Original Article - Urological Oncology

Investig Clin Urol 2025;66:227-235.
https://doi.org/10.4111/icu.20240434
pISSN 2466-0493 • eISSN 2466-054X

INVESTIGATIVE AND CLINICAL UROLOGY
IC UROLOGY

PDK4 expression and tumor aggressiveness in prostate cancer

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Purpose: Prostate cancer ranks as the second most common cancer in men globally, representing a significant cause of cancer-related mortality. Metastasis, the spread of cancer cells from the primary site to distant organs, remains a major challenge in managing prostate cancer. Pyruvate dehydrogenase kinase 4 (PDK4) is implicated in the regulation of aerobic glycolysis, emerging as a potential player in various cancers. However, its role in prostate cancer remains unclear. This study aims to analyze PDK4 expression in prostate cancer cells and human samples, and to explore the gene's clinical significance.

Materials and Methods: PDK4 expression was detected in cell lines and human tissue samples. Migration ability was analyzed using Matrigel-coated invasion chambers. Human samples were obtained from the Kyungpook National University Chilgok Hospital.

Results: PDK4 expression was elevated in prostate cancer cell lines compared to normal prostate cells, with particularly high levels in DU145 and LnCap cell lines. PDK4 knockdown in these cell lines suppressed their invasion ability, indicating a potential role of PDK4 in prostate cancer metastasis. Furthermore, our results revealed alterations in epithelial-mesenchymal transition markers and downstream signaling molecules following PDK4 suppression, suggesting its involvement in the modulation of invasion-related pathways. Furthermore, PDK4 expression was increased in prostate cancer tissues, especially in castration-resistant prostate cancer, compared to normal prostate tissues, with PSA and PDK4 expression showing a significantly positive correlation.

Conclusions: PDK4 expression in prostate cancer is associated with tumor invasion and castration status. Further validation is needed to demonstrate its effectiveness as a therapeutic target.

Keywords: Aggression; Biomarkers; Metastasis; Prostate cancer

INTRODUCTION

Prostate cancer is the second most frequent cancer worldwide and the fifth leading cause of cancer death among men in 2022, with an estimated 1.5 million new cases and 397,000 deaths [1,2]. The major reason for difficulties in cancer management is that cancer cells gain invading ability, leading to metastasis [3]. Cancer metastasis is the dissemination of cancer cells from primary site to distant ones [4]. In the early stages, prostate cancer grows slowly, remain-

Received: December 9, 2024 • **Revised:** January 22, 2025 • **Accepted:** February 20, 2025 • **Published online:** April 7, 2025
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ing a local tumor [5]. However, in the late stages, cancer cells cross the cancer capsule barrier and invade other organs, such as bones, liver, lungs, and lymph nodes, which are the most common locations of metastasis [6,7]. Furthermore, metastases require a complicated treatment approach, declining the patient's quality of life [8,9].

Pyruvate dehydrogenase kinase 4 (PDK4) is a member of pyruvate dehydrogenase kinases (PDKs) that phosphorylate pyruvate dehydrogenase (PDH). PDKs control the switch of aerobic glycolysis by regulating PDH [10]. PDH converts pyruvate to acetyl-CoA to generate cellular energy for cell proliferation [11]. Control of pyruvate oxidation is primarily attributed to PDK-dependent PDH phosphorylation. PDK4 prevents pyruvate from entering the tricarboxylic acid cycle, thus inducing aerobic glycolysis to facilitate the survival and progression of cancer cells [12].

Recently, PDK4 has been associated with various cancers [13-15]. PDK4 participates in cell proliferation, invasion, and chemoresistance in ovarian cancer. In human colon cancer cells, PDK4 is involved in cell transformation [15]. Additionally, PDK4 can promote the growth and cisplatin resistance of lung adenocarcinoma cells via endothelial PAS domain–containing protein 1 (EPAS1) [16]. PDK4 knockdown inhibited cell proliferation and arrested the G_0–G_1 phase in bladder cancer cells [13]. However, the role of PDK4 in prostate cancer has not been completely elucidated. Understanding how PDK4 influences prostate cancer biology could have significant clinical implications. It may uncover novel therapeutic targets for inhibiting tumor growth and metastasis, potentially improving patient outcomes. Additionally, insights gained from studying PDK4 in prostate cancer may have broader implications for understanding the metabolic underpinnings of cancer progression and identifying common pathways for targeting multiple cancer types.

