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Elevated Protein Tyrosine Phosphatase Kappa Expression Is Associated With Disease Progression and Poor Prognosis of Pancreatic Cancer

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Abstract

Background/Aim: Protein tyrosine phosphatase kappa (PTPRK), a recognized tumor suppressor, has been implicated in cancer progression of certain solid tumors. This study investigated the role of PTPRK in the progression of pancreatic cancer.
Materials and Methods: PTPRK transcripts were determined in a pancreatic cancer cohort using real-time PCR. The functional impact of PTPRK was evaluated in pancreatic cancer cells with PTPRK knockdown, followed by an assessment of its implications in disease progression.
Results: Elevated PTPRK expression was observed in pancreatic cancer and was positively correlated with tumor T stage. Knockdown of PTPRK led to reduced cellular proliferation and decreased expression of cyclin-dependent kinase 6 (CDK6). Additionally, an increase in VEGFC expression was noted in PTPRK knockdown cells.
Conclusion: Up-regulation of PTPRK in pancreatic cancer is associated with disease progression and poor prognosis. PTPRK facilitates cancer cell proliferation through CDK6, highlighting the potential for therapeutic strategies targeting PTPRK and CDK6 in pancreatic cancer treatment.

Keywords: PTPRK, pancreatic cancer, prognosis.

Introduction

Pancreatic cancer is associated with an exceptionally high mortality rate, ranking among the top five causes of cancer-related deaths (1). Owing to the absence of early symptoms, the disease often remains undetected until advanced stages, with approximately 80% of patients presenting with metastasis (1). The five-year survival rate

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remains below 6%, reflecting the limited effectiveness of current therapeutic strategies.

Phosphorylation is crucial in regulating cellular functions (2), with tyrosine, threonine, and serine being the most frequently phosphorylated amino acids (2). Dysregulated phosphorylation has been implicated in cancer progression (2-4). Tyrosine kinases such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and vascular endothelial growth factor receptors (VEGFRs) respond to growth factors and hormones. Mutations in these kinases often lead to aberrant phosphorylation. Targeted therapies, including imatinib and gefitinib, have been developed to inhibit these kinases (5, 6).

EGFR and its downstream signaling molecule RAS, particularly KRAS, play critical roles in pancreatic cancer progression (7, 8). *KRAS* mutations promote uncontrolled proliferation by activating MAPK and PI3K pathways (9, 10). Although inhibitors targeting the MAPK pathway, such as BRAF kinase inhibitors, have been explored, they may inadvertently activate the pathway through BRAF and CRAF dimerization. Similarly, inhibitors of PI3K, AKT, and mTOR have demonstrated anti-tumor effects in preclinical models but show limited clinical benefit in pancreatic cancer (11-13).

Protein tyrosine phosphatase kappa (PTPRK) is a transmembrane tyrosine phosphatase belonging to the type IIb family of receptor protein tyrosine phosphatases (RPTP), also known as the R2B superfamily. Structurally similar to cell adhesion molecules (CAMs), the PTPRK gene is located on the long arm of chromosome 6 (14). PTPRK shares the conserved structural organization characteristic of RPTP, consisting of an extracellular region, a transmembrane segment and intracellular catalytic domains (15). Its extracellular region contains a MAM domain, an immunoglobulin-like domain and four fibronectin type III repeats, enabling interactions with β- and γ-catenin at adherens junctions and contributing to the regulation of cell-cell adhesion (16-18). While PTPRK plays a role in nervous system development, its exact mechanism remains unclear (14).

PTPRK is considered a tumor suppressor in breast cancer, where its reduced expression is associated with poor prognosis, increased proliferation, adhesion disruption, and enhanced invasion capacity (14, 19). Similarly, PTPRK inhibits the proliferation and invasion of glioma and melanoma cells by modulating oncogenic signaling pathways including EGFR and β-catenin (14, 20). In lung cancer, PTPRK suppresses tumor cell proliferation, invasion, and migration through an inhibition of STAT3 (21).

A recent study has also demonstrated that PTPRK regulates cell-cell adhesion and epithelial organization, suppressing epithelial-mesenchymal transition (EMT) and tumor invasion in colorectal cancer models (22). At the molecular level, PTPRK can directly dephosphorylate receptor tyrosine kinases such as EGFR, thereby attenuating downstream signaling pathways that drive tumor cell proliferation and migration (23). Structural alterations involving PTPRK, including PTPRK-RSPO3 gene fusions, have been reported in gastrointestinal cancers and are known to activate Wnt signaling pathways (24). Recent evidence indicates that PTPRK also participates in metabolic regulation, controlling glycolysis and de novo lipogenesis during hepatocyte metabolic reprogramming (25). Additionally, Epstein-Barr Virus infection can disrupt PTPRK expression, contributing to Hodgkin lymphoma development (26).

