: Dinucliec Acid; S Phase: Synthesis Phase; M Phase: Mitosis Phase; G1: Gap 1; G2: Gap 2; R: Restriction Point; Rb: Retinoblastoma Protein; pRb: phosphorylating The Retinoblastoma Protein; CDKs: Cyclin-Dependent Kinases; CDKIs: Cyclin-Dependent Kinases Inhibitors; CKIs: Cyclic Kinase Inhibitors; CDC: Cell Division Cycle; RNAPII: Ribonucleic Acid Polymerase II; Chk: Checkpoint Kinase; DDR: DNA Damage Response; PLK1: Polo-Like Kinase 1; DSB: Double Strand Breaks; pre-RC: pre-Replication Complex; OP: Oligodendrocyte Progenitors; CAK: CDK-Activating Kinase; CTD: Carboxy Terminal Domain; TFIIH: Transcription Factor IIH; DSIF: DRB-Sensitive-Inducing Factor; NELF: Negative Elongation Factor; JNK: c-Jun N-terminal Kinase; MAPK: Mitogen-Activated Protein Kinase; GTFs: General Transcription Factors; P-TEFb: Positive Transcription Elongation Factor b; TAK: Tat Activating Kinase; snRNA: Small Nuclear RNA; AR: Androgen Receptor; dnCDK9: Dominant Negative Form of CDK9; CLL: Chronic Lymphocytic Leukemia; HCC: Hepatocellular Carcinoma; HIF-1α: Hypoxia Induced Factor 1; GSKs: Glycogen Synthase Kinases; CLKs: CDK-Like Kinases

Introduction

The cell cycle is a mammalian cells proliferation regulation process and has 4 functional phases: S phase (DNA replication); G2 phase (cells prepare for mitosis); M phase (DNA and cellular components division into 2 daughter cells) and G1 phase (cells commit and prepare for another round of replication) [1-3]. S and M phases are the major and common processed to all cell cycles for replication of cells [4]. It requires expression of genes in response to growth factors, which induce cell growth from quiescence or maintain competency for cell cycle progression during periods of active proliferation [5,6].

Errors in cell cycle results in deregulated DNA replication and mitosis which is a major cause for proliferative disorders such as cancer [7]. Loss of cell-cycle control and increased resistance to apoptosis as well as the invasive growth of these cells in to primary tumors and its dissemination to vital organs represent major hallmarks of cancer [8-10].

The cell cycle progression and transcription is governed by a biochemical known as CDKs that play pivotal roles in G1-S transition, cancer development and metastasis in different neural cell types [11-15]. Deregulated activity of CDK results in loss of cell-cycle checkpoint function and increased expression of antiapoptotic proteins, which has been directly linked to the molecular pathology of cancer [8].

The hallmarks of cancer include sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis [16]. One of the hallmarks of cancer is uncontrolled cell proliferation, leading to malignant tumor development. In addition, inflammation and immune evasion are part of the hallmarks of cancer. Dysregulation of cell-cycle progression, such as evasion of multiple cell-cycle checkpoints, can be caused by abnormal activation of two key classes of regulatory molecules, cyclins and CDK [3,8,17-21].

Cellular proliferation, driven by CDKs and their cyclin partners, is deregulated in cancer [18,22,23], therefore, cancer is regarded as a

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proliferative disorder [20,24] and targeting the cell cycle, therefore, seems to be a good strategy for new targeted anticancer agents [24]. Cancer cells often appear to demonstrate oncogene (ras, cyclin D, erbB, myc, sis, etc) addiction for anti-apoptotic proteins in order to maintain their survival advantage and resist apoptosis [25,26].

Cyclic dependent kinases (CDKs)

The human protein kinases set (kinome), is constituted of 518 identified proteins, divided in seven families. CDKs are part of the CMGC family named after the members: CDKs, MAPKs, GSKs and CLKs. The CDK sub-family comprises thirteen members (CDK1 to CDK13). For their discovery, Hartwell, Nurse and Hunt received the Nobel Prize in 2001 [27].

