PTPN3 Inhibits the Growth and Metastasis of Clear Cell Renal Cell Carcinoma via Inhibition of PI3K/AKT Signaling

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Abstract

The underlying molecular mechanism driving clear cell renal cell carcinoma (ccRCC) progression is still to be explored. The significant downregulation of protein tyrosine phosphatase non-receptor type 3 (PTPN3) expression in the tumor tissues suggested its protective role in ccRCC progression. IHC analysis of PTPN3 protein in 172 ccRCC tissue revealed that PTPN3 was an independently favorable prognostic factor for progression-free survival (P = 0.0166) and overall survival (P = 0.0343) of patients. The ccRCC cell lines SN12C, 1932, ACHN, and Caki-1 were used to evaluate, both in vitro and in vivo, the biological roles of PTPN3. We observed that overexpression of PTPN3 significantly inhibited the proliferation, migration, and invasion of ccRCC cells. Furthermore, the inhibition of phospho-AKTThr308 and phospho-AKT Ser473 reversed PTPN3-induced silencing in tumor cell migration. Our work revealed that the overexpression of PTPN3 could suppress kidney cancer progression by negatively regulating the AKT signaling pathway, and served as a favorable prognostic factor in patients with ccRCC. Our findings provided insight that PTPN3 could be a potential target for therapy aiming to inhibit the malignant behaviors of ccRCC.

Implications: PTPN3 is an independent favorable prognostic factor for patients with ccRCC and could be a potential target for therapy aiming to inhibit the malignant behaviors of ccRCC.

Introduction

Kidney cancer represents about 4% of all new cancer diagnoses (1). The most common form of kidney cancer arises from renal epithelium, termed as renal cell carcinoma (RCC; ref. 2). As the most common histologic subtype, clear cell renal cell carcinoma (ccRCC) accounts for 70%–75% of all RCC cases (3). The worldwide incidence and mortality rate of ccRCC has been estimated rising by 2%–3% per decade (4). In spite of the fact that the small renal masses have been more frequently detected in recent year, one third of patients with ccRCC will suffer from metastatic diseases after the diagnosis (5). The treating of metastatic ccRCC still remains a challenge as the underlying mechanism(s) is yet to be elucidated (6, 7).

The PI3K/protein kinase B (also named AKT) signaling pathway has been shown to regulate a series of cellular functions in various types of cancer, including proliferation, autophagy, apoptosis, cell cycle, and metastasis (8, 9). Consequently, several potential therapeutic targets of this signaling pathway have been proposed (10), which have also been found to be activated and playing important roles in ccRCC progression (11, 12).

Protein tyrosine kinases and protein tyrosine phosphatases (PTP) reversibly regulate the phosphorylation of tyrosine proteins, acting as a molecular switch for the regulation of various biological processes (13). As a membrane-associated nonreceptor of PTP, PTPN3 contains a C-terminal phosphatase domain, a middle PDZ domain and an N-terminal FERM domain (14). These three domains involve in the regulation of cellular proliferation and growth (15). As a tyrosine phosphatase, PTPN3 could dephosphorylate several substrates, for example, the EGFR pathway substrate 15 (13). However, its role as a nonreceptor protein tyrosine kinase is still unclear.

Accumulating evidence has suggested an equivocal role of PTPN3 in the progression of a variety of human cancers (13, 14, 16). Li and colleagues found that the ectopic expression of PTPN3 in non–small cell lung cancer cells suppressed cellular motility, proliferation, and tumor growth via the regulation of EGFR endocytic trafficking, degradation, and signaling (13). On the contrary, Hou and colleagues showed that PTPN3 may increase malignant growth by cooperating with its substrate, p38 (16). Gao and colleagues also found that the overexpression of PTPN3 in ccRCC could potentially serve as an independent favorable prognostic factor (17). However, the exact role of PTPN3 in ccRCC remains undetermined.
In this study, through the findings of various investigations, we reported that PTPN3 could suppress ccRCC progression by negatively regulating the AKT signaling pathway, providing insight that PTPN3 could be a potential target for therapy aiming to inhibit the malignant behaviors of ccRCC.

