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Inhibitors of cyclin-dependent kinases as cancer therapeutics

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ABSTRACT

Over the past two decades there has been a great deal of interest in the development of inhibitors of the cyclin-dependent kinases (CDKs). This attention initially stemmed from observations that different CDK isoforms have key roles in cancer cell proliferation through loss of regulation of the cell cycle, a hallmark feature of cancer. CDKs have now been shown to regulate other processes, particularly various aspects of transcription. The early non-selective CDK inhibitors exhibited considerable toxicity and proved to be insufficiently active in most cancers. The lack of patient selection biomarkers and an absence of understanding of the inhibitory profile required for efficacy hampered the development of these inhibitors. However, the advent of potent isoform-selective inhibitors with accompanying biomarkers has re-ignited interest. Palbociclib, a selective CDK4/6 inhibitor, is now approved for the treatment of ER+/HER2- advanced breast cancer. Current developments in the field include the identification of potent and selective inhibitors of the transcriptional CDKs; these include tool compounds that have allowed exploration of individual CDKs as cancer targets and the determination of their potential therapeutic windows. Biomarkers that allow the selection of patients likely to respond are now being discovered. Drug resistance has emerged as a major hurdle in the clinic for most protein kinase inhibitors and resistance mechanism are beginning to be identified for CDK inhibitors. This suggests that the selective inhibitors may be best used combined with standard of care or other molecularly targeted agents now in development rather than in isolation as monotherapies.

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1. Introduction

The notion of the cell cycle and its regulatory restriction points was first proposed in the 1970s and early 1980s. The machinery components associated with this process were identified and characterized through many genetic and biochemical studies, mainly in yeast, but also in sea urchin, xenopus, and eventually higher eukaryotic cells (Nurse, 2000). The core of this work resulted in the identification of the CDKs and their partner cyclins for which the Nobel Prize in Physiology and

Abbreviations: AML, acute myeloid leukemia; CAK, CDK-activating kinase; CDK, cyclin-dependent kinases; CLL, chronic lymphocytic leukemia; CT, RNA polymerase II C-terminal domain; DLT, dose-limiting toxicities; DSIF, DRB-sensitivity inducing factor; ER, estrogen Receptor; LRP, low-density receptor-related lipoproteins; MAPK, mitogen-activated protein kinase; RB, retinoblastoma protein; NELF, RNA polymerase II–associated negative elongation factor; PFS, progression free survival; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase.

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Medicine was awarded to Hartwell, Hunt and Nurse in 2001. The regulation of the growth and division of cells came to the attention of the biomedical research community when it became clear that unconstrained proliferation, in part due to a loss of cell cycle regulation, played a key role in the initiation and progression of cancer. More recently, sustained proliferation through the deregulation of cell cycle control has been recognized as one of the key hallmarks of cancer (Hanahan & Weinberg, 2011), and our understanding of how specific CDKs regulate transcription and maintain the oncogenic state has advanced considerably. This has led to considerable efforts to develop CDK inhibitors as cancer therapeutics, which is the subject of this review. Here we will review the role of CDKs in cancer and particularly those for which inhibitors have currently been identified. These inhibitors include the early non-selective inhibitors that suffered from toxicity and poor efficacy, but more importantly the more recent developments in selective CDK inhibitors that have led to the approval of palbociclib for the treatment of breast cancer.

1.1. The CDK family

The human genome encodes 26 serine/threonine protein kinases that form a CDK and CDK-like branch of the CMGC subfamily of the human kinome; of these, 21 are classified as CDKs (Malumbres, 2014; Malumbres et al., 2009). The CDKs have specific or redundant roles in many aspects of cell growth, proliferation and transcriptional regulation in response to extracellular and intracellular signals. The evolutionary relationships between these CDK subfamilies have been identified (Fig. 1) and indicate that the CDK subfamilies can be divided into subfamilies that directly or indirectly regulate the cell cycle (CDKs1-6, 11 and 14-18) or transcription (CDKs7-13, 19 and 20).

