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Review article

Structural insights of cyclin dependent kinases: Implications in design of selective inhibitors

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ABSTRACT

There are around 20 Cyclin-dependent kinases (CDKs) known till date, and various research groups have reported their role in different types of cancer. The X-ray structures of some CDKs especially CDK2 was exploited in the past few years, and several inhibitors have been found, e.g., flavopiridol, indirubicin, roscovitine, etc., but due to the specificity issues of these inhibitors (binding to all CDKs), these were called as pan inhibitors. The revolutionary outcome of palbociclib in 2015 as CDK4/6 inhibitor added a new charm to the specific inhibitor design for CDKs. Computer-aided drug design (CADD) tools added a benefit to the design and development of new CDK inhibitors by studying the binding pattern of the inhibitors to the ATP binding domain of CDKs. Herein, we have attempted a comparative analysis of structural differences between several CDKs ATP binding sites and their inhibitor specificity by depicting the important ligand-receptor interactions for a particular CDK to be targeted. This perspective provides futuristic implications in the design of inhibitors considering the spatial features and structural insights of the specific CDK.

Contents

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1. Introduction

Cell cycle dysregulation resulting in mitogenic signaling and leading to uncontrolled proliferation is one of the hallmarks of cancer [1–4]. Cyclin-dependent kinases (CDKs), a family of serine/threonine protein kinases are known to play a vital role in cell cycle regulation and modulate transcription activity [5,6]. Unlike other kinases, CDKs require cyclin (a protein subunit) that provides additional sequences for enzymatic activity [7]. Till date, 20 subfamilies of CDKs are known; three (CDK1, 4 and 5) are involved in cell cycle, and five (CDK 7, 8, 9 and 11) are associated with transcription [8–10]. In brief, all the CDKs have a two-lobed structure-N-terminal having beta sheets and C-terminal composed of α-helices. N-terminal lobe contains G-loop (rich in glycine) inhibitory component, and C-terminal contains activation segment that also includes phosphorylation residues; serine or threonine (known as T-loop in the case of CDKs) (Fig. 1).

The role of various CDKs in the cell cycle progression is represented in Fig. 2. Briefly, p53 which is an important regulator of both G1/S, and G2/M checkpoint interacts with cyclin B and CDK1 [30]. After that cell enters early G1 phase, which is mitogen dependent and acted upon by cyclin D in conjugation with CDK 4 and 6 [31]. The growth factors are required to play their role at this point. Once the cell progress pasts the restriction point, mitogens are no longer needed for cell cycle progression. Cyclin D in conjugation with CDK4 and 6 promotes and ensures the cell progression beyond the limit point by phosphorylating and thus inhibiting retinoblastoma (RB), which allows E2F-mediated S-phase gene transcription [32,33]. The cell then enters S-phase where DNA replication occurs. The G1/S checkpoint allows checking of DNA integrity before cell DNA is replicated. Cyclin A and CDK1, 2 play a vital role in S phase. CDK inhibitors thereby halt the progression of the cell cycle by inhibiting the cyclins and the CDKs. They act at multiple phases of cell cycle primarily at G1/S and G2/M checkpoints.

Activation of CDK involves binding of CDKs with their respective cyclins at the C-terminal via noncovalent interactions and leads to the accessibility of ATP to the catalytic site for phosphorylation of threonine. A list depicting the association of cyclins with CDKs and their overexpression in various cancers has been presented in Table 1. Some of the CDKs do not require cyclin for activation; for instances, such as viral cyclins (cyclins from a virus), CDK5 activators (p35 and p39 have no homology with cyclins), RINGO/Speedy family (small proteins with no homology to cyclins) [34,35].

The endogenous ligands that activate the CDKs are mainly cyclins.

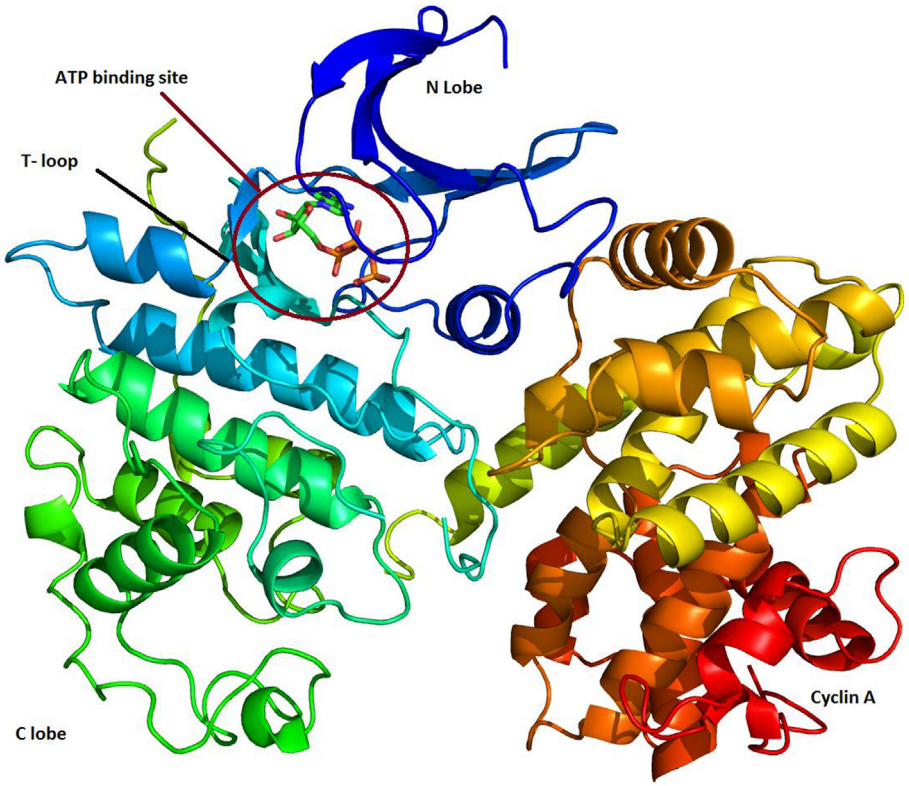

Fig. 1. Representation of CDK2 as a prototype CDK protein bound with cyclin A and ATP and T loop helps in activation of the ATP binding site when cyclin gets bound to the CDK.