**Materials and Methods**

**Cell lines and culture**

Originally bought from ATCC, ccRCC cell lines SN12C, 1932, Caki-1, ACHN were routinely maintained in liquid nitrogen in our laboratory (17, 18). The cell lines were cultured in DMEM or 1640 (Gibco) supplemented with 10% FBS (Gibco) with 100 μg/mL of penicillin in a humidified atmosphere of 5% CO₂ at 37°C as described previously (19). We used the short tandem repeat (STR) testing to authenticate all cells and make sure that they were maintained Mycoplasma-free.

**Patient tissue samples**

Twelve ccRCC tissues and matched paracancerous tissues were retrieved from the Department of Urology, Sun Yat-sen University Cancer Center (SYSUCC, Guangzhou, China) and stored at −80°C before use for quantitative real-time reverse-transcription PCR (qRT-PCR) analysis. Another cohort of 172 formalin-fixed, paraffin-embedded primary ccRCC specimens collected from the Department of Pathology, SYSUCC was used for IHC evaluation. Written informed consent was obtained from all patients and the study was approved by the ethics committees of SYSUCC as described previously (19).

**RNA isolation and qRT-PCR**

We used TRIzol reagent (Invitrogen) to isolate total RNA. Complementary DNA (cDNA) was synthesized using a reverse transcription kit (K1622, Thermo Fisher Scientific) following the manufacturer’s instructions as described previously (19). qRT-PCR analysis was performed using the SYBR Green PCR Kit (Novazym), and β-actin

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**Figure 1.** PTPN3 mRNA and protein expression levels in ccRCC tissues and cell lines. A, qRT-PCR analysis of PTPN3 mRNA expression levels in ccRCC matched tissues (n = 12). The mRNA levels of PTPN3 in ccRCC tissues were lower than the paired normal tissues (P = 0.0006, paired t test). B, Levels of PTPN3 protein expression in ccRCC tissue chip are shown under both low and high magnifications of a light microscope; low PTPN3 level correlated with shorter overall survival and progression-free survival in patients with ccRCC. C, In ccRCC tissue chip from our hospital, the overall survival (OS) and progression-free survival (PFS) rate were significantly higher in the higher PTPN3 group rate. D, Similarly, using data from the TCGA database, we observed that the overall survival and progression-free survival rate was significantly higher in the higher PTPN3 group.
was used as the internal control. The sequences of real-time PCR primers for β-actin and PTPN3 were as follows: forward: 5′-CAC-CATTGGCAATGACGGGTTC-3′ and reverse: 5′-AGGTCTTGGG-GATGCTGGACGCT-3′, and forward 5′-GGACATGTCAAGACAGAACAGCA-GCAGATG-3′ and reverse 5′-GAAGTCACGAAAATGAGCGGACAGCAG-3′, respectively.

**MTS assay**

The cells were plated into 96-well plates at a density of 2,000 cells/well in 200 μL normal culture medium. Cell growth was determined using MTS (Cell Titer 96 Aqueous One Solution Cell Proliferation Assay solution; Promega), as described previously (19). Every day at the same time, 10 μL of the MTS reagents were added to 100 μL culture medium per well and incubated for 2–4 hours at 37°C. The microplate reader (Bio-Tek EPOCH2) was used to read the OD490 of these cells seeded into 96-well plates. All experiments were repeated three times independently.

**RNA interference**

For transient knockdown of PTPN3, by using the Lipofectamine RNAiMAX Reagent (Invitrogen), siRNAs targeting human PTPN3 were transfected into cells. Gene-Pharma Biological Technology made the siRNAs whose sequences target human PTPN3: 5′-GCCUGUGUA-CAGAUGCUCUAAAT-3′ (si1) and 5′-GCUAGAUUGCCGAGAACA-UATT-3′ (si2), and 5′-CATTAATGTCGGACAAAC-3′ for the negative control sequence.

