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PBK/TOPK as a Potential Therapeutic Target in Glioblastoma and Other Malignancies

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PBK is a Mitotic Kinase Expressed in Rapidly Proliferating Cells

A serine/threonine kinase PDZ binding-kinase (PBK) is a member of the mitogen-activated protein kinase (MAPK) kinase (MAPKK) family [1-3]. This enzyme is also known under the name T-lymphokine-activated killer cell-originated protein kinase (TOPK). PBK was discovered as a factor that binds PDZ2 domain of hDLg (human homologue of the Drosophila Discs-large (Dlg) tumor suppressor protein) [2]. This study also demonstrated that the mitotic phosphorylation of PBK is required for its kinase activity [2]. Due to this specific activation during the mitotic-phase of the cell cycle, PBK is also denoted as a "mitotic kinase". PBK protein is phosphorylated by cdk1/cyclin B during mitosis and its presence is necessary for formation of the mid-zone of the mitotic spindle [3]. The *PBK* gene is especially highly expressed in placenta [2] and was also implicated in spermatogenesis [4,5]. Since *PBK* is expressed in seminiferous tubules of testis, where the male gametes are produced, it has been speculated that *PBK* might be essential in spermatocytogenesis during which mitosis occurs [4]. While *PBK* is not expressed in the adult human brain [2] its mRNA is abundant in the human fetal brain [4] and rapidly dividing neuronal stem/progenitor cells (NS/PCs) [6]. In mouse NS/PCs both Pbk and its downstream target p38 are essential for proliferation and self-renewal [6]. In the adult mouse brain, *Pbk* is expressed in rapidly proliferating NS/PCs of the adult subventricular zone and early postnatal cerebellar external granular layer [6]. The notion that PBK represents a stemness-associated kinase is further supported by the evidence that PBK is down regulated during differentiation [6,7]. PBK is specifically expressed in all germinal zones during brain development and is not expressed in mature neurons and glial cells [6]. A study conducted in HL-60 myeloid leukemia cells, induced to differentiate, using phorbol ester, showed that PBK protein expression was strongly down-regulated in differentiated cells [7]. This study also showed that the expression of PBK correlated positively with the expression of a cell cycle regulator c-Myc.

The Implication of PBK in Human Malignancies

PBK expression was originally linked to hematologic tumors such as leukemia, lymphoma and myeloma where its up-regulation correlates with the malignant potential of these tumors [1,7-10]. A vast body of evidence links this enzyme also to solid tumors such as glioblastoma [11,12], melanoma [13], neuroblastoma [14], colorectal carcinomas [15-17], cholangiocarcinomas [10], renal cell carcinomas [18] and cancers of prostate [19,20], breast [21-24], cervix [25], lung [26-28] and urinary bladder [29].

PBK is associated with very poor prognosis in hematologic malignancies such as acute myeloid leukemia [9]. Also in many solid tumors, increased levels of PBK correlates with shorter patient survival. A survival analysis in patients with prostate cancer identified PBK as an independent factor for predicting recurrence-free survival [19]. In colorectal cancer *PBK* levels strongly correlated with poor overall and disease-free survival of patients [30]. A combination of high PBK and Interleukin-8 (also known as CXCL8) had the worst prognosis [30]. In lung cancer patients, increased PBK protein expression was associated with poor prognosis and could serve as an independent prognostic factor [27,28,31]. In human urinary bladder, transitional cell carcinoma expression levels of PBK were found to be significantly associated with the stage of the disease [29]. Interestingly in cholangiocarcinoma expression levels of PBK correlated positively with patient survival [10].

In glioblastoma, PBK was highly up-regulated both at mRNA and protein levels [11]. Furthermore PBK was up-regulated in GBM when compared to both normal NS/PCs from the adult human brain and the low grade gliomas [11,32]. *PBK* could serve as a patient survival prediction marker both alone [12] and as a part of a 9-gene signature [11]. PBK and eight other genes: *CENPA, KIF15, DEPDC1, CDC6, DLG7, KIF18A, EZH2* and *HMMR* were highly co-expressed in glioblastoma tumours and were part of the same protein-protein interaction network [11]. The Cancer Genome Atlas (TCGA) recently classified all GBM tumors into four categories according to their gene expression profiles [33]. These were: *mesenchymal, classical, proneural* and *neural* tumours [33]. PBK was found particularly up-regulated in the proneural GBM samples [11,12]. However, gene expression of PBK and the 9-gene signature correlated with survival of *mesenchymal* GBM patients [11,12].