This study aimed to elucidate the role of PDK4 in prostate cancer using both *in vitro* cell line models and human tissue specimens. Accordingly, researchers can assess the potential contributions of PDK4 to disease aggressiveness and treatment resistance by examining its expression and activity in prostate cancer cells and tissues.

MATERIALS AND METHODS

1. Reagents

Anti-PDK4, anti-E-cadherin, anti-vimentin, anti-phospho-ERK, anti-phospho-SRC, and β-actin antibodies were purchased from Abcam. Goat-anti-rabbit and rabbit-anti-mouse IgG horseradish peroxidase–conjugated secondary antibodies were purchased from Invitrogen. Alexa-Fluor™ 594 antibodies, bovine serum albumin, dimethyl sulfoxide (DMSO), and crystal violet solution were obtained from Sigma-Aldrich.

2. Cell culture

RWPE-1, DU145, PC3, and LnCap cell lines were purchased from the American Type Culture Collection (ATCC). Each cell line was maintained in a recommended media (Keratinocyte Serum Free Medium [K-SFM] with a K-SFM growth factor kit for RWPE-1, DMEM-high glucose for DU145 and PC3, and RPMI-1640 for LnCap) from ATCC at 37°C in a humidified 5% CO_2 atmosphere.

3. siRNA treatment

Silencing PDK4 expression using siRNA allows for investigating the functional role of PDK4 in prostate cancer cells. DU145 and LnCap cells were seeded into 6-well plates (3×10^5 cells) and grown up to 70% confluency. The cells were treated with 10 μmol of ON-TARGETplus Human TRPM7 siRNA (4 siRNA sets in a single mixture; Dharmacon) and Lipofectamine™ RNAiMAX Transfection Reagent (Invitrogen) according to the manufacturer's protocol in a serum-free medium. After 24 hours, the serum-free medium was changed to a serum-containing growth medium. The cells were harvested 48 hours and 72 hours after siRNA treatment for protein and mRNA analysis, respectively.

4. Quantitative real-time polymerase chain reaction (qPCR)

RNA extraction was performed by Maxwell® RSC simply RNA cell kit using Maxwell™ 16 instrument (Promega). After RNA concentration measurement, 1 μg of RNA was used to synthesize cDNA using GoScript™ Reverse Transcriptase (Promega). PCR was performed in the StepOnePlus™ Real-Time PCR System (Applied Biosystems). Table 1 lists the primer sequences used.

5. Invasion assay

DU145 and LnCap cells were seeded in a Matrigel-coated 8.0 μm insert (#353097; BD Falcon) with 300 μL of serum-free medium and 700 μL of serum-containing medium and loaded in 12-well plates. After 48 hours of siRNA treatment, invaded cells were stained with crystal violet solution and dissolved in the DMSO for absorbance measurement using a microplate spectrophotometer (wavelength 590 nm; BioTek Instruments).

6. Western blotting analysis

The cells were lysed with RIPA buffer according to the manufacturer's protocol to obtain proteins, followed by load-

https://doi.org/10.4111/icu.20240434

Table 1. The used primer sequences

Gene	Forward (5′ to 3′)	Reverse (5′ to 3′)
E-CADHERIN	GCCTCCTGAAAAGAGAGTGGAAG	TGGCAGTGTCTCTCCAAATCCG
VIMENTIN	AGGCAAAGCAGGAGTCCACTGA	ATCTGGCGTTCCAGGGACTCAT
GAPDH	GTCTCCTCTGACTTCAACAGCG	ACCACCCTGTTGCTGTAGCCAA
PDK4	GTCGAGCATCAAGAAAACCGTCC	GCGGTCAGTAATCCTCAGAGGA

ing 15–20 μg of proteins on the SDS-PAGE gel. After transferring to a PVDF membrane, the membrane was incubated with primary antibody (1:1,000) overnight at 4°C. Then, after washing with TBST (Tris-buffered saline+Tween 20), the membrane was incubated with HRP-conjugated secondary antibody (1:5,000) for 2 hours at room temperature. An electrogenerated chemiluminescence (ECL) reagent (Amersham Life Science) was used to detect the signals. Protein expression was visualized by enhanced chemiluminescence (iBright 1500 Imaging System; Invitrogen).