**Clonogenic assay**

Equal numbers of cells were seeded at a density of 500 cells/mL into 6-well plates and incubated for 10 days at 37°C. At the end of the experiments, the cells were stained with 0.1% crystal violet for 15 minutes. We used the microscope (NIKON ECLIPSE 80i) to count the number of positive colonies, those with >50 cells.

**Lentiviral transduction studies**

PTPN3-overexpressing plasmid or vector were purchased from Genecopoeia Co. Ltd. as described previously (19). Lentiviruses were produced in 293 T cells co-transfected with lentiplasid and packing plasmids using the X-treme GENE DNA transfection reagents (Roche). The cells were first incubated with infectious lentiviruses for 12 hours and then exchanged to incubation with fresh medium for another 12 hours, after which they were selected with puromycin (2 ng/L) for 3 days and validated by qRT-PCR and immunoblotting (19).

**Western blot analysis**

The primary antibodies used were PTPN3 (#GTX54572, GeneTex), GAPDH (#60040-1-Ig, ProteinTech), Phospho-AKT (Thr308; #13038, Cell Signaling Technology), Phospho-AKT (Ser473; #4060P, Cell Signaling Technology), AKT (#60203-2-Ig ProteinTech). We purchased the horseradish peroxidase–conjugated goat anti-rabbit or anti-mouse secondary antibodies from Vazyme Biotech. Proteins were visualized with an enhanced chemiluminescence detection system (Bio-Rad) as described previously (19).

**Migration and invasion assays**

A total of 5 × 10⁴ cells of ACHN, 3 × 10⁴ cells of Caki-1, 4 × 10⁴ cells of SN12C, or 2 × 10⁴ cells of 1932 were seeded in a serum-free medium in the top chambers (Corning) with 700 μL of DMEM with 10% FBS in the bottom chambers. After culturing for 24 hours, the cells were fixed with methanol and then they were stained with 0.1% crystal violet for 30 minutes at room temperature. For invasion assays, the top chamber membranes were coated with Matrigel (Corning, Life Sciences). Three random fields per well were observed, and cells were counted under a microscope (NIKON ECLIPSE 80i) as described previously (19). The inhibitor of AKT–MK-2206 (1 μmol/L) was purchased from Selleck Chemicals. Both experiments were performed in triplicates.

**Wound healing assays**

Cells were seeded into 6-well plates (Corning) and cultured to a 90% confluent followed by 24-hour starvation in a serum-free medium. We used the sterile 200-μL tip to create artificial wounds in the cell monolayer and the floating cells were removed by washing with PBS as described previously (19). We used an inverted microscope (OLYMPUS IX73) to capture respective images at 0, 6, 12, 24, 48, 72, and 96 hours.

**IHC staining**

Rabbit anti-PTPN3 antibody (1:100 dilution, #GTX54572, GenTex) was used, and the IHC staining results were assigned a mean score considering both the intensity of staining and the proportion of tumor cells with an unequivocal positive reaction as described previously (19). Two pathologists without prior knowledge of patient data assessed each section independently. The percentage of stained cells was scored as follows: 0% as 0; 1%–10% as 1; 11%–25% as 2; 26%–50% as 3; 51%–75% as 4; >75% as 5.

**Table 1. Association between expression of PTPN3 and clinicopathologic characteristics in 172 patients with ccRCC.**

<table>
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<tr>
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<td>65</td>
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Table 2. Univariate and multivariate analyses of different parameters for overall survival (OS) and progression-free survival (PFS) of patients with ccRCC.