Despite these findings, the role of PTPRK in pancreatic cancer remains poorly understood. Recent genomic studies have identified alterations in several classical protein tyrosine phosphatases, including PTPRK, in pancreatic ductal adenocarcinoma, suggesting that dysregulation of this phosphatase may contribute to tumor progression and could represent a potential prognostic biomarker (27). This study aimed to investigate the involvement of PTPRK in the progression of pancreatic cancer.

Materials and Methods

Tissue sample collection. Tissue samples from pancreatic cancers (n=201) and adjacent non-tumor pancreatic

tissues (n=201) were collected immediately after surgery at Peking University Cancer Hospital. All procedures used are approved by the Peking University Cancer Hospital Research Ethics Committee (MTA01062008).

Public pancreatic cancer datasets. The implication of PTPRK in disease progression and prognosis was also analyzed with RNA sequencing data of pancreatic cancer (n=177) [The Cancer Genome Atlas (TCGA)_PAAD)] and two gene array datasets: GSE15471 (N=39, tumor samples with paired adjacent normal pancreatic tissues) (28) and GSE71729 (N=357) (29).

Cell lines and cell culture. Human pancreatic cancer cell lines PANC-1 and CFPAC-1 were purchased from ATCC (American Type Culture Collection, Manassas, VA, USA). Both cell lines were cultured in DMEM-F12 medium supplemented with 10% FCS and antibiotics. Unless specifically stated, materials and reagents were purchased from Sigma Aldrich (Dorset, UK).

RNA extraction, reverse transcription, and quantitative real-time PCR (qPCR). TRIzol reagent (Sigma-Aldrich) was used to extract the RNA. GoScript reverse transcription mix (Promega, Southampton, UK) was used for reverse transcription. FAST 2X qPCR MasterMix (Primer Design, Chandler's Ford, UK) was used for qPCR. Primers used for quantitative PCR include the GAPDH forward (5'-CTGAGTACGTCGTGGAGTC) and GAPDH reverse (5'-ACTGAACCTGACCGTACACAGAGATGATGACCCTTTTG); PTPRK forward (5'-AATTACAATTGATGGGGAGA) and PTPRK reverse (5'-ACTGAACCTGACCGTACATATTGTGTGACGATG AAAGC); CDK6 forward (5'-AAATCTTGGACGTGATT GGA) CDK6 reverse (5'-ACTGAACCTGACCGTACAT TCAGAAGTAGGTCTTTGCC); cyclin D1 forward (CGGTGTCCTACTTCAAATGT) cyclin D1 reverse (5'-ACTGAACCTGACCGTACACAAAGCGGTCCAGGTAGTTC); and VEGFC forward (5'-GGAAAGAAGTTCCACCA CCA) VEGFC reverse (5'-ACTGAACCTGACCGTACAGAA AATCCTGGCTCACAAGC). The $2^{-\Delta\Delta CT}$ method was applied to the quantitative analysis (30).

Western blot. RIPA lysis buffer was used to extract the cellular protein, which was quantified using a BioRad protein quantification kit (BioRad, Hertfordshire, UK). For each sample, 34 µg protein was loaded and separated in 8% SDS-PAGE gel. Proteins were then transferred onto the 0.45µm PVDF membrane (Merck Millipore, Hertfordshire, UK) with a semi-dry blotter. After a blocking with 10% skimmed milk in room temperature for 1 h, anti-GAPDH (1:4,000; sc32233; Santa Cruz Biotechnology, Dallas, TX, USA) and anti-PTPRK (1:1,000; sc28906; Santa Cruz Biotechnology) were applied respectively with an incubation at 4°C for overnight. After another incubation (1 h, room temperature) with secondary antibodies: anti-mouse IgG (1:1,000; A5278; Sigma Aldrich) and anti-rabbit IgG (1:1,000; A6154; Sigma Aldrich), protein bands were visualized using EZ-ECL solution (Cat. No. 1921593; Biological industries, Cromwell, CT, USA). UVITech imager (UVITech, Cambridge, UK) was used for photographing.

Establishment of PTPRK knockdown cell line model. PTPRK ribozymes were synthesized and then cloned into pEF6/V5-His TOPO® TA plasmid vectors (Thermo Fisher Scientific, Waltham, MA, USA) as previously described (31). PANC-1 and CFPAC-1 cells were transfected with the PTPRK ribozymes (PTPRK kd) and the empty vectors (PEF) as control followed by a selection with 4 µg/ml blasticidin. After a verification of the knockdown using PCR and western blot, the cells were maintained in a culture medium containing 0.5 µg/ml blasticidin.