CDKs are a family of serine/threonine kinases, whose activity is tightly associated with specific cyclin co-factors [2,8,18,24,28-31] and at least 12 separate genetic loci are known to code for the CDKs [3]. Over the last decade, more than 20 CDKs have been characterized and are generally classified into two major groups, based on whether they control cell cycle progression or regulate gene transcription by RNAPII [2,3,8,23,27,29]. CDKs also regulate neuron biology [14,32].

The mammalian cell cycle is controlled by the periodic association of CDKs with their cyclin partners and kinase inhibitor proteins (for example, p21Waf1/Cip1 and p27Kip1). The primary positive and negative regulation of CDK activity is mediated by the binding of a cyclin and of a CDKI, respectively [2,3,8,23,28,29].

In mammals, two families of seven CDKI have been identified that dimer in both structure and mechanism of action. Members of the CIP/KIP family contain three genes, p21CIP1/WAF1, p27KIP1 and p57KIP2, which inhibit CDK activity by forming a ternary p21-cyclin D-CDK4 complex. The main function of CDKIs is believed to couple diversified growth inhibitory signals to the cell cycle clock [23,28,29].

Multiple CDKs control the cell cycle which includes CDK1 to CDK6, while CDK8, CDK9, CDK12 and CDK19 are linked to regulation of transcription. The first group is essential for normal proliferation, development and homeostasis. CDK4/cyclin D, CDK6/cyclin D and CDK2/cyclin E facilitate the G1-S phase transition by sequentially pRb, while CDK1/cyclin A, CDK2/cyclin A and CDK1/cyclin B are essential for S-phase progression and G2-M transition, respectively. CDK7 and CDK20 act in cell cycle control and transcription processes (Figure 1) [18,20,23,26,29,31,33].

In an undamaged cell, progression through G1, S and G2 phase of the cell cycle is dependent on temporal activation of CDK1 and CDK2 in complex with cyclins E, A and B. CDK1/2 usually exist in a phosphorylated and inactive form that requires dephosphoryation for activation at an appropriate time in the cell cycle. Many anticancer agents damage DNA thereby activating a cell cycle checkpoint that arrests cell cycle progression and permits repair and recovery. The arrest requires activation of Chk1 that inhibits CDC25 and thereby prevents activation of CDK1/2 [34].

Inactivation of individual genes encoding members of these complexes (cyclins D1, D2, D3, E1, and E2 and CDK2, CDK4, and CDK6) has revealed that none of these proteins considered to be important for the control of the G1/S transition are essential for viability per se and that their loss causes few cell cycle defects [22].

