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Invited review

Cyclin-dependent protein kinase inhibitors including palbociclib as anticancer drugs

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Dinaciclib (PubMed CID: 46926350)
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ABSTRACT

Cyclins and cyclin-dependent protein kinases (CDKs) are important regulatory components that are required for cell cycle progression. The levels of the cell cycle CDKs are generally constant and their activities are controlled by cyclins, proteins whose levels oscillate during each cell cycle. Additional CDK family members were subsequently discovered that play significant roles in a wide range of activities including the control of gene transcription, metabolism, and neuronal function. In response to mitogenic stimuli, cells in the G1 phase of the cell cycle produce cyclins of the D type that activate CDK4/6. These activated enzymes catalyze the monophosphorylation of the retinoblastoma protein. Then CDK2-cyclin E catalyzes the hyperphosphorylation of Rb that promotes the release and activation of the E2F transcription factors, which in turn lead to the generation of several proteins required for cell cycle progression. As a result, cells pass through the G1-restriction point and are committed to complete cell division. CDK2-cyclin A, CDK1-cyclin A, and CDK1-cyclin B are required for S, G2, and M-phase progression. Increased cyclin or CDK expression or decreased levels of endogenous CDK inhibitors such as INK4 or CIP/KIP have been observed in various cancers. In contrast to the mutational activation of EGFR, Kit, or B-Raf in the pathogenesis of malignancies, mutations in the CDKs that cause cancers are rare. Owing to their role in cell proliferation, CDKs represent natural targets for anticancer therapies. Abemaciclib (LY2835219), ribociclib (Lee011), and palbociclib (Ibrance® or PD0332991) target CDK4/6 with IC_{50} values in the low nanomolar range. Palbociclib and other CDK inhibitors bind in the cleft between the small and large lobes of the CDKs and inhibit the binding of ATP. Like ATP, palbociclib forms hydrogen bonds with residues in the hinge segment of the cleft. Like the adenine base of ATP, palbociclib interacts with catalytic spine residues CS6 and CS7. CDK antagonists are in clinical trials for the treatment of a variety of malignancies. Significantly, palbociclib has been approved by the FDA for the treatment of hormone-receptor positive/human epidermal growth factor receptor-2 negative breast cancer in conjunction with letrozole as a first-line therapy and with fulvestrant as a second-line treatment. As inhibitors of the cell cycle, it is not surprising that one of their most common toxicities is myelosuppression with decreased neutrophil production.

Contents

Abbreviations: AS, activation segment; CDK, cyclin-dependent protein kinase; CIP/KIP, CDK interacting protein/kinase inhibitor protein; CS or C-spine, catalytic spine; CL, catalytic loop; ER^+, estrogen receptor positive; GRL, glycine-rich loop; $HER^{+/-}$, human epidermal growth factor receptor positive or negative; HR^+, hormone receptor positive with either or both estrogen and progesterone receptors; HΦ or Φ, hydrophobic; INK4, inhibiting CDK4; NSCLC, non-small cell lung cancer; pCDK4/6, phosphorylated cyclin-dependent protein kinases 4 and 6; PI3-kinase, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PR, progesterone receptor; Rb, retinoblastoma protein; RS or R-spine, regulatory spine; Sh1, shell residue 1; WAF1, wild type p53-activated fragment.

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1. Introduction to the somatic mitotic cell cycle

1.1. Overview of cyclin-dependent protein kinases and their regulatory cyclins

The replication of each cell in every tissue and organ is exactingly controlled during development and throughout the life of the individual. In a normal adult, cells divide only when and where they are needed. Moreover, the contents of a cell including each chromosome must be accurately replicated. The cell cycle consists of G1 (presynthetic growth, or gap 1), S (DNA synthesis), G2 (premitotic growth, or gap 2), and M (mitotic) phases (Fig. 1A) [1]. During G1 cells are preparing for DNA synthesis and during G2 cells perform surveillance to establish the integrity of newly synthesized DNA before commencing mitosis. The chromosomal DNA is replicated during the S-phase and all of the cellular components are partitioned between two identical daughter cells during mitosis or the M-phase. When cells cease proliferation owing to the absence of mitogenic signaling or to the presence of specific antimitogenic signaling, they exit the cycle and enter a nondividing quiescent state known as G0. In contrast, senescence is an irreversible state of G1 cell cycle arrest in which cells are refractory to growth factor stimulation.

Cells within the hematopoietic system or cells that line the gut epithelium actively proliferate and cycle continuously [2]. Most cells in adult animals are mostly in a quiescent or G0 phase, but they can reenter the cell cycle. In contrast, terminally differentiated cells such as neurons and cardiac myocytes have lost the capacity to proliferate and are locked permanently in the G0 phase. Loss of the normal controls of cellular replication is a fundamental defect in cancer. Thus, understanding the mechanisms that control cell division represents an essential component of one strategy toward the development of therapeutic modalities for cancer treatment. The dilemma is to target and inhibit cancerous growth while not blocking the physiological proliferation of needed cells.

Cyclins and cyclin-dependent protein kinases (CDKs) are important components required for passage through the cell division cycle [3]. Human cells possess 20 CDKs (1–20) and 29 cyclins. The CDKs are protein-serine/threonine kinases that belong to the CMGC family (Cyclin-dependent protein kinases, Mitogen-activated protein kinases, Glycogen synthase kinases, and CDK-like kinases) [4]. As their name implies, CDKs interact with cyclins as a first step in producing enzyme activity. After the formation of a CDK-cyclin complex, the CDK activation segment undergoes phosphorylation at a conserved threonine residue as catalyzed by CDK7 for the full expression of CDK-cyclin enzyme activity. In much of the literature, the CDK activation segment is called the T-loop in reference to its conserved threonine. This class of enzymes was initially discovered as proteins that participate in the normal transit through the cell cycle (CDK1/2/3/4/6/7/8/10). Subsequently, the CDKs were found to play important regulatory roles in many diverse functions including the control of gene transcription (CDK7/8/9/10/12), neuronal activity (CDK5/16), metabolism (CDK5/8), hematopoiesis, angiogenesis, proteolysis, and DNA damage and repair (CDK1/3/9/12), epigenetics (CDK1/2/4), and spermatogenesis (CDK16) [5].

The levels of the CDKs are generally constant throughout the cell cycle. The activities of the cell cycle group of CDKs are controlled by cyclins, proteins whose levels oscillate during the cell cycle (Fig. 1B) [6]. The oscillation of cyclins accounts for their names as they oscillate or cycle up and down during the cell cycle. CDKs are regulated by a mechanism involving the synthesis (which increases protein kinase activity) and degradation (which decreases enzyme activity) of their cognate cyclins. Most of the CDKs possess about 300 amino