

CDK inhibitors as anti-cancer drugs; Present and Future

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The cell reproduces itself via replication. The cyclical replication processes from the resting state (G1 phase) to cell division (M Phase) called cell cycle. Cell cycle requires complicated steps are composed of G1, S, G2, and M. These step transitions from one to another are strictly controlled by mechanisms which ensure division of the cell correctly. Control of eukaryotic cell growth and division occurred at the three critical points: late G1, G2/M, and metaphase-to-anaphase transition. These critical steps are also known as “checkpoints” which ensure correct timing of cellular events. The checkpoints trigger the passing through the phases of the cycle which requires organized set of proteins control proper cell growth and DNA integrity. The most well-known monitoring proteins for late G1 and G2/M checkpoints are cyclic dependent kinases (CDKs) which are activated by cyclin proteins, however, unlike the other two checkpoints, metaphase-to-anaphase transition checkpoint is controlled by anaphase promoting complex (APC/C). Many CDKs have specificity for cell cycle checkpoints, for instances CDK4 and CDK6 for late G1, CDK2 for S and CDK1 for G2/M (1).

Central players of cell cycle progress are CDKs and associated proteins cyclins. CDKs are activated or inhibited by CDK cyclins or inhibitors, respectively. CDKs are kinase enzymes which are blocked by inhibitors break the cell cycle progression and induce cell growth arrest. Cancer is characterized by loss of cell cycle control and accumulation of mutations. These mutations also result in increased mutagenic signals and defective anti-mitogen signaling pathways. The expression and inhibition of CDKS are deregulated in cancer, hence the successful inhibition of CDKs is focused for cancer therapy (2).

To drive the cells from G0 or G1 phase into S phase through CDK4 and CDK6, the D-type cyclins (that is, cyclin D1, cyclin D2 and cyclin D3) are needed to control activity of the CDKs. The different D-type cyclins seem to show tissue specific expression in normal cells.

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Interaction of cyclin D with CDK4 is the regulation of starting S phase, in addition to control mechanism, transcriptional regulation of CDK4 and CDK6 is also the one of way to control late G1 checkpoint. Inhibitor proteins of CDK4 (INK4 (INHibitors of CDK4)) are composed of p16INK4a, p15INK4b, p18INK4c, p19INK4d which by interacted with CDK4 and CDK6 inhibit the activity of these CDKs. The INK proteins can bind both CDK4, CDK6 and D type cyclins. CDK4 and CDK6 association with D-type cyclins phosphorylate the tumor suppressor retinoblastoma proteins (RB) which drive the cell cycle arrest at late G1 phase. The CDK4/6-RB pathway is critical to continue cell duplication; therefore, deregulation of this pathway is expected in most cancers. CDK4 and CDK6 are also hyper activated or overexpressed in a wide variety of tumors (3).

CDK2 and cyclin E association is essential to drive the G1 to S transition. INK4 inhibitor proteins does not regulate the CDK2, however which is regulated by “CDK interacting protein/kinase inhibitory protein” (CIP/KIP) class of CDK inhibitors. The CIP/KIP proteins, p21CIP1, p27KIP1, inhibit CDKs activity by binding CDK2-cyclin complex (4).

CDK1 associated with cyclins, cyclin A2 or cyclin B1, is essential for initiating M phase in eukaryotes. The cell in the M phase with the mis-replicated DNA leads to the cell death. The onset of M phase is under strictly controlled by checkpoint signalling kinases, CHK1 and WEE1, to overcome contributing the death of cell with mis-replicated DNA (5).

In addition to the mentioned CDKs above, there are cell cycle-independent CDKs (i.e. CDK7, CDK8, CDK9) which contribute to the basal transcriptional regulation of the cell cycle, so that they can be potential target for anti-cancer therapeutics.

The 21 human CDKs are encoded by the genome, however only 7 CDKs have functional role in the cell cycle progression. Hyper activation of CDKs may lead to the tumor progression by unregulated proliferation. INK4 inhibitors are also blocked by some mutations in some type of cancers (6). The CDK inhibitors have been investigated as potential anti-cancer drugs for 20 years. The CDKs inhibitor drug candidates are divided three groups which are ATP-competitive, ATP-noncompetitive (including some small mimetic peptides for p21, p27 and p57), Allosteric inhibitors.

CDK4 and CDK6 are valuable targets to fight against cancer due to their essential role in the starting of cell cycle. Although the importance of the CDK4 and CDK6 for proliferation, the first investigated CDK inhibitors are “pan CDKs” (i.e. flavopiridol (alvocidib; developed by Sanofi-Avantis), olomucine (not commercial), roscovitine (seliciclib; developed by Cyclacel)), which have relatively low affinity for CDK4 and CDK6 (7).

The first CDK inhibitor drug approved by US FDA is palbociclib (Ibrance), a CDK4/6 inhibitor, in Feb 2015. In currently, there are 11 inhibitors -Palbociclib, Pfizer (Onyx Pharmaceuticals); Abemaciclib, Eli Lilly; Ribociclib, Novartis/Astex; Alvocidib, Sanofi (Tolero); Milciclib, Nerviano; MM-D37K, MetaMax; G1T28-1, G-1 Therapeutics; TG-02, Tragara Pharmaceuticals; Seliciclib, Cyclacel; AT-7519, Astex; Roniciclib, Bayer- under clinical evaluation (8).

All types of CDK inhibitors have great interest as therapeutic cancer agents for researchers, but still more specific CDKs inhibitors are needed to take control of cell division in different check points.

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