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REVIEW ARTICLE

Emerging Therapeutic Role of CDK Inhibitors in Targeting Cancer Stem Cells

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ABSTRACT

Within a tumor, Cancer Stem Cells (CSCs) exists and own similar characteristics of a normal stem cell thus contributing towards aggressiveness of cancer by playing crucial role in tumor recurrence and metastasis capability. Various studies have been conducted to therapeutically target CSCs. One of the approaches include is to inhibit cell cycle progression in CSCs. Within last two decades cell cycle and role of various components in its regulation is firmly established. Cell cycle is regulated by Cyclin Dependent Kinases (CDK) bound to cyclin. CDK activity can be blocked by Cyclin-Dependent Kinase Inhibitors (CKIs) which can either bind cyclin/CDK complex or CDK alone and thus stops cell cycle. In this review various studies are discussed that have investigated the therapeutic role of CKIs in eradicating CSCs by inhibiting cell cycle. Overall, the analysis suggests that CKIs could be a potential therapeutic option in controlling CSCs populating in a tumor.

INTRODUCTION

Cancer Stem Cells (CSCs) are a population of cells in a tumor that encompasses features similar to normal stem cells particularly their capability to arise into all cell types present in a tumor through differentiation and self-renewal. This distinct population of cells promotes tumor recurrence and metastasis [1].

CSCs and stem cells share the property of extensive proliferation, more specifically self-renewal is s. Upon critical observation it was revealed that the genes that inhibit self-renewal are tumor suppressor genes while the genes that promote self-renewal are oncogenes. Hence these oncogenes also enhance self-renewal ability of CSCs. Wnt/β-catenin, Hedgehog (Hh), Bim 1 and Notch signaling are the pathways reported to play important role in self-renewal for both CSCs and normal stem cells [2]. The continuous irreversible propagation of dysregulated tissue clones gives rise to a rare but distinct subset of the cells: cancer stem cells. These hyper-malignant cells can regenerate the tumor cells or can give rise to non-tumerogenic population of cells [3].

Hallmarks of cancer

The normal stem cells have to maintain their genomic integrity as losing it will result in dire consequences. Any mutation in stem cells would result in the passage of this mutation to all progeny cells thus stem cells avoid genetic mutations by carefully regulating their genomic integrities. While on the other side, tumerogenic stem cells have capabilities to acquire and retain genomic mutations: the hallmarks of cancer [4]. These cells pass these mutations to other cells of the progeny giving

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rise to large number of cancerous cells while some mutations are used to deteriorate the barriers and enhance metastasis [5].

Normal stem cells have also the ability to interconvert into different fates as well as to change the fate of proliferation and differentiation as a result of environmental factors [6]. For instance Hair Follicle Stem Cells (HFSCs) can contribute to wound healing by temporarily converting into interfollicular epidermal cells [7]. In the same way, tumerogenic stem cells can interconvert to different malignant fates and also give rise to resistant cells with different susceptibility towards therapies [8]. Some of these hypermalignant cells can also become quiescent during chemotherapy to avoid the cytotoxic-induced death [9].

Cancer stem cells in therapeutics

Therapeutic targeting of CSCs holds key importance and value in cancer treatment. Many tumor populations are phenotypically and functionally heterogenous. This feature is one of the success key in tumor aggressiveness. In a cancer cell population, microenvironment interactions, gene mutations and epigenetics contribute to this heterogeneity. This heterogenous nature of a tumor is a major hurdle in cancer therapy [10].

About four decades ago, in 1997 Bonnet and Dick observed a population of cells in acute myeloid leukemia similar to stem cells. In this study they reported the presence of 0.1-1% of stem cell like cells having ability to generate tumor in Non-Obese Diabetic Mice with Severe Combined Immunodeficiency Disease (NOD/SCID mice) [11]. Since then many of the researchers have been trying to investigate their mechanism of propagation, resistance against chemotherapies and possible targets for therapeutics. CSCs have high potential to metastasize to other tissues causing secondary cancer. These cells also show resistance towards the chemo and radio therapies and can relapse after treatment due to similarities with the normal stem cells [12] (Table 1).

