Research Letter

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Targeting protein kinase D in oral squamous cell carcinoma: a promising therapeutic approach

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Dear Editor,

Oral squamous cell carcinoma (OSCC) is the most aggressive tumor which rises in Oro-maxillofacial region under the subtype of head and neck squamous cell carcinoma (HNSCC)[1,2]. Regarding lip and oral cavity cancers, according to Globocan cancer observatory (GCO) 2024, there were 389 846 cases worldwide and 143 759 cases in India, with a mortality of 75.1% in Asia[3]. 40% of all cancer diagnosis in India are OSCC, compared to 5% globally. This high incidence rate is linked to lifestyle factors, with approximately 80% of cases associated with tobacco use. In India, lifestyle choices could be one of the main causes of oral cancer, while genetics may also be involved[4]. Risk factors include smoking, betel nut chewing, hereditary conditions, viral infection like human papilloma virus (HPV), immune deficiency, insufficient nutrition, uncontrolled alcohol use, tobacco and chronic exposure to heavy metals. Gene mutation, dysregulated epigenetic modifications, and exposure to carcinogenesis and mutagenesis can participate in tumor formation and development of OSCC. Aberrant signaling transduction and tumor suppressor signaling inactivation contributes to tumorigenesis. Aberrations in cell signaling pathways, including MET pathway, Wnt/β catenin pathway, RAS/RAF/MAPK pathway, PI3K/AKT/mTOR pathway, and JAK/STAT pathway are integral to the formation and growth of OSCC. The aberrations in these signal transduction can lead to increased proliferative potential, tissue invasion and metastasis[5]. Lymphatic metastasis occurs first when OSCC cells migrate to the regional lymph nodes in the head and neck region. Patients with OSCC metastasis have worst prognosis and the migration of tumor cells occurs to other regions/ organs including lymph nodes, lungs, liver, and bone. Intra-tumoral lymphatic vessel density linked with lymph node metastasis and reduces the survival rate[6]. OSCC progression is caused by epigenetic modifications including DNA methylation, histone acetylation, and chromatin modification. DNA hypermethylation is linked to tumor formation and development, increased cell migration risk, and poor prognosis in OSCC. Development of OSCC is influenced by DNA methylation abnormalities and both hypo and hypermethylation rises the incidence of oral malignancies[5]. Aberrations in histone acetylation is associated with the progression of oral malignancies[5].

The gene protein kinase D (PKD) is a family of serine-threonine kinase. PKD1, PKD2, PKD3 are the three forms of PKD. PKD activation leads to uncontrolled cell growth, cell migration, cell invasion, and epithelial mesenchymal transition (EMT)[2,7,8]. PKD, the major signaling molecule plays a role in various malignancies including OSCC, colorectal, breast, pancreatic carcinomas, glioma multiforme, and leukemia[9]. PKD can be activated by hormones, growth factors, cytokines, and chemokines (Fig. 1). Upregulation of PKD3 can promote the tumor progression and also cause uncontrolled cell growth, cell migration, diapedesis in OSCC, prostate cancer and breast cancer[2,7,8,10]. PKD3 is involved in multiple signaling pathways including nuclear factor-kappa B (NF-κB), signal transducer and activator of transcription 1/3 (STAT1/3), protein kinase B, and extracellular signal-regulated kinase 1/2 (ERK1/2)[2]. PKD3 can promote angiogenesis and metastasis as well as it inhibits apoptosis and cell senescence in OSCC cells[9]. PKD3 plays an important role in immunosuppressive protein expression, PD-L1 (programmed death-ligand 1). PD-L1 is

HIGHLIGHTS

- Targeting protein kinase D (PKD) in oral squamous cell carcinoma.
- Potential therapeutic approach for oral squamous cell carcinoma.
- Small molecule inhibitors targeting PKD for oral squamous cell carcinoma.
- CRT0066101, a potent PKD3 inhibitor.
- CID755673 inhibits PKD3.
- SD-208 inhibits PKD3.

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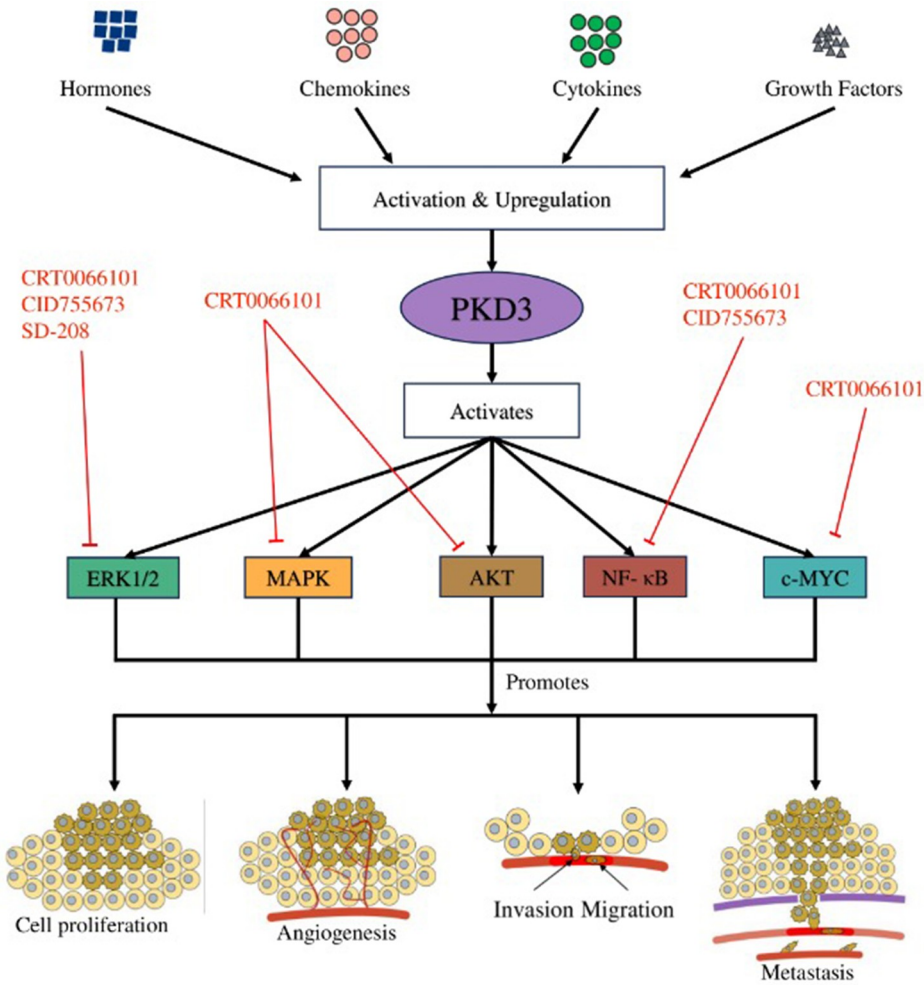