In vitro proliferation. Proliferation of PANC-1 CFPAC-1 over a duration up to five days was determined in cultures initially seeded 3,000 and 5,000 cells per well, respectively. Cells were fixed with 4% formaldehyde and then stained with Crystal violet (0.5%). Absorbance was measured at a 590 nm wavelength using a spectrophotometer (BIO-TEK, Elx800, Cheadle, UK).

In vitro adhesion. A 96-well plate was precoated with 5 µg Matrigel/well (BD Matrigel™ Basement Membrane Matrix, Corning Incorporated, Flintshire, UK) and air dried. After

a rehydration for 30 min at room temperature, 30,000 cells were seeded into each well followed by an incubation at 37°C for 40 min. After two washes with PBS, adherent cells were fixed with 4% formaldehyde, following staining with crystal violet. Absorbance at a 590 nm wavelength was determined using a spectrophotometer.

In vitro invasion. Transwell inserts with 8-μm pores were precoated with 50 μg Matrigel. 30,000 cells were added into each insert. After a 3-day incubation, cells that invaded through the Matrigel were fixed with 4% formalin, stained with 1% crystal violet and counted.

In vitro wound healing assay. Cells were seeded into a 24-well plate to form a monolayer before the test. The cells were scratched and migration of the cells was then monitored using EVOS system (Thermo Fisher Scientific). Closure of the wounds was measured using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

CDK inhibitor treatment and cell viability assay. To evaluate the role of CDKs in the proliferation of pancreatic cancer cells following PTPRK knockdown, cells were treated with specific CDK inhibitors. The CDK6 inhibitor BSJ-03-123 (Cat. No. 6921; TOCRIS, Bristol, UK), the dual CDK4/6 inhibitor Palbocicilib (Cat. No. S1116 Selleckchem, Houston, TX, USA), and the CDK4 inhibitor 3-ATA (Cat. No. sc-202414; Santa Cruz Biotechnology) were dissolved in DMSO to prepare stock solutions and further diluted in culture medium, with the final DMSO concentration kept below 0.1%. Cells were seeded into 96-well plates and exposed to serial dilutions of BSJ-03-123 (0.015-250 μM), Palbociclib (0.049-800 nM), or 3-ATA (0.012-200 μM) for 72 h. Following treatment, cells were fixed with 4% formaldehyde, then was stained with 0.5% crystal violet. The absorbance was measured at 590 nm using a spectrophotometer (BIO-TEK, Elx800). IC_{50} values were determined from the dose-response curves using GraphPad Prism software (Version 10, GraphPad Software, San Diego, CA, USA).

Statistical analysis. Mann–Whitney *U*-test was used for non-normally distributed data, and *t*-test was used for normally distributed data. The correlation between genes was analyzed using the Spearman test. All the statistical analyses were performed with SPSS software (version 26, SPSS, Chicago, IL, USA). Kaplan–Meier survival analysis was conducted using KMplot, or using SPSS for the GSE71729 (28). $p<0.05$ was considered as statistically significant.

Results

Aberrant expression of PTPRK in pancreatic cancer. In the Beijing clinical cohort, the qPCR results showed that PTPRK expression was significantly increased in pancreatic tumors compared with adjacent normal pancreatic tissues. In comparison with pancreatic ductal carcinomas, the PTPRK transcript levels were higher in adenocarcinomas. Moreover, PTPRK expression in the tumors with lymph node metastasis was lower than its expression in the tumors without lymph node metastasis. PTPRK expression was also higher in larger and more invasive tumors with a higher T stage including T2, T3, and T4 compared with T1 tumors (Table I).

To determine whether PTPRK expression is altered in pancreatic cancer, its expression in normal and tumor tissues was further analyzed in both GSE15471 and GSE71729 cohorts. An up-regulation of PTPRK in pancreatic cancers was also revealed in both cohorts (Figure 1A and B). Kaplan–Meier survival analysis showed that higher PTPRK transcript levels were associated with poor overall survival (OS) (cut off value=2,199) and shorter relapse-free survival (RFS) (cut-off value=2,673) (Figure 1C and D).

Influence of PTPRK on the proliferation of pancreatic cancer cells. PTPRK Knockdown was established in both PANC-1 and CFPAC-1 cell lines (Figure 2). Reduced proliferation was observed in both PANC-1PTPRK kd and CFPAC-1PPTPRK kd cell lines in comparison with corresponding control cells (Figure 3A and B). More interestingly, reduced expression of CDK6 was seen in

Table I. *Quantitative analysis of PTPRK transcripts in the Beijing cohort of pancreatic cancer using real-time PCR.*