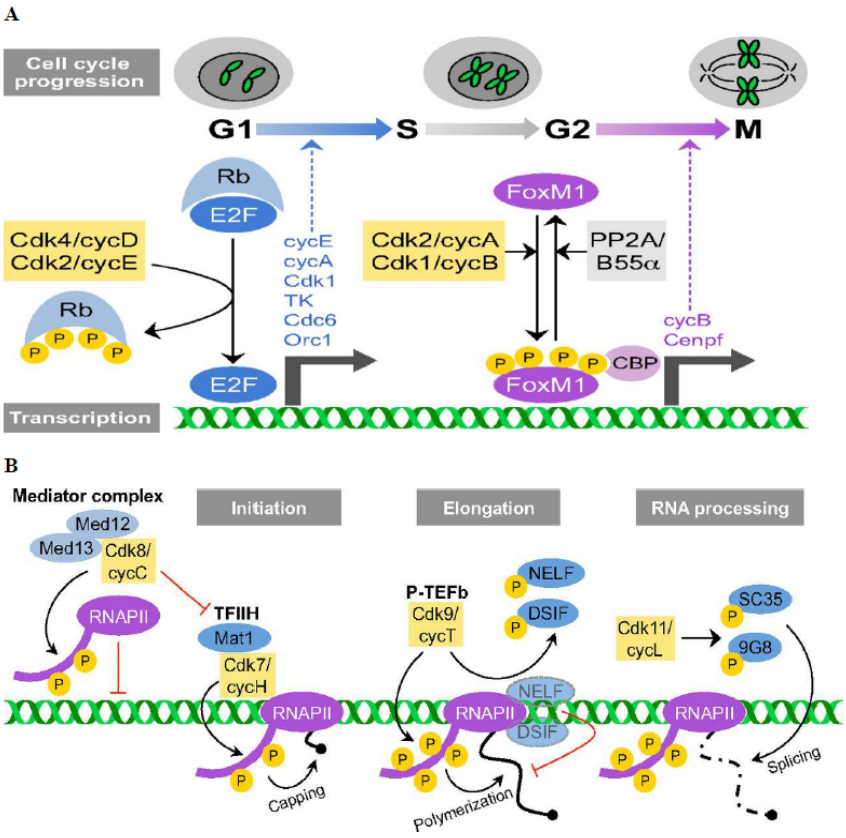

Figure 1: The graphical diagram of the mechanistic outline of cyclic dependent kinases (A): Cyclic dependent kinases role in cell cycle progression; (B): Cyclic dependent kinases role in transcription.

Drug Candidate	Company	Administration Mode	CDK Inhibition Profile (IC50, nM)	Clinical Trial Stage
Flavopiridol	Sanofi-Aventis	Intravenous	CDK1: 30, CDK2: 100 CDK4: 20, CDK6: 60 CDK7: 10, CDK9: 10	II
Roscovitine	Cyclacel	Oral	CDK1: 2700, CDK2: 100, CDK7: 500, CDK9: 800	II
Dinaciclib	Merck	Intravenous	CDK1: 3, CDK2: 1 CDK5: 1, CDK9: 4	III
SNS032	Sunesis	Intravenous	CDK2: 38, CDK7: 62 CDK9: 4	I
AT7519	Astex/Novartis	Intravenous	CDK1: 190, CDK2: 44 CDK4: 67, CDK5: 18 CDK9: <10	I/II
Palbociclib (PD-0332991)	Pfizer, Inc.		CDK4 (CyclinD1): 11 CDK4 (CyclindD3): 9 CDK6 (CyclinD2): 15	Approved
EM-1421	Erimos	Intravenous	CDK1: N/A	I/II
RGB-286638	Agennix	Intravenous	CDK1: 2, CDK2: 3 CDK3: 5 nM, CDK4: 4 CDK9: 1	I
P276-00	Nicholas Piramal	Intravenous	CDK9: 20, CDK1: 79 CDK2: 224, CDK4: 63	II
BAY-1000394	Bayer	Oral	CDK1-4, 7, 9: 5-25	I
TG02/SG1317	S*BIO/Tragara	Oral	CDK9: 3, CDK5: 4, CDK2: 5, CDK3: 8, CDK1: 9	I
PHA-848125 AC	Nerviano	Oral	CDK1: 2, CDK2: 3 CDK4: 5, CDK5: 4	II
Ribociclib (LEE011)	Novartis	Oral	CDK4 (CyclinD1): 10 CDK6 (CyclinD2): 40	III
Abemaciclib (LY2835219)	Eli Lilly	Oral	CDK4 (CyclinD1): 2 CDK6 (CyclinD1): 9.9	III

Table 1: CDKs inhibitors in clinical development.

CDKIs negatively regulate the activity of these complexes. The expression of dominant negative forms of CDK4 or CDK6, but not CDK2 or CDK3, protects NGF-deprived sympathetic neurons from death [35,36]. The genome maintenance programs of post replicative cells, including DDR, are regulated by the overall level of CDK activity and not by specific CDKs. CDK inhibition in cultured cells results in activation of the DDR [37].