PBK is Expressed in Glioblastoma Cancer Stem Cells

PBK is implicated in regulation of stemness during brain development [6]. Several studies also implicate PBK in regulation of stemness properties in cancer stem cells (CSCs) [7,11,12]. Populations of cancer cells with stem-like properties were originally identified in hematological malignancies but their presence was also confirmed in many solid tumors [34-37]. New cancer treatments that involve eradication of cancer stem cells (CSCs) typically comprise either inhibitor-mediated targeting of known biochemical signaling pathways or immune therapy [38-40].

Glioblastoma is the most common primary brain malignancy and one of the deadliest human cancers with median patient survival time of less than 15 months [41]. In spite of combined surgery, radiation and chemotherapy the prognosis remains dismal. It has been suggested that the GBM cells with cancer stem-like properties contained within these tumours, infiltrate the surrounding brain tissue and cause recurrence [42]. Glioblastoma stem cells are typically resistant to radiation [43] and chemotherapy [44] and remain predominantly unaffected by the adjuvant treatment that targets the bulk tumor. Assuming that

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glioblastoma stem cells play a central role in GBM recurrence [42,45,46], novel targeting therapies must therefore include eradication of these cells. Glioblastoma primary cells can be grown as spheres in serum free and mitogen containing medium in order to promote stemness and enrich for CSCs [47,48]. PBK is highly up-regulated in GBM CSCs both at the mRNA and protein levels [11,12].

Mechanisms of PBK Action

Recent interest in PBK revealed its involvement in numerous biochemical-signaling pathways. PBK and several key-players in cancer signaling pathways such as growth receptors and cell-cycle regulators were part of the same protein-protein interaction network [11].

A study performed in human malignant melanoma cells identified PBK as an upstream activator of JNKs in response to UVB irradiation [49]. This study showed that PBK could phosphorylate UVB-induced c-Jun-NH2-kinase 1 (JNK1) thus increasing JNK's capability to mediate H-Ras–induced cell transformation [49]. A study in prostate cancer identified PBK as a direct target for E2F1 [19]. Furthermore the *PBK* gene represents a likely candidate for an IL-6 target gene. This is suggested by its significant up-regulated expression in hybridoma cells induced to grow by a brief IL-6 pulse [50]. PBK is also identified as a molecular target of doxorubicin and mediates doxorubicin chemoresistance in cervical cancer cell [51]. PBK directly interacts with and phosphorylates IκBα at Ser-32, leading to p65 nuclear translocation and NF-κB activation [51]. The same study revealed that PBK-mediated IκBα phosphorylation was enhanced in response to doxorubicin [51].

It has been shown that the overexpression of PBK in normal lung fibroblasts enhanced the migration and invasion in a PI3K/AKT-dependent manner [28]. PBK both promoted AKT phosphorylation at Ser (473) and decreased the phosphatase and tensin homolog (PTEN) levels in lung cancer cells. KD of PBK had opposite effects. A PI3K-specific inhibitor could not abolish the negative effect of PBK on PTEN expression, while co-expression of PTEN significantly reduced PBK-induced AKT phosphorylation in a dose-dependent manner. The PBK-mediated decline in PTEN transcript levels was therefore suggested to act upstream from the PI3K/AKT-stimulated migration [28]. A study of colorectal cancer cells revealed the existence of a positive feedback loop between PBK and ERK2 that served as a promoter of tumorigenic properties in vitro and in vivo [17]. A study of breast cancer cells showed that PBK is needed for the activation of the p38 pathway by growth factors [21].

PBK's actions through p38 and ERK signaling were also shown in glioblastoma stem-like cells [12]. Levels of phospho-p38 MAP kinase (Thr180/Tyr182) were down-regulated in GBM CSC cultures treated with HI-TOPK-031 and those featuring shRNA mediated knockdown of PBK [12]. Down-regulation of PBK also induced significant reduction in phosphorylated ERK1/2 levels [12] thus confirming the results obtained in other cancers [17,21,30].