Clinical samples	N	Median (Interquartile range)	*p*-Value
Tumor	201	195.2 (44.6~568.1)	0.01
Normal	201	68.9 (0~398.9)	
Patients' sex			
Male	121	202.4 (66.1~611.9)	
Female	80	175 (34~499)	
Distant metastasis			
No distant metastasis	186	193.5 (45.4~571.9)	0.38
With distant metastasis	15	202 (38~470)	
Node status			
Node negative	82	181 (45~506)	0.003
Node positive	5	66.0 (3.3-210.5)	
T staging			
T1	5	66 (3.3~210.5)	
T2	27	230 (45.4~571.9)	0.019 *vs.* T1
T3	112	198 (38~470)	0.0051 *vs.* T1
T4	22	184.6 (1.7~190.7)	0.046 *vs.* T1
Subtypes			
Adeno carcinoma	174	202.0 (61.9~608.9)	
Ductal carcinoma	7	114.1 (16.1~284.3)	0.014 *vs.* adeno
Other subtypes	18	99 (34~272)	0.59 *vs.* adeno
Patient status			
Alive	44	219 (67~1071)	
Deceased	171	187 (37~497.9)	0.16

both PANC-1^{PTPRKrib} and CFPAC-1^{PTPRKrib} cells whilst CCND1 was decreased in PANC-1 cells following the knockdown of PTPRK (Figure 3C and D). Further analyses showed that PTPRK transcript levels were positively correlated with both CDK6 and CCND1 in pancreatic tumors (Figure 3E and F). No significant changes were observed in the migration and invasion of those two pancreatic cancer cell lines following the knockdown of PTPRK (data not shown).

CDK6 and tumor growth in pancreatic cancer with PTPRK knockdown. CDK inhibitors were applied to examine the involvement of CDKs in the proliferation of pancreatic cancer cells following the knockdown of PTPRK. Both CFPAC-1$^{PTPRK\ kd}$ and PANC-1$^{PTPRK\ kd}$ exhibited a resistance to the CDK6 inhibitor BSJ-03-123 with significantly increased IC_{50} concentrations in comparison with CFPAC-1^{pEF} and PANC-1^{pEF}, respectively (Figure 4A and B). The PTPRK knockdown also resulted in a tolerance to the treatment with Palbociclib, which is an inhibitor targeting both CDK4 and CDK6 (Figure 4C and D), but less compared with the CDK6 inhibitor BSJ-03-123. IC_{50} of Palbociclib was 2222.49 nM for the PANC-1PTPRK kd and higher than the control (p=0.031). The IC_{50} of Palbociclib was also higher in the CFPAC-1PTPRK kd compared with the control (p=0.051) but not significant. In contrast to BSJ-03-123 and Palbociclib, both CFPAC-1$^{PTPRK\ kd}$ and PANC-1$^{PTPRK\ kd}$ presented similar responses to the treatment with the CDK4 inhibitor 3-ATA in comparison with the corresponding control (Figure 4E and F).

PTPRK and lymph node metastasis in pancreatic cancer. In the Beijing cohort, reduced expression of PTPRK was seen in the primary tumors which developed lymph node metastases (Table I). A further analysis revealed an inverse correlation between PTPRK and the pro-lymphangiogenic factor VEGFC in the TCGA cohort of pancreatic cancer. Increased transcript levels of VEGFC were also seen in both PANC-1^{PTPRKrib} and CFPAC-1^{PTPRKrib} cell lines (Figure 5).