Regulators of cell cycle and transcription through inhibition of CDKs are considered as a good strategy for cancer drug discovery and development as well as therapy. It has been shown that the combined depletion of CDK9, CDK1 and CDK2 resulted in effective induction of apoptosis through both RNAPII CTD- and E2Fmediated effects [20,29,38]. Flavopiridol and roscovitine are among the first generation CDKs inhibitors to enter clinical trials for use in anticancer therapy (Table 1) [3,27].

Cell cycle progression regulators

The cell division cycle is controlled by checkpoint mechanisms that arrest further progression if a critical process such as DNA replication or mitotic spindle assembly. Continued defective cell cycle progression could result in tumor development. The balance between cell cycle controls and the threshold at which apoptosis is initiated are likely to be critical in determining the cellular response to genomic damage. Initiation of apoptosis in response to many stimuli, including oncogenes, cellular stresses, DNA-damaging agents, and many chemotherapeutic drugs, involves a cysteine protease, caspase-9 [38-40].

Cell-cycle dysregulation is prevalent in multiple malignancies. Progression from G1 to S phase is an important checkpoint in regulating cell proliferation. Cell cycle progression through the G1 phase is regulated by the action of cyclin D-cdk4, cyclin D-cdk6, and cyclin E-cdk2. This transition is mediated through the Rb, which is regulated through sequential phosphorylations by CDK [22,41-43].

CDK1

CDK1 (also known at CDC) is the major mitotic serine/threonine kinases that interacts with cyclin B1 to form an active heterodimer, driving progression from G2-M phase, and is a key player in cell cycle regulation and particularly mitosis [20,38,44-46]. CDK1 plays an important role in the maintenance of pluripotency and genomic stability in human pluripotent stem cells. Down regulation of CDK1 led to the loss of typical pluripotent stem cell morphology, down regulation of pluripotency markers and upregulation of a large number of differentiation markers. Thus, CDK1 has a key role in balancing survival and cell death signals to dictate cell fate during mitotic arrest [20,45,46].

Plk1 is also the major mitotic serine/threonine kinases required for the timely progression through mitosis. Plk1 co-ordinates a variety of cell division processes including centrosome maturation, recruitment of important mitotic spindle components and cytokinesis. Overexpression of Plk1 has a pro-survival role in tumourigenesis and its depletion leads to apoptosis. The co-operative action of CDK1 and Plk1 towards the novel substrate PTP1B during mitotic arrest is important for mitotic cell death [39,46,47].

CDK1 inhibition selectively reduces viability of MYC-dependent cells. CDK1 inhibitor-induced cell apoptosis is MYC-dependent [38]. The function of Nedd1 is regulated by CDK1 and Plk1. CDK1 phosphorylates Nedd1 at T550 and this phosphorylation enhances the subsequent phosphorylation of Nedd1 at T382, S397, S426 and S637 by Plk1, during mitosis [48-51].

CDK2/3

CDK2 controls entry and progression through the S phase (DNA synthesis) of the cell cycle [52]. Cyclin E-CDK2 kinase activity plays a central role in the regulation of cell cycle progression in mammalian cells, including glia. The time course of regulation of cyclin E-CDK2 activity is consistent with cell cycle withdrawal or arrest in G1 phase. The decrease in cyclin E-CDK2 activity is attributable to inhibition of cyclin E-CDK2 complex formation. Cyclin E and CDK2 levels and cyclin E–CDK2 activity decrease in corpus callosum during development *in vivo*. CDK2 controls OP cell cycle progression and is down regulated in adult OP cells [12,35].