7. Immunohistochemistry (IHC) staining

Immunohistochemical staining of prostate cancer tissue sections allows for the visualization of protein expression patterns within tumor samples. Tissue samples were fixed in 10% formalin solution to be embedded in paraffin. Tissue sections were cut into 4-μm slices and applied on coated slide glasses. The slides were hydrated and incubated in a citrated buffer solution for antigen retrieval after hydration. Then, a blocking solution (5% bovine serum albumin) was applied to slides for 1 hour at room temperature and incubated with primary antibody (1:100) at 4°C overnight. A secondary antibody (1:1,000) was applied for 2 hours at room temperature, and the slides were mounted with DAPI containing a mounting medium.

8. Patients' samples

The 77 biospecimens and data used for this study were provided by Kyungpook National University Chilgok Hospital, a member of the Korea Biobank Network-KNUH. These were obtained (with informed consent) under Institutional Review Board of Kyungpook National University Hospital approved protocols (approval number: KNUMC 2016-05-021). The patient samples were collected after informed consent for sample donation. The diagnosis of prostate cancer was verified based on the outcomes of pathological analysis. Additionally, all collected biospecimens were stored at a -80°C deep freezer before use. Table 2 lists the baseline characteristics of the 77 patients enrolled in the study.

Table 2. Patients' demographics

Parameter	BPH (n=17)	Pca (n=60)
Age (y)	69.68±6.68	68.76±6.81
PSA level (ng/mL)		
<4	16	1
4.1–10	1	25
10.1–20	-	16
>20.1	-	18
Pathological stage		
T2	-	24
T3a	-	21
T3b	-	15
Gleason score		
6–7	-	35
8–10	-	25

Values are presented as mean±standard deviation or number only.
BPH, benign prostatic hyperplasia; Pca, prostate cancer; PSA, prostate-specific antigen.

9. Statistical analysis

Statistical analysis was used to interpret experimental results and determine the significance of observed differences among treatment groups. The IBM SPSS software version 27 (IBM Corp.) was used to perform one-way ANOVA, which allowed for the comparison of means between the groups. Setting the significance level at $p<0.05$ or $p<0.01$ ensures reliable identification of statistically significant findings.

RESULTS

1. PDK4 expression in normal prostate and prostate cancer cell lines

We performed quantitative real-time PCR and western blot analysis to determine PDK4 expression in normal prostate (RWPE-1) and prostate cancer cell lines (DU145, PC3, and LnCap). PDK4 expression (both mRNA and protein levels) was high in all prostate cancer cell lines used in the study (Fig. 1A). Among the three prostate cancer cell lines, DU145 and LnCap showed extremely high PDK levels compared to RWPE-1 cells. The PC3 cell line also showed high PDK4 expression; however, DU145 and LnCap showed a