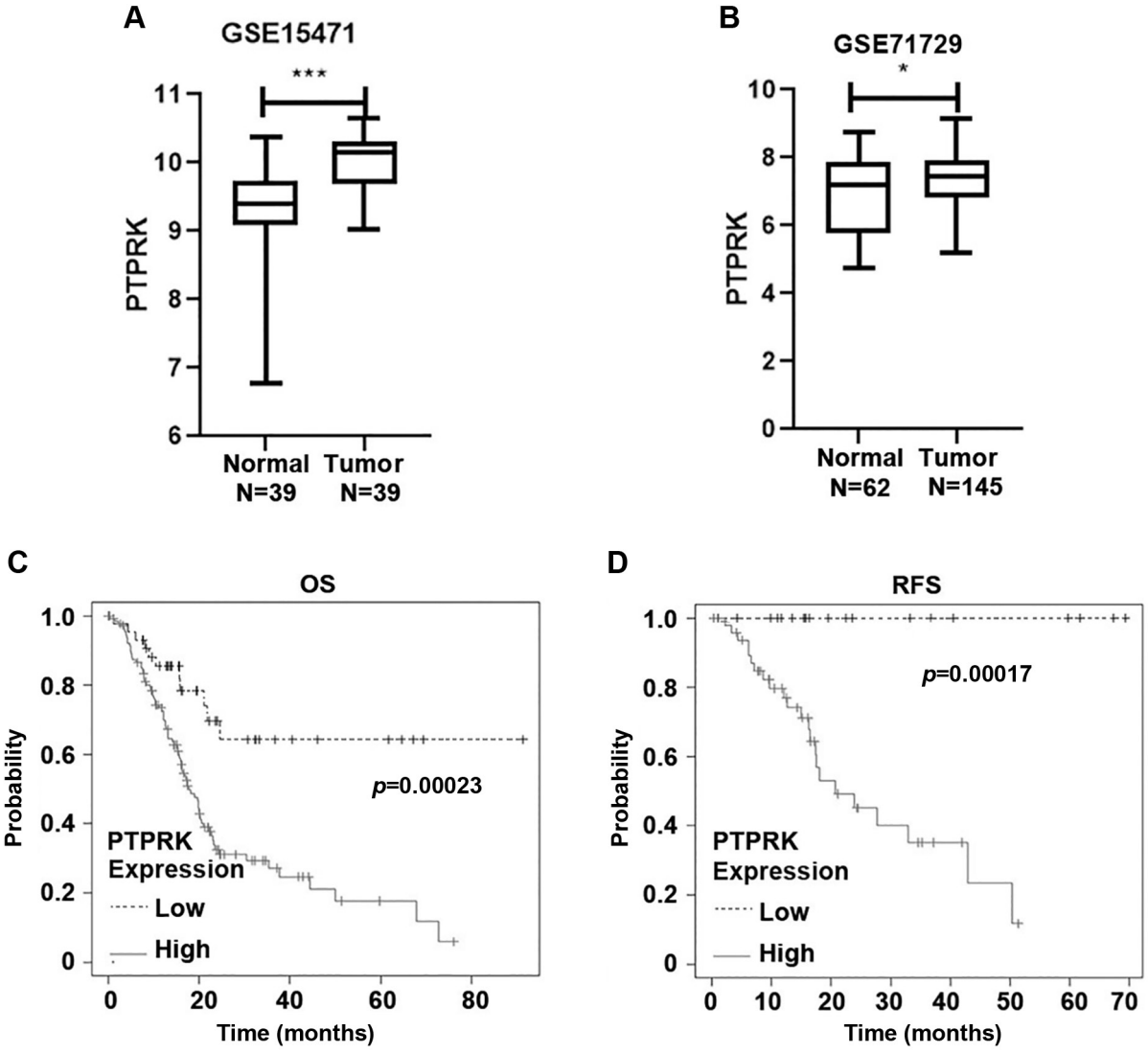

Figure 1. *Protein tyrosine phosphatase kappa (PTPRK) expression and its prognostic significance in pancreatic cancer. PTPRK expression in pancreatic tumors was compared with normal pancreatic tissues in GSE15471 (A) and GSE71729 (B). Association between PTPRK and the overall (OS) (C) and relapse-free survival (RFS) (D) in patients with pancreatic cancer were analyzed using Kaplan–Meier plot. *p<0.05, **p<0.01, ***p<0.001.*

Discussion

PTPRK has been widely regarded as a tumor suppressor; in breast cancer, its reduced expression is associated with poor prognosis and increased proliferation, adhesion, and invasive capacity of cancer cells (14, 19, 21). Mutations or loss of PTPRK function have been linked to the development of various cancers, including colorectal cancer, glioma, breast cancer, central nervous system lymphomas, lung cancer, and primary intraocular lymphoma (14, 19, 20, 26).

Interestingly, this study found an up-regulation of PTPRK in pancreatic cancer. Its expression is positively correlated with higher T stages. Patients with elevated PTPRK transcript levels had poorer prognosis. PTPRK knockdown resulted in an inhibition of proliferation in the

two pancreatic cancer cell lines examined. However, little impact on adhesion, migration and invasion was observed (data not shown). This suggests that PTPRK may play a contrasting role in pancreatic cancer compared with its previously reported tumor-suppressive functions in other malignancies (21, 26).

The study further observed that PTPRK knockdown led to decreased transcript levels of CDK6 and CCND1, which are key regulators of cell growth. CDKs regulate cell cycle progression, with CDK4 and CDK6 interacting with cyclins D1, D2, and D3 to promote the G1-to-S phase transition by phosphorylating the RB protein (32, 33). CDK4/6 activity is tightly regulated by cyclin-dependent kinase inhibitors, including p15, p16, p18, p19, WAF1, p21, p27, and p57 (32-38). Dysregulation of CDK4/6 activation and expression has been implicated in numerous human cancers.

Independent of CDK4/6 alterations, up-regulation of cyclin D expression can drive cancer progression (39, 40). CCND1 expression is regulated by the MAPK and PI3K-AKT pathways (41, 42). CDK4/6 inhibitors, such as palbociclib, have demonstrated efficacy in clinical trials for mantle cell lymphoma (43). Moreover, PTPRK knockdown resulted in a good tolerance to the CDK6 inhibitor BSJ-03-123, but to a lesser extent to the Palbociclib. This suggests that PTPRK may serve as a marker for CDK6 targeted therapy, which could be further evaluated in a clinical trial. Furthermore, this research highlights the potential of targeted therapies against PTPRK and CDK6 in pancreatic cancer.