CDK2 inactivation accompanies cell cycle arrest by MYC depletion, and leads to a subsequent decrease of pRb phosphorylation and E2F1 activity, contributing to MYC RNAi-induced cell cycle arrest [38]. Sensitivity to Chk1 inhibition is regulated upstream of CDK2 and correlates with accumulation of CDC25A [34]. The E type cyclins and their catalytic partner, CDK2, participate in the regulation of Rb inactivation, establishment of the pre-RC, and initiation of S phase; their participation in these critical regulatory steps has resulted in the assumption that both cyclin E and CDK2 are indispensable for cell cycle progression. CDK3 is the closest relative to CDK2 among the nine mammalian CDK genes identified thus far and its activating cyclin subunit has yet to be identified [28,53].

DK4/6

Progression through the cell cycle from G1/G0 to S, G2, and M phases is initiated by CDK4 and the highly homologous enzyme CDK6. They act as master integrators in the G1 phase, coupling with the cell cycle mitogenic and antimitogenic signals as well as with their oncogenic perversions in cancer cells. It is crucial for cortical neural progenitor cell proliferation. In astrocytes, CDK4 is an essential component of cell division. They phosphorylate and inactivate the cell cycle/tumor suppressor proteins of the pRb family (p105*Rb*, p107, and p130*Rb2*) and Smad3. This leads to both E2F-dependent transcription of essential cell cycle enzymes and regulators and assembly of the prereplication complex [3,12,19,40,54-56].

CDK4 and CDK6 form a complex with one of their activating subunits, which are the cyclins D1, D2, and D3. The activity of CDK4/6 is negatively regulated by the INK4 proteins. Deregulation of the G1 checkpoint is crucial for various oncogenic transformation processes [3,12,19,54-56]. Hyperphosphorylation of Rb is mediated by CDK4 and CDK6 in early G1 phase through the interaction with cyclin D. This results in Rb inactivation and release of transcription factors that allows cells progress toward S phase [57]. Increased activity of CDK4 is observed in cancer and CDKI has been shown to induce G1 arrest and apoptosis. It is noteworthy that inhibition of CDK4 reduced the expression of both HIF-1α and HIF-2α [22,49,56].

Cell cycle deregulation is crucial for various oncogenic transformation processes, suggesting that many cancer cells depend on high CDK4/6 activity. Transition through the restriction point requires pRb by CDK4/6, which are highly validated cancer drug targets [1,19,32,41,42]. Emerging evidence suggests that certain tumor cells require CDK6 for proliferation. Consequently, CDK6 represents a promising target for anti-cancer therapy. In contrast to CDK4, CDK6 is poorly phosphorylated, restricting its activity in a variety of systems [2,55,58].

Transcription regulators

CDKs are key cell cycle regulators and some also have regulatory functions in mRNA transcription at the level of RNAP-II. CDKs 1, 2, 7, 8, 9, and 11 have all been implicated in the phosphorylation of the CTD of the largest RNAP-II subunit, but the most important ones are CDK7-cyclin H and CDK9-cyclin T [6]. Dysregulations of mRNA transcription is common event in human cancers. CDK7/cyclin H is a component of TFIIH that phosphorylates the serine-5 residues within the heptad repeats of RNAPII CTD to initiate transcription. CDK9/cyclin T, the catalytic subunit of positive transcription elongation factor P-TEFb, phosphorylates two elongation repressors, i.e. the DSIF and the NELF, and serine-2 of the CTD heptad repeats to facilitate a productive transcription elongation. RNAPII-mediated transcription initiation and elongation is regulated by the CDK7 and CDK9, which phosphorylate the CTD of RNAPII [14,21,25,31].

CDK8/cyclin C and CDK11/cyclin L are involved in mRNA splicing. CDKs 12 and 13 (both activated by cyclin K) regulate, like CDK9, transcription elongation by phosphorylating the RNAPII CTD. Inhibitors of CDKs have been reported to have activities in many types of cancer cells by inhibiting CDK7 and CDK9, which control transcription. Thus, the identification of more selective and potent CDK inhibitors is imperative for the development of effective cancer therapies [13,14,18,58].