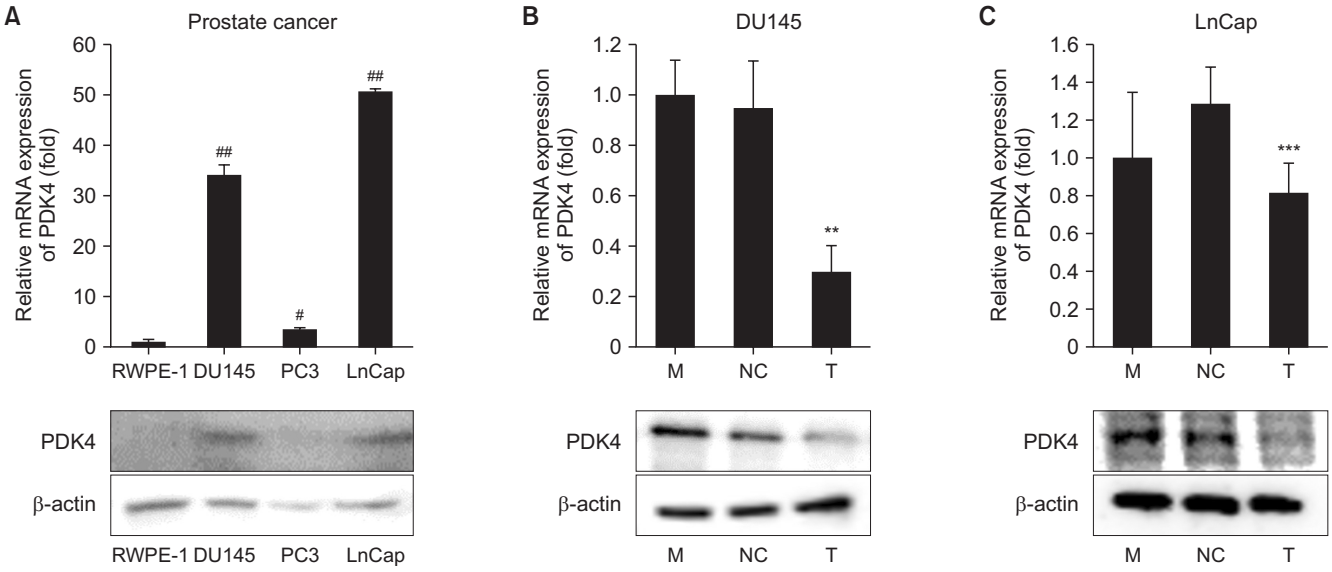

Fig. 1. PDK4 expression in normal prostate and prostate cancer cell lines (A), PDK4 suppression in DU145 (B) and LnCap (C) cells. All data are presented as mean±standard deviation of three independent experiments ($^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ between RWPE-1 and DE145, PC3, and LnCap; **p<0.01, ***p<0.001 between NC and T). PDK4, pyruvate dehydrogenase kinase 4; M, mock; NC, negative control siRNA-treated; T, siRNA-treated.

significantly high PDK4 protein activity. Thus, we treated DU145 and LnCap cells with siRNA for PDK4 downregulation. Moreover, we proceeded to confirmation of suppressed PDK4 expression by using siRNA treatment on DU145 (Fig. 1B) and LnCap (Fig. 1C) cells to clarify the role of PDK4 in prostate cancer.

2. The role of PDK4 in prostate cancer invasion

After confirming PDK4 suppression by siRNA, we performed the invasion assay to explore the role of PDK4 in the migratory ability of prostate cancer cells. In the invasion assay, PDK4 knockout showed low effectiveness in DU145 cells (Fig. 2A). However, PDK4 knockout in LnCap cells suppressed their invasion ability (Fig. 2B). Thus, PDK4 inhibition may play a role in hormone-sensitive cancer. Additionally, we performed further experiments by using LnCap cells. We performed the cell proliferation assay with PDK4 siRNA treatment in DU145 and LnCap cells (data not provided); however, PDK4 suppression showed no significant change in prostate cancer cell proliferation. Therefore, PDK4 was considered to be related to the progression to an aggressive stage, such as metastasis, rather than cancer proliferation.

3. The relationship between PDK4 and prostate cancer

We examined the expression of PDK4 in benign prostatic hyperplasia (BPH), hormone-naïve radical prostatectomy, neo-adjuvant hormone therapy–radical prostatectomy, and castration-resistant prostate cancer (CRPC) (Table 3). As tumor progressed from BPH to CRPC and as prostate-specific antigen (PSA) level increased, the PDK4 mRNA expression level also increased. However, PDK4 was not related to tumor stage, Gleason score, and biochemical recurrence. For PDK4 expression, we proceeded with qPCR and IHC staining using patients' samples. As we expected, PDK4 was highly expressed in prostate cancer that was becoming aggressive (Fig. 3A) and as PSA level increased (Fig. 3B).

