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Review

An insight into the emerging role of cyclin-dependent kinase inhibitors as potential therapeutic agents for the treatment of advanced cancers

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ABSTRACT

Cancer denotes a pathological manifestation that is characterized by hyperproliferation of cells. It has anticipated that a better understanding of disease pathogenesis and the role of cell-cycle regulators may provide an opportunity to develop an effective cancer therapeutic agents. Specifically, the cyclin-dependent kinases (CDKs) which regulate the transition of cell-cycle through different phases; have been identified as fundamental targets for therapeutic advances. It is an evident from experimental studies that several events leading to tumor growth occur by exacerbation of CDK4/CDK6 in G1-phase of cell division cycle. Additionally, the characteristics of S- and G2/M-phase regulated by CDK1/CDK2 are pivotal events that may lead to abrupt the cell division. Although, previously reported CDK inhibitors have shown remarkable results in pre-clinical studies, but have not yielded appreciable clinical results yet. Therefore, the development of clinically potent CDK inhibitors has remained to be a challenging task. However, continuous efforts has led to the development of some novel CDKs inhibitors that have emerged as a potent strategy for the treatment of advanced cancers. In this article, we have summarized the role of CDKs in cell-cycle regulation and tumorigenesis and recent advances in the development of CDKs inhibitors as a promising therapy for the treatment of advanced cancer. In addition, we have also performed a comparison of crystallographic studies to get valuable insight into the interaction mode differences of inhibitors, binding to CDK isoforms with apparently similar binding sites. The knowledge of ligand-specific recognition towards a particular CDK isoform may be applied as a key tool in future for the designing of isoform-specific inhibitors.

1. Introduction

Cancer has remained one of the major medical apprehensions and a leading cause of mortality worldwide [1,2]. Although, survival rates for certain cancers have slightly increased during the last half-century due to early diagnosis and the development of innovative therapies, the successful treatment for advanced stage cancers still remains to be elucidated due to lack of effective treatment strategies [3]. Clinical evidences have shown that almost 80% of cancer mortality is attributed to lack of early diagnosis [4,5]. Advanced cancers are the most difficult challenges for patients and clinicians because these cancers have not yet shown much improvement in prognosis or therapy [6]. Conventional treatment modalities (i.e. radiotherapy and chemotherapy) for advanced cancers have been found to destroy the normal cells along with malignant cells in an indiscriminate manner, leading to severe toxicities with modest improvements [7]. Targeted therapy via kinase inhibition is one of the major modalities of cancer treatment that is progressing in the medical treatment of advanced cancers [8].

Abbreviations: CDK, cyclin dependent kinase; CDK4/6, cyclin dependent kinase 4 and 6; cdc, cell division cycle; CDC25C, cell division cycle 25 homolog; Ser/Thr, serine/ threonine; kDa, kilodaltons (molecular weight); Cip/Kip, CDK interacting protein/kinase inhibitory protein; CKIs, cyclin-dependent kinases inhibitors; CGB, cyclin binding groove; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; HTS, high throughput screening; pRb, retinoblastoma protein; NSCLC, non-small-cell lung carcinoma; SAR, structure activity relationship; ECG, electrocardiogram; FDA, US Food and Drug Administration; HER2, human epidermal receptor 2; HR, hormone receptor; ER, estrogen receptor