However, another important observation from the present study was the lower PTPRK transcript level seen in primary tumors that presented lymph node metastases at the diagnosis of the disease. Further analysis revealed an inverse correlation between PTPRK and VEGFC, which is a key promotive factor for lymphangiogenesis and lymph node involvement (44). In line with this observation, an increased expression of VEGFC was also detected in pancreatic cancer cell lines following the PTPRK knockdown. This suggests that PTPRK plays as different role in lymph metastasis, which is yet to be further investigated.

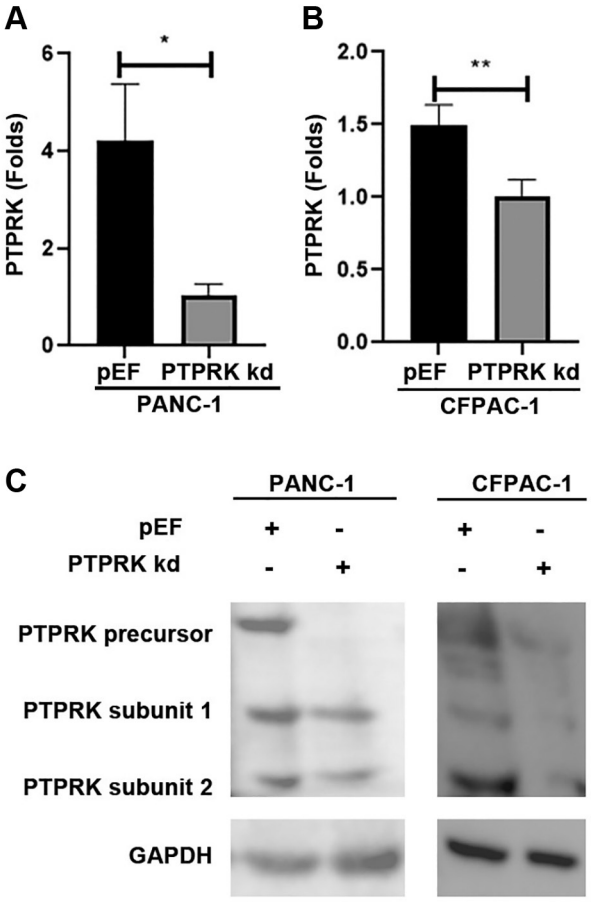

Figure 2. *Verification of protein tyrosine phosphatase kappa (PTPRK) knockdown in pancreatic cancer cell lines. (A) QPCR results show the PTPRK expression in control cell line PANC-1^{pEF} and PTPRK knockdown cell line PANC-1$^{PTPRK\ kd}$. (B) PTPRK expression in CFPAC-1^{pEF} and CFPAC-1$^{PTPRK\ kd}$ cell lines. (C) Western blot results show the PTPRK protein expression in both PANC-1 and CFPAC-1 cell lines with PTPRK knockdown. *p<0.05, **p<0.01, ***p<0.001.*

In conclusion, PTPRK is up-regulated in pancreatic cancer, and its increased expression is associated with poor prognosis. PTPRK can promote proliferation through regulation of CDK6, although it may play a different role in lymph node metastasis. Collectively, these findings identify PTPRK as a potential prognostic biomarker and therapeutic target. Further investigation is required to elucidate its mechanistic roles and to validate its suitability for targeted therapeutic intervention in pancreatic cancer.