DISCUSSION

In recent years, the number of newly diagnosed and clinically recurred prostate cancer patients has been increasing [17]. This surge presents a formidable challenge in the field of cancer treatment, particularly due to the obstacles posed by metastasis and chemoresistance, which significantly impede favorable treatment outcomes in various cancer types [17]. Primary cancer can be cured using local surgical resection or radiation treatment, chemotherapy, and immunotherapy. However, metastatic cancer is a systemic disease [18]. Metastasis, accounting for >90% of cancer-related deaths, is intricately linked with cancer recurrence and represents a pivotal turning point in disease progression [19]. Similar to previous studies, PDK4 was associated with tumor aggressiveness in the present study. Previous research predominantly focused on elucidating the roles of PDK1, PDK2, and PDK3 in various cancers, leaving a significant gap in our understanding of the potential involvement of PDK4, par-

https://doi.org/10.4111/icu.20240434

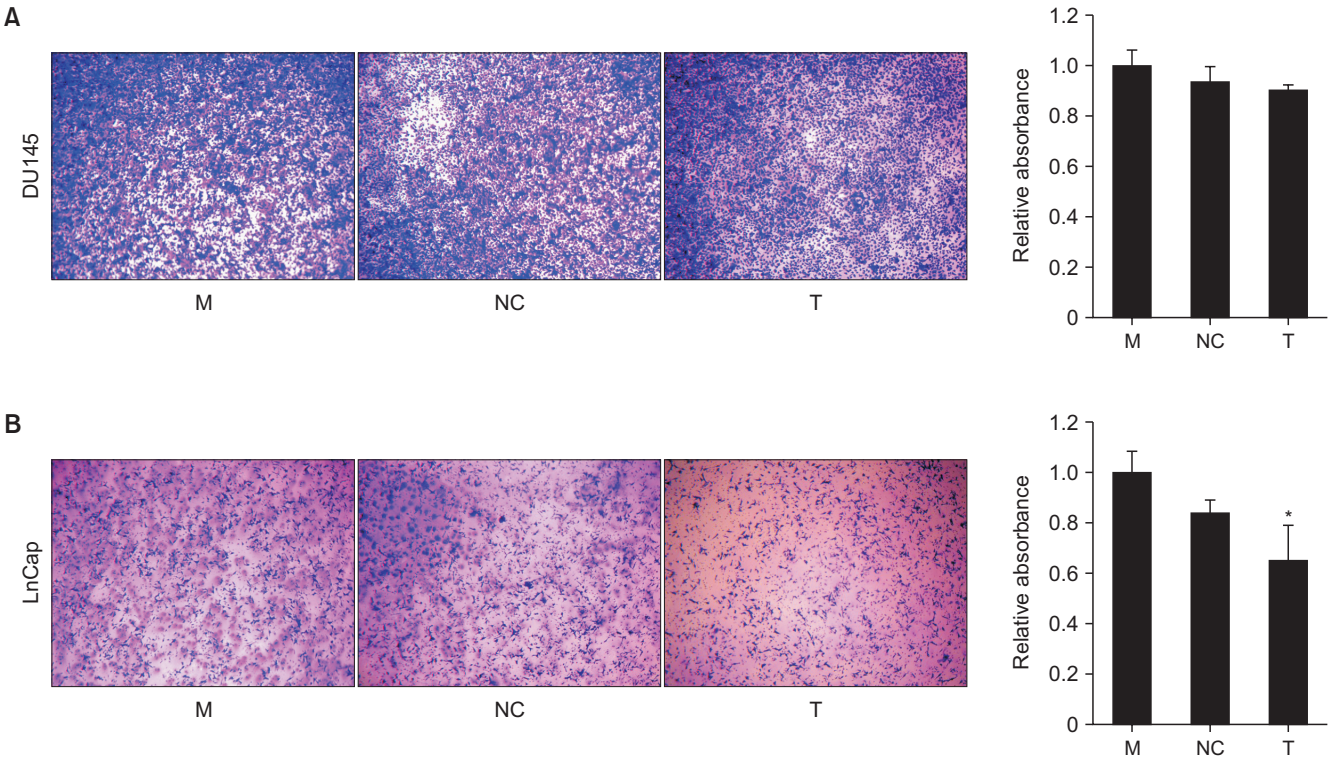

Fig. 2. The invasion assay of DU145 (A) and LnCap (B) cells. The representative images are taken from cells stained with crystal violet solution (magnification, ×4). All data are presented as mean±standard deviation of three independent experiments (*p<0.05 between NC and T). M, mock; NC, negative control siRNA-treated; T, siRNA-treated.

ticularly in prostate cancer metastasis.