Cyclin Dependent Kinases (CDKs)

CDKs are serine/threonine kinases that along with cyclin proteins regulate the cell cycle progression. Dysfunctional cell cycle is a major contribution in CSCs generation and cancer progression. This includes altered expression regulation of Cyclin Dependent Kinases (CDKs) and/or CDK Inhibitors (CKIs). In cell cycle, at specific phases these kinases are activated through phosphorylation of specific Threonine residue by CDKs Activating Kinase (CAK). This enhances cyclins binding to their specific CDKs due to

Table 1: CDK inhibitors and their effect on Cancer Stem Cells.

CDK	Inhibitor and Cyclin interactions	Affected protein complexes	Cancer type	References
CDK1	RO3306 Cyclin A	CDK1/PDK1/β-Catenin signaling	Hepatocellular carcinoma	[18]
CDK 2	SU9516 Cyclin E	cyclin E/Cdk2 oncogenic signaling	TNBC cells	[43]
CDK 2 CDK 4	Celastrol CyclinD1	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) regulated signaling	ovarian cancer	[7]
CDK 4	Palbociclib Cyclin D1	Knocking down CDK4 gene increased BMP4 expression BMP4 strongly inhibit tumorsphere formation and reduce $CD44^{+}/CD24^{-}$ CSCS	TNBC	[27]
CDK 4	API-2 Cyclin D1 siRNA Cyclin D1	AKT/cyclin D1/Cdk4	Radioresistant glioblastoma and liver cancer	[31]
CDK 4/6	Palbociclib, Ribociclib, Abemaciclib Cyclin D	Cyclin D-CDK4/6-INK4-Rb	HR+ breast cancer	[44]
CDK 4/6	PD-0332991	Target telomerase high proliferative CSCs	Lung (A549) and ovarian (SKOV3) cancer cells	[4]
CDK 4/6	MicroRNA miR-302 Cyclin D	Promoted tumor suppressor functions of p16Ink4a and p14/p19Arf directed against CDK4/6-mediated cell proliferation	Tumorigenicity of human pluripotent stem cells	[32]
CDK 5	CP681301	CDK5 regulates self-renewal by directly activating CREB1 independently of PKA/cAMP inhibition of CDK5 prevents GSC self-renewal in vitro and in xenografted tumors, at least partially by suppressing CREB1 activation independently of PKA/CAMP	Glioma	[35]
CDK 9	γ-secretase inhibitors (GSIs) Cyclin T	Targeting CDK9 or c-MYC, an upstream regulator of RBPJ, with small molecules also decreased BTIC propagation, and prolonged survival in mice bearing orthotopic GBM xenografts.	glioblastoma	[41]
CDK 9	Atuveciclib Cyclin T	Pharmacologic inhibition of CDK9 with atuveciclib in high-**CDK9** expressing TNBC cell lines reduced expression of CDK9 targets **MYC** and **MCL1** and decreased cell proliferation and survival.	TNBC	[40]
CDK 9	21e Cyclin T	21e inhibited cell proliferation, colony-formation, and cell cycle progression and induced apoptosis in NSCLC	Lung cancer	[42]

conformation changes [13]. CKIs are inhibitory proteins which counteract the CDK activity. They regulate CDKs by binding to CDK-cyclin complex or only CDK [14].

Transduction and multiplication of proliferative and anti-proliferative signals occurs in the cell or outside the cell. So the level of CDK indicates that it can be targeted therapeutically with the help of CKIs. Role of CKIs in normal and cancer stem cell cycle is well known [15]. A therapeutic intervention for enhancing and restricting their role in cell cycle is an active area of research. In therapeutics, both natural and artificial CKIs are exploited to gain therapeutic efficacy. The current review will focus on role of CKIs in therapeutically targeting CSCs in various cancer types.