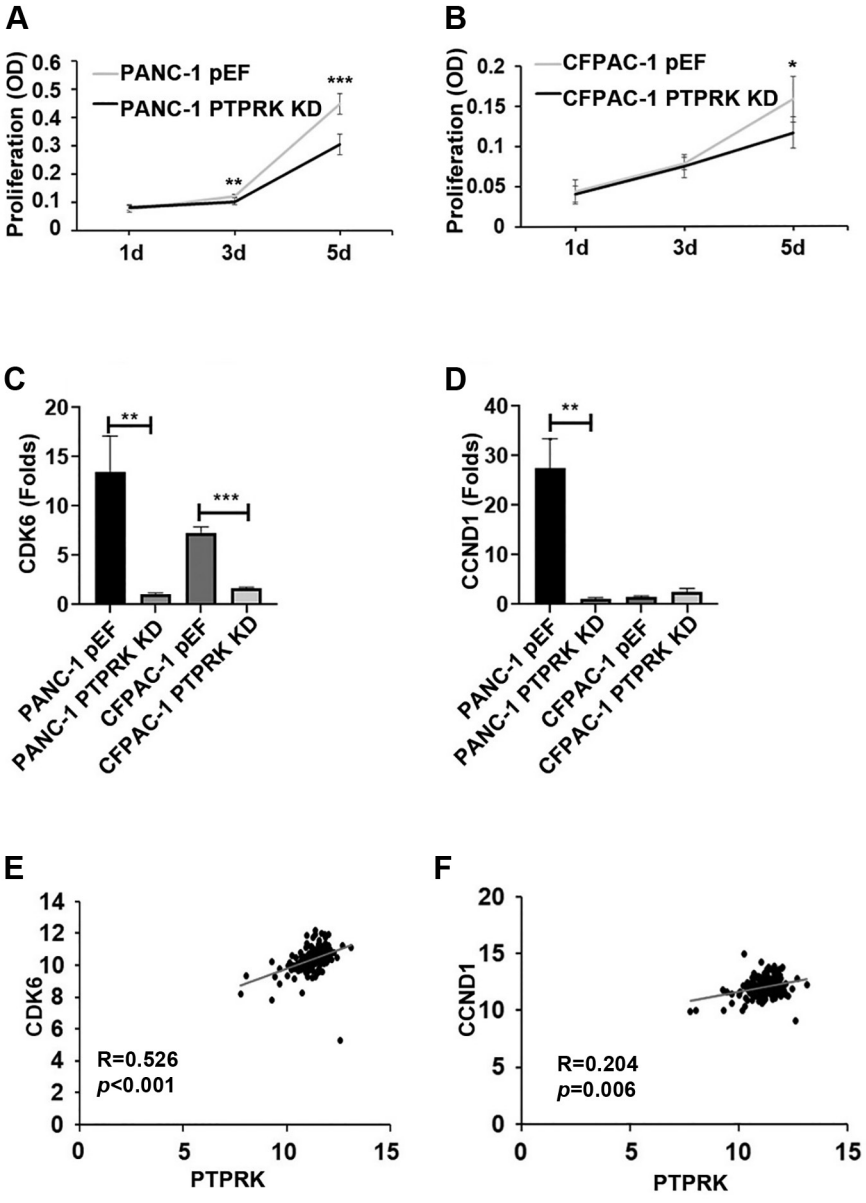

Figure 3. *Protein tyrosine phosphatase kappa (PTPRK) and cell proliferation. (A, B) A proliferation was performed to examine whether PTPRK is associated with pancreatic cell proliferation. (C, D) QPCR results show the expression of CDK6 and CCND1 in control cell lines PANC-1^{pEF}/CFPAC-1^{pEF} and PTPRK knockdown cell lines PANC-1$^{PTPRK\ kd}$/CFPAC-1$^{PTPRK\ kd}$. (E) TCGA dataset is used to draw a scatter plot showing the association between CDK6 and PTPRK at transcripts level. (F) In the TCGA dataset, the association between CCND1 and PTPRK transcript levels is shown. *p<0.05, **p<0.01, ***p<0.001.*

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

LY and WJ conceived the study. XT, CH and WJ collected tissues and performed data analysis. ZF and XL performed