Many studies investigated PDK1, PDK2, and PDK3 [20-22] and examined PDK4 in various cancer types [12-14]. However, PDK4 has been poorly researched in terms of metastasis in prostate cancer. The present study demonstrated that PDK4 was highly elevated in the tissue samples of prostate cancer patients and was related to metastasis using the invasion assay and migration-related protein detection. In human samples, PDK4 expression was increased in tumor and CRPC tissues compared to normal ones. Additionally, it showed a significant association with PSA level, reflecting the malignant nature of prostate cancer. Invasion is the first step of cancer cells toward metastasis. After the detachment of cancer cells from the tumor mass, they acquire high motility and start to invade the surrounding tissue by decomposing the adjacent basement membrane [23]. This event differentiates carcinoma *in situ* from invasive carcinoma and is called the epithelial-mesenchymal transition (EMT) [24]. The EMT is characterized by (1) the loss of intercellular adhesion molecules (i.e., E-cadherin), (2) downregulation of epithelial markers (i.e., cytokeratins), and (3) upregulation of mesenchymal markers (i.e., vimentin) [25]. In cell-to-cell adhesion, E-cadherin is a key mediator. Additionally, the loss of E-cadherin may promote invasive and metastatic behavior of epithelial tumor cells [26]. We validated the expression of EMT-related proteins to clarify the function of PDK4 in cancer metastasis. In our results, PDK4 knockdown increased E-cadherin and decreased vimentin levels in western blotting analysis (Fig. 4A).

Moreover, we evaluated PDK4-related mechanisms to deeper study the role of PDK4 in prostate cancer. In PC3 cell lines, PDK4 expression is lower compared to DU145 and LnCaP, which may reflect the unique metabolic characteristics and molecular profile of this cell line. Both PC3 and DU145 are androgen-independent prostate cancer cell lines. However, PC3 cells lack functional androgen receptor (AR) expression entirely, whereas DU145 cells may retain trace levels of AR under certain conditions. These differences in AR signaling, combined with distinct metabolic adaptations, could contribute to the observed variation in PDK4 expression. Further research is needed to elucidate the interplay between AR-independent pathways and PDK4 regulation, as well as the metabolic and molecular differences between these cell lines.

Additionally, pathways involved in cell proliferation and survival may contribute to the observed effects of PDK4. For instance, extracellular signal-regulated kinase (ERK) 1/2 belongs to the mitogen-activated protein kinase (MAPK)

Table 3. PDK4 expression in patients' samples

Parameter	PDK4 expression (fold)	p-value
Patient's status		
BPH	47.66±24.15	-
Radical prostatectomy (hormone naive)	78.83±50.87	0.017
Radical prostatectomy (neo-adjuvant hormone therapy)	91.57±52.68	0.002
CRPC	113.95±57.77	<0.001
PSA level (ng/mL)		
<4	53.35±32.26	-
4.1–10	78.73±60.00	0.101
10.1–20	80.74±44.90	0.026
>20.1	98.17±41.73	<0.001
Radical prostatectomy (hormone-naive)		
Tumor stage		
T2	57.92±58.94	-
T3a	63.36±64.77	0.692
T3b	69.47±41.85	0.296
Gleason score		
6–7	63.00±52.30	-
8–10	67.12±52.41	0.752
Biochemical recurrence		
No	62.38±51.10	-
Yes	64.02±60.39	0.639
Radical prostatectomy (neo-adjuvant hormone therapy)		
Tumor stage		
T2	83.21±53.86	-
T3a	102.86±64.77	0.362
T3b	69.47±41.85	0.451
Gleason score		
6–7	88.22±66.56	-
8–10	82.77±43.47	0.735

Values are presented as mean±standard deviation.
Patient status in the PSA analysis: BPH was used as the comparator group for both radical prostatectomy (hormone-naive) and radical prostatectomy (neo-adjuvant hormone therapy). For the PSA level analysis, a PSA level of <4 ng/mL was used as the comparator group. For the radical prostatectomy (hormone-naive), T2 (tumor stage), 6–7 (Gleason score), and no (biochemical recurrence) were used as the comparator group. For the radical prostatectomy (neo-adjuvant hormone therapy), T2 (tumor stage) and 6–7 (Gleason score) were used as the comparator group.
PDK4, pyruvate dehydrogenase kinase 4; BPH, benign prostatic hyperplasia; CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen.