Similar to all protein kinases, the CDKs have a two-lobed structure comprising a beta sheet-rich amino terminus and an alpha helix-rich carboxy terminus, with the active site sandwiched between the two (Malumbres, 2014; Malumbres et al., 2009). Members of the CDK family have a conserved catalytic core containing an ATP-binding pocket, a cyclin subunit - binding domain and an activating T-loop motif. Collectively these features participate in CDK activation. The CDKs are constitutively expressed but, as their name suggests, typically require association with a cyclin subunit in order to become active (Fig. 1). Regulation of the CDKs predominantly occurs by means of the control of cyclin production and destruction, as cyclin binding displaces the T-loop, exposing the substrate binding site and realigning critical residues in the active site that primes the kinase for activity (Jeffrey et al., 1995; Russo, Jeffrey, & Pavletich, 1996). In addition to the regulatory effects of cyclin-binding, phosphorylation also coordinates the activity of the CDKs in response to various stimuli (Mueller, Coleman, Kumagai, & Dunphy, 1995). Most CDKs have inhibitory phosphorylation sites in the P-loop of the active site which when phosphorylated interfere with ATP binding at the catalytic site (Mueller et al., 1995). Some CDKs also have activating phosphorylation sites in their T-loops that are substrates of CDK-activating kinases that includes other CDKs. Phosphorylation of these T-loop sites enhances substrate binding and complex stability, promoting full CDK activation (Russo et al., 1996).

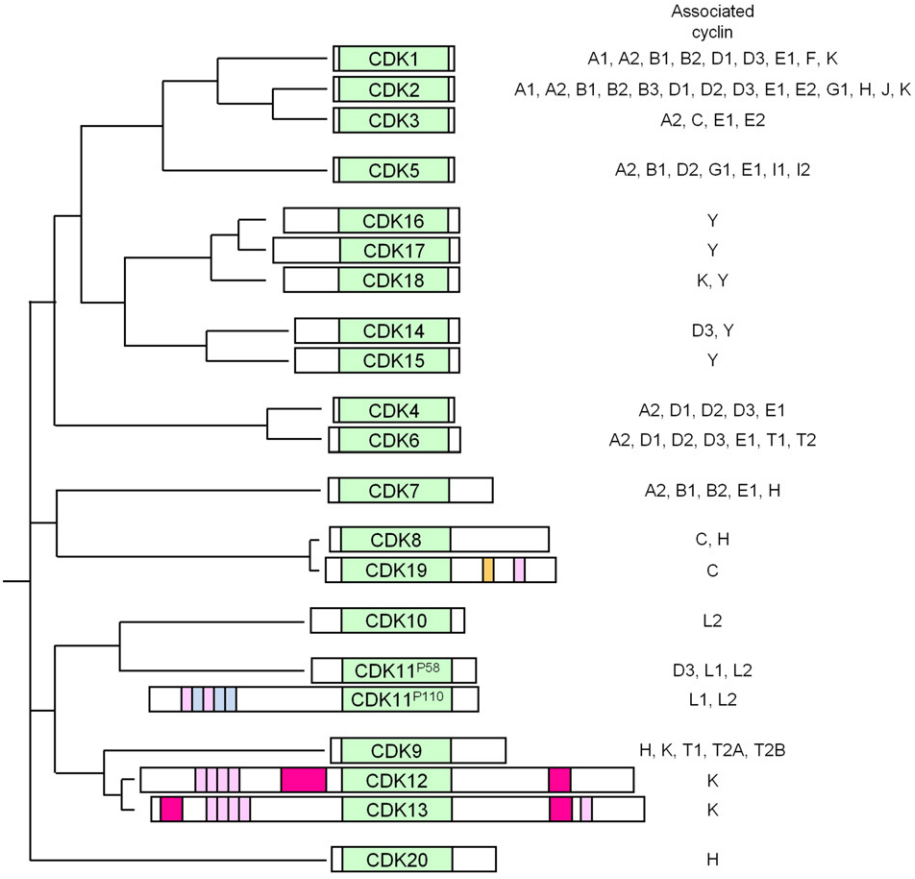

Fig. 1. The evolutionary relationships between human CDK subfamilies determined by phylogenetic analysis based on gene sequence similarity. Conserved domains are color-coded: green, kinase domain; pink, arginine/serine-rich domain; blue, glutamic acid-rich domain; yellow, glutamine-rich domain; red, proline-rich domain. CDK11 is encoded by two separate genes, *CDK11A* and *CDK11B*, which each encode two isoforms (adapted from (Malumbres, 2014). Cyclins required for CDK activation are also indicated.