Figure 1. Schematic representation of the activation of PKD3 and its possible inhibitions. The figure illustrates the mechanisms of three compounds. Each compound plays a role in regulating immune responses and blocking kinases related to cell proliferation. CRT0066101 inhibits major signaling pathways shown in the figure, induces apoptosis, leading to reduced cancer cell growth; SD-208 inhibits ERK1/2 and improves anti-tumor effect; and CID755673 inhibits ERK1/2 and NF-κB as well as enhances NK cell function to eliminate cancer cells.

highly expressed in OSCC as well as the levels of PKD3 and PDL1 are positively correlated. OSCC cells when exposed to inflammatory cytokines such as IFN-γ, PKD3, leads to an increases in the production of PD-L1. This occurs through the phosphorylation of STAT1 and STAT3, which activates PD-L1 transcription. The interaction between PKD3 and PD-L1 creates a positive feedback loop that increases PD-L1 levels and stimulates PKD3 activity, promoting EMT and enhancing tumor aggressiveness. Additionally, the interaction of PKD3 with ERK1/2 contributes to the modulation of PD-L1 expression and the immunosuppressive microenvironment that allows tumor cells to evade T cell mediated immune responses[2].Upregulation of PD-L1 leads to the aggressiveness of the tumor[11]. PKD3/PD-L1 can activate the ERK1/STAT1/3 signalling pathways through EMT and promotes the cell proliferation, migration, and invasion by increasing the EMT proteins including vimentin, SNAIL, E-cadherin[2]. The upregulation of PKD3 is reported to have aggressiveness in ER negative breast cancer and there are reports suggesting the role of PKD3 in promoting cell progression, survival, migration, and invasion in prostate cancer[7,12]. PKD3 has also been shown to have upregulated the ERK1 and c-MYC pathways and thereby leading to breast cancer progression[10].

Small molecule inhibitors (SMI) targeting PKD have shown to have antitumor activity, both *in vitro* and *in vivo* (Table 1). PKD3 inhibition reduces the expression of PD-L1 in OSCC, thereby inhibiting the proliferation and migration of OSCC cells[11]. CRT0066101, a small molecule inhibitor, inhibits PKD and showed to have increased apoptosis in pancreatic, breast, colorectal and bladder cancer cell lines. This molecule also reduced the tumor growth *in vivo* and downregulated signaling pathways including NF-κB, ERK, MYC, MAPK and AKT. PKD3 inhibition with CRT0066101 reduced the pro-invasive proteins, such as tenascin-C (TNC) and stanniocalcin-1 (STC-1), in triple negative breast cancer (TNBC) cells[8]. As PKD3 activity is also associated with cell invasion in prostate cancer with an ERK dependent signaling mechanism[12], PKD3 inhibitors helps in checking the cancer progression. A recent study showed inhibition of PKD using CID755673, SD-208, and kb-NB142-70 on prostate cancer cells, resulting in reduced metastasis and invasion as well as increased cytotoxicity. These inhibitors are reported to have downregulated signaling pathways including NF-κB, and ERK. Another SMI

Table 1

Different targeting molecule/approaches with its significance and limitations.

Targeting molecule	Significance	Limitations	Ref.
CRT0066101	Modulates the phosphorylation of signaling and inhibits the PKD, which is involved in cancer cell proliferation and survival. It inhibits cancer cell growth and angiogenesis and promotes apoptosis.	Potential off-target effects, cancer cells may develop resistance over time and reducing long-term effectiveness of the treatment.	[8,9]
CID755673	The activity of PKD3 is disrupted with different IC_{50} values, which reduces metastasis and improve patient outcome. Targets PKD to modify the immune system and modulate NK cell function	Off-target effects. Resistance mechanisms may need combination therapies.	[9]
SD-208	It inhibits cell proliferation and invasion of cancer cells. By inhibiting PKD3, it reduces phosphorylation of downstream targets involved in cell cycle regulation pathways which can lead to cell cycle arrest, and block cancer cell proliferation.	Lack of clinical trial data on safety and efficacy. Potential off-target effects. Potential resistance and may need combination therapies to improve patient outcomes.	[9]

namely kb-NB165-09 inhibited PKD in pancreatic cancer cells and showed cell cycle and proliferation arrests[9].

Thus targeting PKD in OSCC holds promise in clinical settings. PKD inhibitors already showed antiproliferative effects, both *in vivo* and *in vitro*. Multilevel studies including clinical studies in OSCC are warranted to confirm these observations in the bed side.

Ethical approval

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Consent

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