family. ERK regulates cell proliferation, survival, growth, metabolism, migration, and differentiation. ERK 1/2 belongs to the MAPK family [27]. ERK regulates cell proliferation, survival, growth, metabolism, migration, and differentiation [28]. The role of signal-regulated kinase (SRC) in cancer invasion has been widely studied in diverse cancer types. The importance of SRC has been implicated in proliferation, invasion, metastasis, suppression of apoptosis, and stimulation of cancer cell motility [29]. PDK4 suppression downregulated phosphorylated-SRC, the activated form of SRC (Fig. 4A). In the *in vitro* assay for the mechanism study, PDK4 was highly expressed in cancer cells compared to non-cancer cells. Among LnCap and DU145 cells, only LnCap cells showed a response to PDK4 inhibition. PDK4 downregulation significantly suppressed cancer cell invasion. Hence, PDK4 mediates prostate cancer in the hormonal-sensitive state with AR expression. Recent clinical trials have explored treatments using various agents in hormone-sensitive conditions [30]. Consequently, concurrent targeting of PDK4 holds potential to enhance therapeutic outcomes, though further validation is required.

Our study has several limitations that must be acknowledged. First, while we demonstrated the association of PDK4 with invasion in hormone-sensitive prostate cancer cells, we

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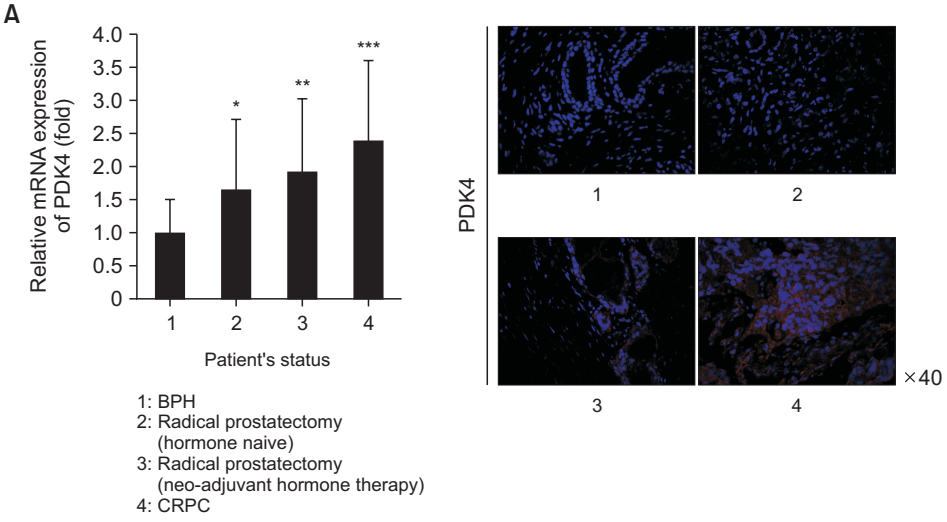

Fig. 3. Representative images of PDK4 expression in human patients' samples. (A) Grouping by the patient's status. (B) Grouping by the PSA level. Magnification ×40. All data are presented as mean±standard deviation of three independent experiments (*p<0.05, **p<0.01, ***p<0.001 between 1 vs. 2, 3, 4 or <4 vs. 4.1–10, 10.1–20, >20.1). PDK4, pyruvate dehydrogenase kinase 4; BPH, benign prostatic hyperplasia; CRPC, castration-resistant prostate cancer; PSA, prostate-specific antigen.