PBK as a Potential Therapeutic Target in Cancers

There are many evidences suggesting that PBK might be a new promising therapeutic target. In malignancies such as acute myeloid leukemia KD of PBK significantly decreased proliferation of promyelocytes and induced apoptosis [9]. KD of PBK also induced cell cycle arrest in G2/M and induced mitochondrial dysfunction [9]. Similar effects were observed in lung adenocarcinoma where KD of PBK resulted in reduced proliferation and viability in cancer cell lines A549 and GLC82 [27]. KD of PBK in HeLa cells triggered doxorubicin-mediated apoptosis that was associated with caspase-dependent signaling pathways [51]. In colorectal cancer cells, knockdown of PBK reduced tumorigenic properties of the cell line HCT116 in vitro and in vivo [17]. When the colorectal cancer cells were treated with epidermal growth factor, knockdown of PBK resulted in a decreased phosphorylation of ERK2 [17]. PBK/TOPK interacts with the DBD domain of tumor suppressor p53 and modulates expression of transcriptional targets including p21 [15].

Atorvastatin (Lipitor) or the geranylgeranyltransferase I inhibitor GGTI-298, is an inhibitor of hydroxymethylglutaryl co-enzyme A (HMG-CoA) reductase, a rate-limiting enzyme of the mevalonate pathway. A recent study showed that atorvastatin can down-regulate expression of PBK by impairing protein geranylgeranylation [22]. This study also showed that Yes-associated protein (YAP) mediates geranylgeranylation-regulated expression of PBK.

In breast cancer cells PBK knockdown impaired p38 activation after long-term stimulation with different growth factors and reduced the cells' motility [21]. However the suppression of PBK expression did not prevent progression through the cell cycle, but caused decreased proliferation over time in culture, and reduced stemness as shown by the clonogenic assay [21]. Suppressed PBK expression in breast cancer also resulted in an impaired response to DNA damage, increased DNA damage and decreased cell survival [21]. KD of PBK could suppress cell proliferation, invasion and migration of prostate cancer cell lines in vitro [19]. Interestingly, down-regulation of PBK in cholangiocarcinoma QBC 939 cells, did not affect their proliferation [10].

PBK-specific inhibitor HI-TOPK-032 was tested in colon cancer [16]. Its application reduced growth of colon cancer cells by decreasing ERK-RSK phosphorylation as well as increasing apoptosis through regulation of p53, cleaved caspase-7 and cleaved PARP [16]. In vivo, administration of HI-TOPK-032 suppressed tumor growth in a colon cancer xenograft model. Although HI-TOPK-032 could efficiently inhibit the PBK kinase activity it had little effect on extracellular signal-regulated kinase 1 (ERK1), c-jun-NH2-kinase 1 or p38 kinase activation [16].

Gene knockdown (KD) of *PBK* in GBM GSC cultures resulted in reduced viability and sphere formation and occasionally also in increased apoptosis [12]. Signaling pathways such as Wnt, EGF and Notch were dysregulated in cultures featuring PBK KD [12]. Treatment of these cells with PBK inhibitor HITOPK-032 almost completely abolished growth and induced apoptosis in all tested cultures [12]. HI-TOPK-032 treatment also resulted in diminished growth of experimentally induced subcutaneous GBM tumors in mice. Inhibition of PBK using HI-TOPK induced significant reduction in phosphorylated ERK1/2 and p38 MAP kinase levels [12]. The effect of this inhibitor seems thus to be even better than previously shown in colon cancer cells [16].

Researchers have recently identified a new compound, OTS964, that blocks PBK kinase activity with high affinity and selectivity [52]. This inhibitor causes a cytokinesis defect and the subsequent apoptosis of cancer cells in vitro as well as in xenograft models of human lung cancer [52]. Clinical trials of OTS964 may start in 2016 [53].

Summary: This review shows that PBK is involved in initiation and progression of numerous malignancies. Its impact as a predictor of patient survival in many cancers is undeniable. Down-regulation of PBK generally reduces tumorigenic features in breast and colon cancers, glioblastoma, melanoma and several other malignancies. The potential of PBK in targeted therapies is therefore paramount. However the availability of only a few inhibitors is a limiting factor at the moment. New specific inhibitors against this oncogenic-kinase are therefore dearly sought.

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