CDK7

Besides its role in CDK activation, CDK7, is also known as the CAK, as a component of the GTF TFIIH and is involved in transcription initiation, phosphorylates the CTD of RNAPII and is thus required for its activity which activates other CDKs by phosphorylation of the activation segment. It also participates in the full activation of CDKs by promoting phosphorylation of the conserved threonine residue within the T-loop region of these kinases. CDK7 controls mRNA synthesis by affecting stability of preinitiation complexes, leading to altered gene expression, cell cycle progression, and survival of tumor cells. The inhibition of CDK7 may induce to block transcription and cell cycle progression [6,7,18,30,55,59-63].

CDK8

Mediator is a large complex containing up to 30 subunits that consist of four modules each: head, middle, tail and CDK/Cyclin. Recent studies have shown that CDK8, a subunit of the CDK/Cyclin module, is one of the key subunits of Mediator that mediates its pivotal roles in transcriptional regulation [64]. Mediator is a general cofactor implicated in the functions of many transcriptional activators. Mediator functions by facilitating activator-mediated recruitment of pol II and also promoter recognition by TATA-binding protein (TBP), both of which can occur in the absence of TBP-associated factors in TFIID [65].

The four proteins CDK8, cyclin C, Med12, and Med13 can associate with Mediator and are presumed to form a stable "CDK8 subcomplex" in cells [66,67]. The human CDK8 subcomplex (CDK8, cyclin C, Med12, and Med13) negatively regulates transcription and the studies suggested CDK8 kinase activity was required for its repressive function. Notably, the CDK8 submodule strongly represses even reinitiation events, suggesting a means to fine tune transcript levels. Structural and biochemical studies confirmed that the CDK8 submodule binds the Mediator leg/tail domain via the Med13 subunit, and this submodule-mediator association precludes pol II recruitment. The CDK8 subcomplex functions as a simple switch that controls the Mediator-pol II interaction to help regulate transcription initiation and reinitiation events. As Mediator is generally required for expression of protein-coding genes, this may reflect a common mechanism by which activated transcription is shut down in human cells [65,66,68,69].

The CDK8 and cyclin C pair may act as a negative regulator in transcription either as a heterodimer or as part of Mediator components. Nevertheless, several CDK8/cyclin C-containing human mediator complexes are also active in supporting activator-dependent transcription with either naked DNA or chromatin templates [65]. CDK8 and its paralog CDK19, in complex with CCNC, MED12 and MED13, are transcriptional regulators that mediate several carcinogenic pathways and the chemotherapy-induced tumor-supporting paracrine network. CDK8 and CDK19 do not function in isolation but require CCNC binding for their kinase activity; CDK8/19-CCNC complex is also associated with MED12 and MED13 in the CDK module of the Mediator [70].

CDK9

CDK9, a member of the CDK family and belongs to a family of 13 protein kinases that share sequence homology and dependence upon the binding of a cyclin subunit for activation, associates with T-type cyclins to form P-TEFb [59,71,72]. CDK9 is required for cell survival and in complex with T-type cyclins is recruited to promoters where it stimulates transcriptional elongation by phosphorylating the CTD of RNAPII and NELF. CDK9 is a key elongation factor for RNA transcription and functions by phosphorylating the CTD of RNAPII [25,31,71].

CDK9 is the catalytic subunit of the P-TEFb and is critical for stimulation of transcription elongation. It associates with T-type cyclins and cyclin K and is also the catalytic subunit of TAK, essential for HIV1 replication and its activity is strongly regulated in cells at different levels. Hence, it is a potential therapeutic target in cancer, AIDS, inflammation, and cardiomyophathy. This enzyme is critical for stimulating transcription elongation of most protein coding genes, including key developmental and stimulus-responsive genes, by RNAPII. Considering CDK9 as a potential target for therapeutic intervention, the variables such as kinetics of inhibition, potency, off-target effects, and selectivity issues affects the outcome [18,24,59,72].

