Cyclin Dependent Kinases: Old Target with New Challenges for Anti-Cancer Drugs

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Abstract

Cyclin-dependent kinases are a family of serine or threonine protein kinases. There are various CDK Inhibitors such as Palbociclib, Abemaciclib and Ribociclib have been developed. First generation CDKIs targeting multiple CDKs were developed but not progressed for further phase-II trials because of high toxicity and low therapeutic index. So there is urgent need to overcome this problem by developing new CDK inhibitors. This mini-review summarizes the role of CDK in cancer progression and challenges for developing new inhibitors in modern perspectives.

Keywords: DNA replication; T-loop; Chromosome; Breast cancer; US-FDA

Introduction

Cell cycle progression is governed by cyclin dependent kinases (CDKs) that are activated by cyclin binding and inhibited by the CDK inhibitors. The CDKs regulate biochemical pathways that integrate mitogenic and growth-inhibitory signals and coordinate cell-cycle transitions [1]. Cell cycle regulation process has four functional phases: S phase, G2 phase, M phase where S phase are DNA replication; G2 phase are cell prepare for mitosis; M phase are DNA and genetic material division into 2 daughter cell and G1 phase are cell prepare for another round for replication. Loss of cell cycle control then DNA replication deregulated and the mitosis in the cell causes a proliferative disorder such as cancer [2].

Cyclin dependent kinases (CDKs)

The human protein kinases set (kinome), is constituted of 518 identified proteins, divided in seven families. Cyclin-dependent kinases are a family of serine or threonine protein kinases; CDKs, MAPks, GSKs and CLKs. CDK sub-family members are thirteen (CDK1 to CDK13). Only four are directly involved in cell cycle control and regulate, namely CDK1, CDK2, CDK4 and CDK6. CDK7 and CDK9 are involved in cell growth and involved in the control of CDK activity. In metazoans, one of the two CKI gene families defined on the evolutionary origins, CDK specificities [1]. CLP/KLP family are the made of three proteins p21cip1/waf1, P27kip1, p57kip2. INK4 gene family codes a p16INK4a, p15INK4b, p18INK4c, and p19INK4d; all INK4 gens are bind to CDK4 and CDK6 and inhibit the activity of kinase by interfering on their confederation with D-type cyclins. CDKs are control the cell cycle in which CDK1 to CDK6, while CDK8, CDK9, CDK12 and CDK19 are linked to regulation of transcription [2]. First group are normal proliferation, development and homeostasis. CDK4/cyclin D, CDK6/cydidin 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 [3].

Cell cycle progression regulators

Cell cycle division is controlled by checkpoint mechanisms that arrest further division process of the cell such as DNA replication or genetic material. Continued defective cell cycle progress and cell division are continued could result in tumor development. G1 to S phase progression is an important checkpoint in regulating cell proliferation. Cell cycle progress through the G1 phase is regulated by the cyclin D-cdk4, cyclin D-cdk6, and cyclin E-cdk2. CDKs have a bi-lobed structure, and undergo 2 conformational changes that inactivate the enzyme, should the partner cyclic be absent. These discovered conformational changes through crystallographic studies on human CDK2 [4]. Firstly, a flexible loop present at the carboxyl-terminal lobe, called the T-loop or the activation loop, blocks the binding of protein substrates at the opening of the active site cleft. Secondly, in inactive CDKs, some catalytically important amino acid side chains are in conformations that do not allow efficient phosphate transfer. Upon cyclin binding two alpha helices induce conformational changes in the kinase that allow efficient catalysis [5].

CDK1 also known as the mitotic kinase is the prototypic cyclin-dependent kinase [6]. CDK2 consists of 298 amino acids in length as has a molecular weight of 33.9kDa. The human CDK2 gene is present on chromosome 12 [7]. CDK4 is found complexed with
CDK inhibitors in ongoing-clinical trials

Till date, many CDKs other than Palbociclib, Abemaciclib and Ribociclib have been developed and some of them have been patented because of their high activity profiles against CDKs and are investigating thoroughly under clinical trials.

Future Perspective and Conclusion

The translational path to impressively target the cell-cycle has been a long journey from basic science studies to eventual preclinical and then clinical testing. Based on the frequent dis-regulation of cell-cycle pathways in cancer by ‘CDK hyper-activation’, the CDKs and their regulators have become an attractive target for cancer-treatment. First generation CDKIs, targeting multiple CDKs were developed but not progressed for further phase-II trials because of high toxicity and low therapeutic index. After unsatisfactory outcomes in clinical-trials of non-selective CDKIs, the significance of specificity and selectivity of drug molecule for particular target now has been broadly accepted and gave a strong impetus for the development and success of second generation CDKIs as anticancer agents. Till now, 3 highly-selective CDK4/6 inhibitors (palbociclib, abemaciclib and ribociclib) have been approved by the US-FDA for breast cancer treatments and have an established safety profile. All these approved inhibitors are being further investigating in ongoing-clinical trials involving an extensive variety of cancer types.

References