CDK1 inhibitors: CDK1 and its cognate cyclins are key regulators of critical phase transitions in cell cycle. CDK1/Cyclin B and CDK1/Cyclin A regulates G1/S and G2/M phase transitions during cell cycle [16]. In various cancer types, levels of CDK1 are aberrantly upregulated resulting in high proliferation and migration of cancer cells. Therefore, CDK1 inhibitors has presented themselves as an effective candidate in down regulating CDK1 which ultimately leads towards cell cycle arrest in cancer cells [17]. In cancer treatment chemo resistivity is one of the major limitations. Several CDKs increase the efficacy of already available commercial drugs. Sorafenib is a commercially available drug for advance primary hepatocellular carcinoma, advance thoracic malignancies, FLT3-ITD positive Acute Myeloid Leukemia (AML) and primary renal carcinoma. In hepatocellular carcinoma, sorafenib efficacy is enhanced by CDK1 inhibitor RO3306 which target CSCs and block CDK1/PDK1/β-Catenin signaling in PDX preclinical tumor model [18]. CDK1 has been found as one of the most important therapeutic drug targets for Endometrial Cancer (EC) which is one of the most life threatening and devastating tumors. Its level is highly increased in endometrial cancer so this is regarded as essential target in future as it arrest G2/M phase of cell cycle leading to apoptosis and activates DNA repair homologous recombination pathway [19]. RO-3306 is one of the CDK1 inhibitors which induces cell cycle arrest at G2 stage. This helps in DNA repair capacity when acted under dose-dependent mechanism [20]. CDK1 inhibitors have also been found useful in β-Catenin/PDK1 pathway inhibition. In another study, RO3306 along with sorafenib decreased the growth of tumor in PDX model. ShRNA, RO-3306 and sorafenib reduces oncogenesis by downregulating CDK1, β-Catenin inactivation and PDK1 down regulation [18]. In colon tumors, constitutive Nuclear Factor κB (NF-κB) plays important role in its development. Constitutive Nuclear Factor κB (NF-κB) and its transcription factor NFE2L3 have been successfully used in reducing colon cancer adenocarcinoma by regulating Double Homeobox Factor 4 (DUX4) [21].

CDK2 inhibitors: CDK2/Cyclin E regulates G1/S checkpoint in cell cycle. Aberrant CDK2 expression is conferred by high cyclin E expression resulting in inactivation of Rb, a tumor suppressor protein. This promotes deleterious outcomes including irregular cell cycle, chromosomal instability, and centrosome duplication [22]. Cyclin E overexpression is associated with aggressive breast cancer. SU9516 (CDK2 inhibitor) obstructs CDK2/Cyclin E oncogenic signaling in $CD44^{+}/CD24^{-}$ CSCs subpopulation of Triple-Negative Breast Cancer Cells (TNBC) resulting in improved sensitivity to cancer chemotherapy [23]. A study highlighted the role of celastrol, a phytocompound in inhibiting cancer stem cells in ovarian cancer by downregulating expression of CDK2, CDK4 and Cyclin D1 through Pin1 signaling network. This resulted in inhibition of migration, clonogenicity, and proliferation potential of ovarian cancer stem cells [24].

CDK3 inhibitors: In cell cycle, CDK3/Cyclin C complex plays critical role in G0-G1 and G1-S phase transitions. Its aberrantly high levels in cancer cells further promote proliferation, malignancy and tumorigenesis. In various studies it has been observed that targeting CDK3 is effective in suppressing cancer [25]. Its high expression in various cancer types is seen that includes nasopharyngeal carcinoma, colorectal cancer and glioblastoma whereas its knockdown in glioblastoma cells suppresses growth and proliferation. In various pre-clinical studies, it is highlighted that CDK3 inhibitors can suppresses cancer cells proliferation [26]. However, mechanism of CDK3 inhibitors action on cancer stem cells is still to be resolved.

CDK4 inhibitors: Triple Negative Breast Cancer (TNBC) tumors contain a lot of CSCs and are resistant to most therapies so resulting in high death rate. Growth of CSCs is regulated by CDK4, it can be used to treat TNBC and so self-renewal of CSCs can be prevented by blocking of CDK4. Epithelial phenotype can be restored by suppressing CDK4 and so it can remove normal cancer cells as well as those which are resistant to chemotherapy [27].