Unlike other CDKs, CDK9 appears to function exclusively in transcriptional regulation and does not regulate the cell cycle but promotes RNA synthesis in genetic programmes for cell growth, differentiation and viral pathogenesis. It forms complexes with cyclin T1, T2, or K, which participate in the P-TEFb. CDK9 phosphorylates both Ser-2 and Ser-5 of the CTD heptad, playing a predominant role during transcriptional elongation, in contrast to CDK7, which primarily phosphorylates Ser-5 of RNAP-II at the promoter as part of transcriptional initiation [6,24].

In addition, CDK9 may have important implication in the Mnk-eIF4E axis, the key determinants of PI3K/Akt/mTOR- and Ras/Raf/MAPK-mediated tumorigenic activity. This causes dysregulation of cellular transcription is a fundamental hallmark of cancer. Subsequently, there is a decreased anti-apoptotic proteins Mcl-1 and Bcl-2 and induced apoptosis [25,31]. Apoptosis is preceded by a decrease in the levels of Mcl-1 protein and transcript possibly due to inhibition of CDK9 [73]. Specific inhibition of CDK9 activity with dnCDK9 leads to a distinctive pattern of changes in gene expression, with more genes being specifically up regulated than down regulated. To date, over 20 potent CDKIs undergo phase I-II clinical trials in patients with different cancers [59,71].

The targeted inhibition of CDK9 might prove to be a useful therapeutic strategy in cancers in which Mcl1 is over expressed [25]. CDKIs are being developed as potential cancer therapeutics based on the promise that they may counteract the unchecked proliferation of cancer cells by targeting the cell cycle regulatory functions of CDKs [26]. Although there are strong signs that CDK9 inhibition would be a useful therapeutic strategy in all cancer, HIV and cardiology indications, the lack of selective inhibitors has so far confounded clinical development [24]. Drugs that target cellular CDK9 kinase activity and down-regulate the RNAPII phosphorylation are considered as CDK9 inhibitors. CDK9 inhibition as an effective anti-cancer strategy has gained strong support in recognizing that cancer cells rely on the production of short-lived apoptosis regulators and mitotic regulatory kinases for survival. In contrast to CDK7, CDK9 appears to have a minimal effect on cell cycle regulation [31].

CDK9 inhibitors suppress the expression of anti-apoptotic proteins Mcl-1 and Bcl-2, leading to caspase-3/7 activation and PARP cleavage. In addition, MDM2 protein level is reduced and this is accompanied by the up-regulation of p53. CDK9 inhibitor treated cells decreased Mcl-1, Bcl-2, procaspase-3/7 protein levels and induced cleaved PARP. It also down-regulates the phosphorylation of RNAPII and eIF4E. CDK9 inhibition causes the down-regulation of Mnk1 [31].

The CDK9 inhibitor is consistently the most potent inducer of apoptosis of the MLL-AF9-driven leukemia cells. This apoptosis correlated with suppression of CDK9 enzymatic activity and down-regulation of previously identified MLL-AF9-target genes *HoxA9* and *Meis1*. In addition to its crucial role in phosphorylating the CTD of RNA Pol II and regulating gene expression, CDK9 also functionally interacts with other cellular proteins including MyoD, p53, pRb and c-Myc and can affect diverse biological processes including cell differentiation, survival and quiescence. The inhibition of CDK9 enzymatic activity resulted in rapid dephosphorylation of RNA Pol II and induction of apoptosis in AML cells and *Mcl-1* is a gene crucial for this response. Proteins with relatively short half-lives such as *Mcl-1* appear to be selectively reduced following CDK9 inhibition [10,58,74].

CDK19

In addition to CDK8, CDK19 was identified in human Mediator with a great deal of similarity to CDK8 but was conserved only in vertebrates. CDK19 was discovered by mass spectrometry in 2004 as an associated subunit of certain Mediator fractions that is conserved only in vertebrates. CDK19 showed high homology to CDK8 and had been thought of as a redundant partner of CDK8. CDK19 also possesses Ser5-specific kinase activity similarly to CDK8. CDK19 was expressed in limited number of tissues in contrast to ubiquitously expressed CDK8 [64].