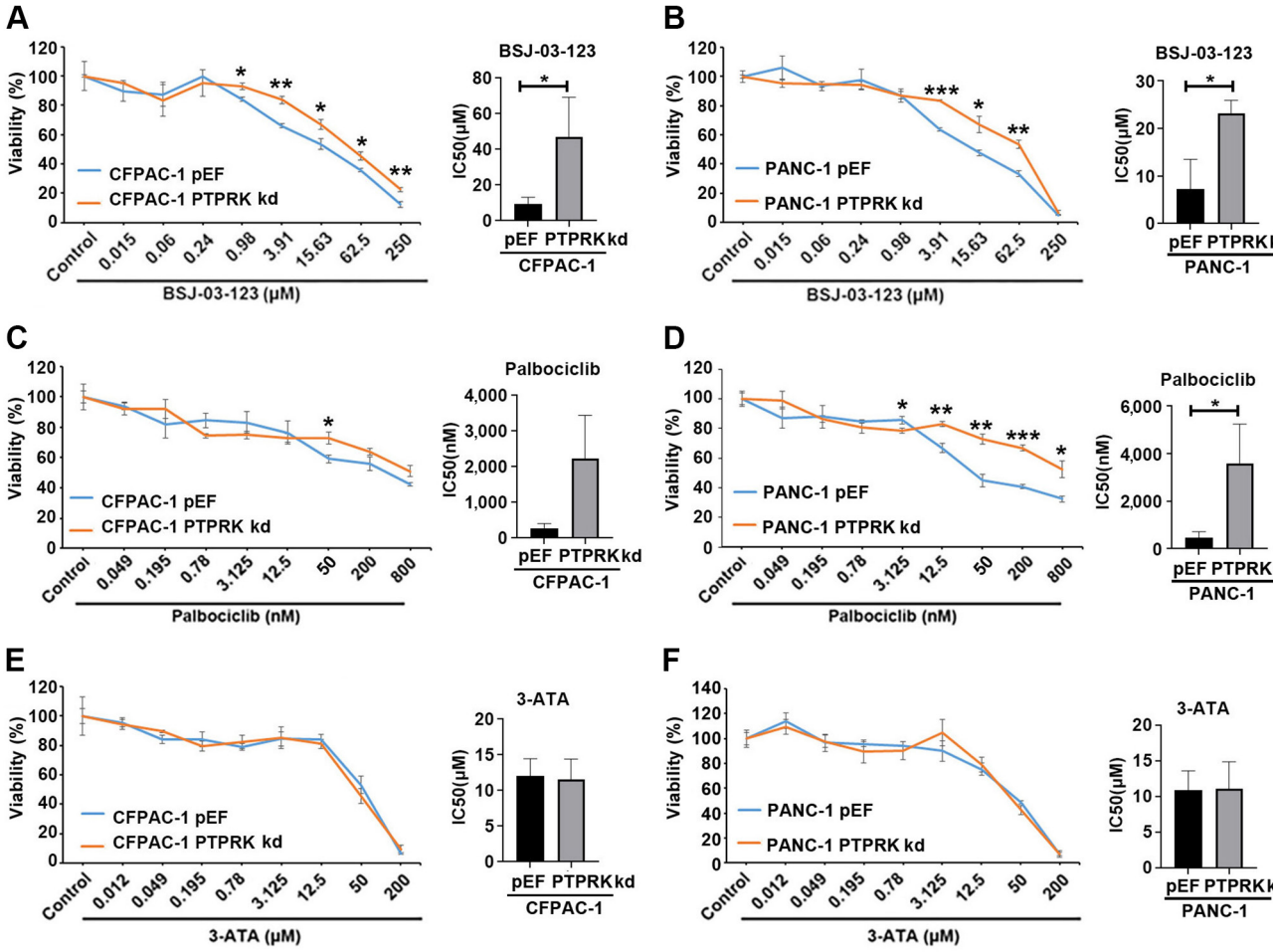

Figure 4. *Response to cyclin-dependent kinase 6 (CDK6) inhibitors in the protein tyrosine phosphatase kappa (PTPRK) knockdown pancreatic cancer cell line models. Both CFPAC-1 and PANC-1 cell lines were treated with different concentration of the CDK6 inhibitor BSJ-03-123 (A and B), CDK4/6 inhibitor Palbociclib (C and D) and CDK4 inhibitor 3-ATA (E and F). Corresponding IC_{50} test results are shown. Cell viability was determined following a 3-day treatment with the inhibitors. *p<0.05, **p<0.01, ***p<0.001.*

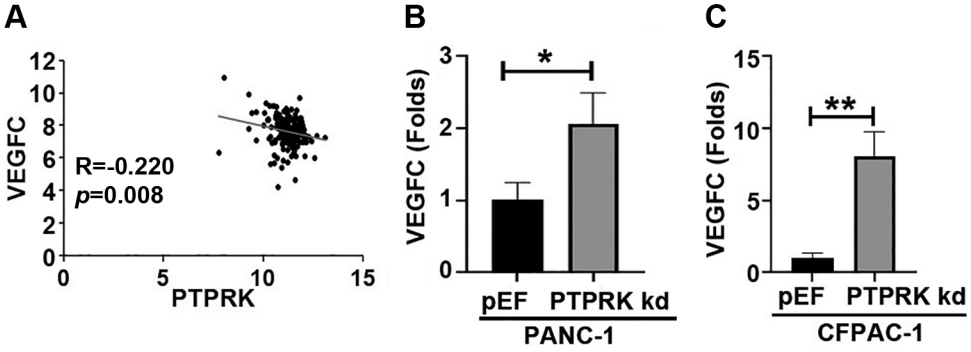

Figure 5. *Protein tyrosine phosphatase kappa (PTPRK) and lymph node metastasis. (A) The scatter plot shows that the lymph angiogenesis marker VEGFC is inversely correlated with PTPRK in the TCGA cohort. QPCR shows the expression of VEGFC in pancreatic cancer cell lines PANC-1 (B) and CFPAC-1 (C) with PTPRK knockdown. *p<0.05, **p<0.01, ***p<0.001.*

experiments and statistical analysis. ZF and XL prepared a draft of the manuscript, which was revised by LY, CH, BA and WJ. All Authors have read and agreed to the published version of the manuscript.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools were used in the preparation of the manuscript and data analysis.

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