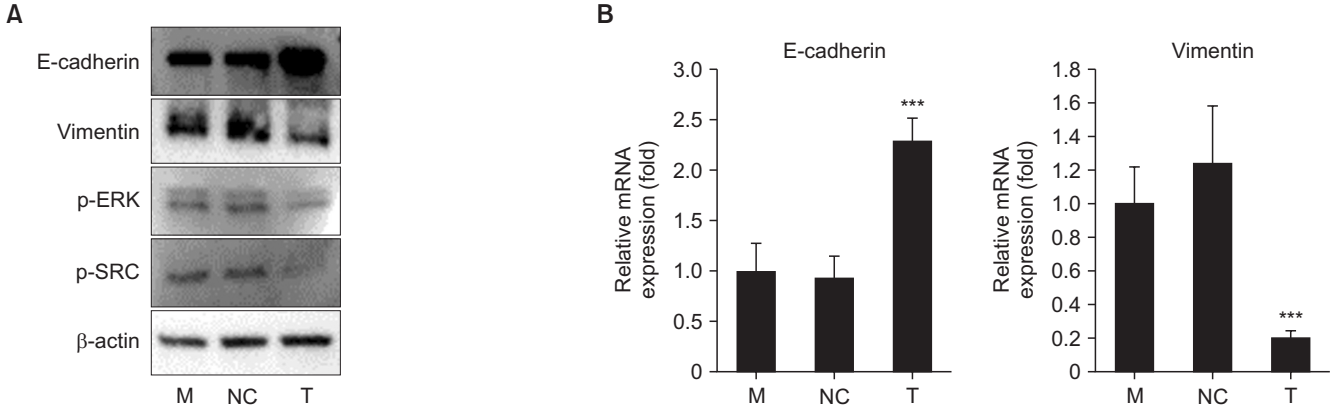

Fig. 4. Invasion-related proteins (A) and mRNA (B) expression in LnCap cells. All data are presented as mean±standard deviation of three independent experiments (***p<0.001 between NC and T). M, mock; NC, negative control siRNA-treated; T, siRNA-treated.

did not include data on metastatic tissues, which limits our ability to fully explore its role in metastasis. The absence of metastatic tissue data particularly affects our understanding of PDK4's role in advanced stages of prostate cancer. Second, the sample size of human tissues was relatively small, potentially affecting the statistical power and generalizability of our findings. Third, while PDK4 expression was found to correlate with PSA levels and prostate cancer progression from BPH to CRPC, no significant association with Gleason score or tumor stage was observed. This lack of correlation suggests that PDK4 may play a role in cancer aggressiveness through mechanisms independent of traditional pathological markers, a hypothesis that requires further investigation. Finally, the lack of functional experiments on PDK4's interaction with AR signaling pathways limits the scope of our conclusions. This represents a critical gap in understand-

ing how PDK4 contributes to prostate cancer progression in hormone-sensitive and castration-resistant states. Future studies addressing these limitations, including *in vivo* models, larger sample sizes, and analyses of metastatic samples, will be essential to validate and expand upon our findings. Additionally, exploring the molecular pathways underlying the observed lack of correlation between PDK4 and Gleason score may uncover novel insights into prostate cancer biology.

CONCLUSIONS

In summary, our study demonstrated that PDK4 is overexpressed in prostate cancer tissues and potentially involved in the regulation of cancer cell invasion. These findings not only enhance our understanding of prostate cancer pathogenesis but also offer potential avenues for developing targeted therapy. Moreover, further research into PDK4-mediated mechanisms in prostate cancer progression holds promise for the development of novel therapeutic interventions aimed at improving patient outcomes.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

FUNDING

This work was supported by a Biomedical Research Institute grant, Kyungpook National University Hospital (2022).

AUTHORS' CONTRIBUTIONS

Research conception and design: Eun Hye Lee, Yun-Sok Ha, and Tae Gyun Kwon. Data acquisition: Bo Hyun Yoon and Minji Jeon. Statistical analysis: Dong Jin Park and Jiyeon Kim. Data analysis and interpretation: Jun-Koo Kang and Jae-Wook Chung. Drafting of the manuscript: Eun Hye Lee and Yun-Sok Ha. Critical revision of the manuscript: Bum Soo Kim and Seock Hwan Choi. Obtaining funding: Yun-Sok Ha. Administrative, technical, or material support: Hyun Tae Kim, Tae-Hwan Kim, and Eun Sang Yoo. Supervision: Yun-Sok Ha and Tae Gyun Kwon. Approval of the final manuscript: Yun-Sok Ha and Tae Gyun Kwon.

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