G1-S checkpoint is regulated by Cyclin D CDK4/6-INK4-Rb and this pathway is dysregulated in many cancers resulting in enhanced proliferation. This pathway can be activated by epigenetic alteration, gene amplification, point mutation, loss of negative regulation and gene rearrangement. CDK4 inhibitors in combination with PI3K inhibitors and endocrine therapy have been proved useful in the treatment of HR+ breast cancer. MEK and RAF inhibitors have been found important in case of tumors with altered MAPK pathway i.e., melanoma [28]. Endocrine therapy using letrozole along with CDK4/6 inhibitor e.g., palbociclib can be used for HR+ breast cancer treatment. Palbociclib (PD-0332991), abemaciclib (LY2835219) and ribociclib (LEE011) are three approved CDK4/6 inhibitors which are very selective [29]. Ribociclib, palbociclib and abemaciclib are efficient for the treatment of a variety of cancers [30]. These are ATP dependent competitive inhibitors of CDK4/6 and function in early G1 phase. High telomerase activity is directly related to high CSCs activity, glycolytic activity, increased mitochondrial function, and enhanced mass in lungs which can be treated with Palbociclib [4].

Palbociclib can decrease phosphorylation of Rb and growth of cells in dose dependent manner by blocking G1-S stage of cell cycle. These increase senescence without increasing apoptosis and reduced CSCs production. If the level of Palbociclib is reduced, estradiol increases which induces CSCs production in ER (+)/HER2 (-) cell lines [8]. Radiotherapy efficiency for breast cancer can be enhanced by CDK4 inhibitors for treatment of CSCs [6]. AKT/Cyclin D1/CDK4 pathway can be targeted to increase radiotherapy efficiency through suppression of radio-resistance of CSCs [31].

miR-302, a microRNA of Induced Pluripotent Stem Cells (IPSCs) and Human Embryonic Stem Cells (HESCs) is a suppressor of cyclin D-CDK4/6 and cyclin E-CDK2 pathway. It causes blockage of more than 70% transition from G1 to S phase resulting in inhibition of human pluripotent stem cell tumorigenicity. miR302 targets BMI-1 (CSC marker) and silences it promoting tumor suppressor like function of the p16Ink4a and p14/p19Arf, which are directed against the CDK4/6–mediated cell proliferation [32]. Fascaplysin, AT7519M, Ryuvidine, PD-0332991 and BAY 1000394 are selective inhibitors of CDK4 but there activity is not checked for CSCs [33].

CDK5 inhibitors: CDK5 plays an important role in epithelial to mesenchymal transition. Its upregulation causes formation of damaging tumor sphere which can metastasize in different organs of the body. Apoptosis can be induced in tumor sphere by inhibition of CDK5 through stabilization of Foxo1 (transcripton factor) which enhances expression of Bim (pro apoptotic protein). So, CDK5 Foxo1-Bim pathway plays role in CSCs death [34]. CDK5 can be pharmacologically inhibited by small molecules. Roscovitin and Dinaciclib are in clinical trials for inhibition of CDK5 and have shown anti-cancer activity against multiple myeloma and lymphocytic leukemia [33].

Neoplastic growth is promoted by CSCs through enhancement of self-renewal and asymmetric division of cells. CDK5 Inhibition can prevent self-renewal of glioma stem cells in xenografted tumors and in-vitro through suppression of activation of CREB1 independent of PKA/cAMP [35]. BML-259 and AT7519M are selective inhibitors of CDK5 but there activity has not been checked for CSCs [14].

CDK6 inhibitors: Palbociclib inhibits CDK6 and is used for treatment HER-2 and ER+ breast cancer. It inhibits CSCs in five breast cancer cell lines in dose dependent manner. It blocks tumor growth by inhibiting cell cycle from G1-S phase [8]. CDK4/6 inhibitors inhibit phosphorylation of Rb and release of E2F. These also show anti-CSC activity by blocking movement from G1 to S phase and so show antitumor activity in HER+ and HER2- breast cancer [36]. PD-0332991 is selective inhibitor of CDK6 but its activity has not been checked for CSCs [14].