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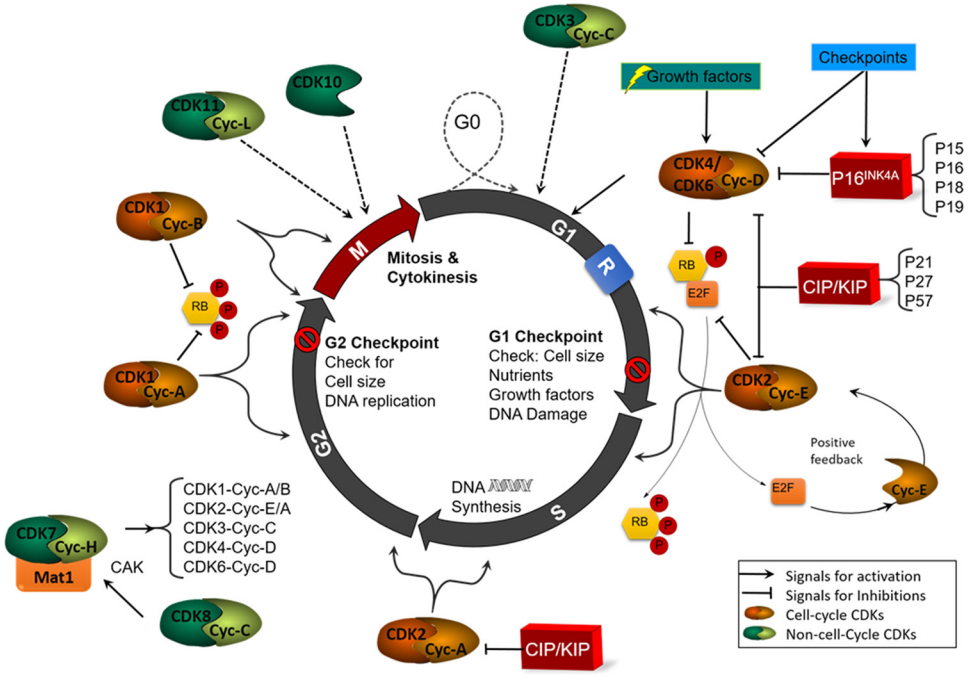

Fig. 1. Proposed roles of CDKs in complex with their respective cyclin partners in cell-cycle regulation. Heterodimeric complexes of CDK4/6 with cyclin D, and CDK3 with cyclin C regulate cell-cycle transition from G0 to G1 phase and early phases of G1 via retinoblastoma protein (pRb) phosphorylation. CDK2-cyclin E complexes have been proposed to retain hyperphosphorylation of pRb, an event that is thought to convey mitogenic independence to dividing cells. CDK2-cyclin E complexes have been also known to participate in regulating the G1→S transition through licensing DNA origins of replication. Later on, CDK2-cyclin A regulates cell-cycle progression through S phase. CDK1 regulates the progression/transition of S→G2 and G2→M by sequential binding to cyclin A and cyclin B. These widely accepted roles for the CDKs are indicated by open arrows. CDK-activating kinase (CAK) phosphorylates, and presumably activates, all cell-cycle CDKs. CDK7, Cyclin H and Mat1, is a substrate for CDK8-Cyclin C (filled arrows). CDK10 and CDK11 have also been proposed to be involved in mitosis, however, their functional relevance is not well understood.

However, the lack of specificity of these inhibitors against particular kinases still exists which may leads to serious toxicities [9]. The appropriate selection of a target and better understanding of the complex interrelationships between inhibitors and their target proteins might be helpful to make major inroads in the treatment of advanced cancers [10].