CDK19, a component of the mediator co-activator complex, was found to be expressed in a diverse range of tissues including fetal eye and fetal brain. CDK8, the closest orthologue of human CDK19 has been shown to play a major role in eye development. CDK19 is disrupted in a female patient with bilateral congenital retinal folds, microcephaly and mild mental retardation [67,75].

The human CDK19 could form the Mediator complexes independent of CDK8. CDK8 and CDK19 possess opposing functions in viral activator VP16-dependent transcriptional regulation. CDK8 supported transcriptional activation, whereas CDK19, however, counteracted it [64].

Other functions of CDKs

In addition to regulation of the cell cycle progress, transcription and gene expression, CDKs, exert a variety of functions through implicating in diverse biological processes such as supporting expression of inflammatory mediators. The involvement of CDKs,

especially CDK6, in proinflammatory gene expression also allows therapeutic targeting of their functions to interfere with tumor-promoting inflammation or chronic inflammatory diseases [76].

CDK5, a unique member of the CDKs, is reported to intimately associate with the process of the pathogenesis of alzheimer's disease. It is of vital importance in the development of central nervous system and neuron movements such as neuronal migration and differentiation, synaptic functions, and memory consolidation. However, when neurons suffer from pathological stimuli, CDK5 activity becomes hyperactive and causes aberrant hyperphosphorylation of various substrates of CDK5 like amyloid precursor protein, tau and neurofilament, resulting in neurodegenerative diseases like Alzheimer's disease [77].

The study done in mice has examined the effects of flavopiridol, an inhibitor of CDKs currently used as antineoplastic drug, against cell cycle reactivation and memory loss induced by intracerebroventricular injection of Aß1-42 oligomers, reverses memory impairment [78].

On the other hand, the study done in rat model of spinal cord injury has suggested that CDKs, especially CDK14, contributes to reactive gliosis via interaction with cyclin Y**. Therefore,** both CDK14 and cyclin Y may play important roles in spinal cord pathophysiology [79].

The *in vitro* study done implicated that early (d-cyclins cdk4/6) and late (cyclin A/E and CDK1/2) G1/S cyclins and CDKs act complementarily to enhance authentic human β-cell proliferation and expansion which is associated with retinoblastoma protein inactivation via sequential phosphorylation [80].

Pharmacotherapy of CDK targeting agents

Personalizing the use of cancer therapeutics is a major focus of current cancer research [81]. Palbociclib showed significant hematologic toxicity and dose reduction for hematologic toxicity was required for 24% of patients in clinical trials [31]. Cancer cells develop dependence on other genes and pathways in order to overcome antitumorigenic effects, such as apoptosis and senescence that result from activation of MYC [38]. Resistance can be circumvented by inhibiting Wee1 kinase and thereby directly activating CDK2 [34].

First-generation CDKIs proved to be disappointing, yielding poor efficacy and significant toxicity and raising the question of whether these agents failed due to poor pharmacologic characteristics and/or specificities of the compounds or a less essential role of CDK signaling in cancer. Additionally, lack of appropriate patient selection and/or lack of predictive markers of response may have also contributed to these initial clinical failures. Recently, the development of more specific CDKIs has renewed interest in targeting the cell cycle as a novel therapeutic approach in cancer [3,81].

Conclusion

CDKs are enzymes that control the cell cycle progression and transcription. Deregulation of CDKs results in imbalance in proliferation and apoptosis which is a hall mark of a cancer. Inhibition of CDKs, which are the key regulators of the cell-cycle and RNA transcription, represents an attractive strategy for cancer therapy. There are numerous drug candidates in clinical trial stages but no CDKI is released yet. Therefore, more work is needed in drug discovery and development to come with CDKIs.

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