CDK7 and CDK8 inhibitors: CDK7 binds with cyclin H and MAT1 proteins forming CDK activating complex which act as Transcription Factors (TFs). The aberrant control of TFs lead to dysregulation of cell cycle which is a hallmark of cancer [37]. Many CDK7 inhibitors have been reported with activity against different cancers. Among these CDK7i, ICEC0942 (CT7001), SY-1365, SY-5609 and LY3405105 are under phase I/II clinical trials [38].

CDK8 also regulates transcriptional process with the help of mediator complex and phosphorylate different TFs. Over expression of CDK8 has been found to be linked with various cancers by aberrant activation of Wnt/β catenin pathway. Hence CDK 8 also presents a candidate to be targeted for cancers like colorectal cancer [39]. But the inactivation of CDK8 is not thoroughly studied for omitting properties of cancers.

CDK9 inhibitors: CDK9 is a transcriptional regulator which controls the expression of anti-apoptotic genes. It interacts with cyclin T and form a positive transcription elongation factor which allows the expression of MYC and MCL1. MYC high level expression is observed in triple negative breast cancer [5].

Approximately 15-20% of breast cancer patients suffer from triple negative breast cancer in which all the three hall marks, Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2), are not expressed 3 (Bhattacharya and Banerjee, 2017). Recurrence is usually observed in the case of TNBC after the treatment while sometimes the phenomenon of metastasis has also been observed. Evidence suggested that this metastasis occurs due to subset of tumor cells known as CSCs. CDKs role is vital in metastasis and invasion which make CDKs inhibitor an important candidate to target stem cells population [7].

High CDK9 expression has been found linked with increased death rate of patients suffering with triple negative breast cancer. Using pharmacologic inhibitor of CDK9 (atuveciclib) in cells with high levels of CDK9 expressing cell lines indicated low levels of MYC and MLC1 expression along with reduced cell proliferation and survival. Reduced growth of mammospheres and less levels of $CD24^{low}$/ $CD44^{high}$ was observed which is the main characteristic of breast cancer stem cells [40].

In another approach, γ secretase inhibitors were found resistant for brain tumor initiating cells with high level of RBPJ. Targeting CDK9 or c-MYC, an upstream regulator of RBPJ, with small molecules also decreased BTIC propagation, and prolonged survival in mice bearing orthotopic GBM xenografts [41].

Different CDK9 inhibitors like 21e have been found to suppress cell proliferation in lung cancer. It reduces sphere formation, marker expression and side population. It has also reduced cell cycle propagation, colony formation and in some cases induce apoptosis in non-small cell lung cancer [42]. All of these results indicate that this drug could be used

to target breast cancer stem cells and could help to properly eliminate the cancer.

In view of these differences that CSCs own; there are possibilities to target these culprits in order to permanently banish the cause of cancer.

CONCLUSION

Accumulating data on therapeutic role of CKIs in CSCs population suggest that these could be employed as an effective tool in eradication of aggressive cancer cell types. As CDK1 inhibit G2 phase of cell cycle and prevent DNA damaging, these could be important drug targets. However, clinical applicability of CDKIs as therapeutic agent in CSCs is still ambiguous. CDKIs known until now are non-selective in their mode of action but as we have noticed that CDKIs can be utilized along with other drug combinations for affective treatment development and selective action. It broadens our knowledge for the development of drugs. Even these strategies could be useful for treatment resistant cancers. During our survey, we find that combined action of CDK2/CDK4 and CDK1/CDK4 could be important for treatment resistant cancers. Similarly, CDK2/CDK7 combination is highly effective against endocrine resistant cancers. PI3K inhibitors and CDKI2 have also proven useful in *in vitro* experiments for the treatment of colorectal cancers whereas CDKI1/CDKI2/PI3K combination has been proven lethal in xenograft glioma models. As the present knowledge is limited so further research is required *in vitro* on different cell lines and animal models to find effective, new and targeted therapies for the treatment of cancer. Further research with clinical trials can provide concrete findings on their clinical relevance.

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