Cyclin-dependent kinases (CDKs) are the essential drivers of cell-cycle regulatory machinery (Fig. 1), thus, considered to be very potential targets for cancer treatment [11]. CDKs are heterodimeric complexes which are constituted by a catalytic kinase subunit and a regulatory cyclin subunit; they belong to the ser/thr sub-family of protein kinases [12]. Based on their functions, CDKs can be distributed into two sub-groups: cell-cycle CDKs (e.g., CDK1, CDK2, CDK4 and CDK6) and transcriptional CDKs (e.g., CDK7, CDK8, and CDK9). As depicted in Fig. 1, members of the first group sequentially regulate various events of the cell-cycle [13]. In response to numerous growth regulatory signals, CDK4 and CDK6-cyclin D complexes (Fig. 1) predominantly control the entry into the cell-cycle and phosphorylate the retinoblastoma proteins (pRb) [14]. CDK2-cyclin E complex maintains the retinoblastoma protein (pRb) in phosphorylation state to cause a transition of cell-cycle from G to S phase and regulates centrosome duplication [15]. Accordingly, CDK2 along with cyclin A (Fig. 1) regulates the progression of S phase, inactivation of G1 transcription factor E2F, and DNA replication. CDK1, a key determinant of mitotic progression; forms active complexes with cyclin A and B during the later portion of S phase and throughout the G_2 phase to regulate the checkpoints of S phase [16]. These checkpoints in replication not only monitor the S phase progression but also moderate the DNA synthesis [17]. In addition, CDK5 has been identified to regulate the post-mitotic events of cell division in specialized tissues. CDK-activating kinase (CAK; CDK7-cyclin H), regulates the normal function of CDKs through positive phosphorylation [13], whereas, the endogenous inhibitors (CKIs) Cip/Kip or inhibitors of CDK4 (INK4) direct the negative phosphorylation events by making protein-protein interactions with either cyclin alone or CDK-Cyclin complexes [18]. Hyper-proliferation in malignant cells is supposed to be associated with altered expression of CDKs and their modulators, i.e. over-expression of cyclins due to loss of their endogenous inhibitors (either by deletion, mutation or proteasome-mediated proteolysis) may deviate the cells from their regular path of cell division and take them to a path of uncontrolled proliferation [19]. The studies conducted on mouse models [20,21] revealed that the activities of interphase CDKs (CDK2 or CDK4) are modulated by CKIs (Cip/Kip and INK4 family) to control the cellular proliferation of normal stem or progenitor cells [19,21]. In human tumors, dysregulation of CDKs or their cyclin partners in various cancer stem cells may lead to tumorigenesis [19]. In addition, the mutations in CDKs structures and/or their regulators may also lead to several human cancer. Ectopic expression of CDK4 and CDK6 has been frequently observed in vide variety of tumors [12,19]. CDK4 expression has been observed to be altered in some of melanoma patients due to miscoding mutation (Arg24Cys) that restrict the binding of INK4 inhibitors. Likewise, the overexpression of CDK6 in a small set of leukemia's patients is the consequence of nearby translocations [12]. Aberration in cyclin D and INK4 inhibitors activities is a commonly observed in specific types of tumor [22,23], suggesting that CDK6 is often overexpressed in mesenchymal tumors (leukaemias and sarcomas) [22]. Whereas, overexpression of CDK4 is mainly linked with epithelial malignancies and some sarcomas [23]. Although, no mutation in CDK2 has been observed in human cancers, cyclin E is found to be overexpressed in some tumors and the expression of endogenous inhibitors p21 and p27 remains quieted during tumor development [19]. These observations suggest a potential involvement of CDK2 in human cancer. Moreover, CDK2 along with cyclin-E/A and CDK1-cyclin A/B are thought to regulate centrosome cycle. Overexpression of these CDKs particularly CDK1 may lead to centrosome amplification in p53-compromised cells [24,25]. Centrosome amplification may contribute to the development of abnormal mitotic spindles (multiple spindle poles) which are responsible for abnormal cell proliferation and aneuploidy [19,24,25]. Since, all major events of the cell-cycle are directly controlled by CDK-cyclin complexes (Fig. 1), it is therefore understandable that the aberrant expression of cell-cycle CDKs would ultimately result in uncontrolled proliferation of cells, which is the major characteristic of cancerous cells [26].

The second subfamily of CDKs includes CDK7, CDK8, CDK9, and CDK12 which have identified to regulate the transcription (Fig. 1) [13,27,28,29]. Among these transcriptional CDKs, CDK7 is considered to be unique due to its dual functions as CDK-activating kinase (CAK), which initiates the phosphorylation of cell-cycle CDKs within the activation segment (T-loop) [13]. Recent studies has revealed that the level CDK7, cyclin H, MAT1 mRNA and related protein is enhanced in breast