<table>
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<th>Multivariate analysis</th>
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<td>HR (CI)</td>
<td></td>
<td>HR (CI)</td>
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<tr>
<td>OS</td>
<td></td>
<td></td>
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<tr>
<td>Fuhrman score</td>
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<td>&lt;0.001</td>
<td>2.322 (1.519–3.550)</td>
<td>&lt;0.001</td>
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<tr>
<td>Sarcomatoid differentiation score</td>
<td>6.031 (1.847–19.692)</td>
<td>0.001</td>
<td>1.695 (0.423–6.788)</td>
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<tr>
<td>PTPN3 level</td>
<td>0.504 (0.264–0.962)</td>
<td>0.034</td>
<td>0.568 (0.294–1.099)</td>
<td>0.071</td>
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<tr>
<td>PFS</td>
<td></td>
<td></td>
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<tr>
<td>Fuhrman score</td>
<td>2.13 (1.420–3.194)</td>
<td>&lt;0.001</td>
<td>2.017 (1.356–2.999)</td>
<td>0.001</td>
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<tr>
<td>Sarcomatoid differentiation score</td>
<td>5.69 (1.753–18.477)</td>
<td>0.001</td>
<td>1.719 (0.435–6.788)</td>
<td>0.435</td>
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<tr>
<td>PTPN3 level</td>
<td>0.483 (0.283–0.888)</td>
<td>0.017</td>
<td>0.527 (0.285–0.974)</td>
<td>0.047</td>
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</table>

Note: Statistical significance (P < 0.05) is shown in bold. Abbreviation: CI, confidence interval.

50% as 2; 51%–80% as 3; 81%–100% as 4, and the intensity of staining: no staining as 0; weak staining as 1; moderate staining as 2; strong staining as 3. Then multiplying the two was the score of each tissue (score range: 0–12).

Animal experiments

Female athymic mice between 4 and 6 weeks of age were obtained from Beijing Vital River Laboratory Animal Center. Mice were cared in accordance with the principles and procedures outlined in the Institutional Animal Care and Use Committee of SYSUCC as described previously (19). A total of 8 × 10^6–15 mL SN12C cells stably expressing scrambled shRNA control or shPTPN3 were injected subcutaneously into the mice. Ten days after the injection, the mice were sacrificed and the tumors were excised and measured. We injected SN12C kidney tumor cells persistently expressing scrambled shRNA control or shPTPN3 into the mice. We also analyzed the gene expression data of patients with ccRCC in the TCGA database. PTPN3 mRNA was found to be significantly lower in tumor tissues as compared with their corresponding adjacent normal renal tissues in the 12 matched human ccRCC tissues (Fig. 1A). We also performed IHC staining in 172 human ccRCC samples (Fig. 1B) to evaluate the expression level of PTPN3 in ccRCC tissue. PTPN3 was mainly expressed in the cytoplasm of tumor cells in those IHC-stained human ccRCC tissue samples. The association between PTPN3 expression and clinicopathologic features to survival results are summarized in Tables 1 and 2. Patients with tumors having high PTPN3 expression (cut-off score > 6) had significantly longer progression-free survival (PFS) and overall survival (OS) than those with low PTPN3 expression tumors (Fig. 1C; P = 0.0343 vs. P = 0.0166). Multivariate analyses revealed that high PTPN3 expression was an independent and favorable prognostic indicator for PFS (P = 0.047) in all patients (Table 2).

We also analyzed the gene expression data of patients with ccRCC in the TCGA database. PTPN3 mRNA was found to be significantly lower in all tumor samples than in paired normal tissues (Supplementary Fig. S1A–S1C; P < 0.05). For separating the cases into low and high PTPN3 expression groups, the mean expression level was used as the cut-off value. Kaplan–Meier survival analyses of TCGA data also showed that lower expression of PTPN3 was associated with poorer survival in ccRCC (Fig. 1D; P < 0.0001). These observations suggest that low levels of PTPN3 may act as a novel prognostic factor for patients with ccRCC.

Knocking down PTPN3 promotes ccRCC cell growth in vitro and in vivo

As is known to us, 1932 and SN12C were derived from primary human RCC, Caki-1 was a widespread model line of metastatic ccRCC, and ACHN was model line of metastatic papillary RCC (20). We transfected SN12C and 1932 cells with siRNA for PTPN3 (si1# and si2#) or negative control siRNA (Fig. 2A and B). PTPN3 suppression significantly increased RCC cell colony formation and proliferation (Fig. 2C) abilities of these two cell lines (Supplementary Fig. S2). Furthermore, PTPN3 was stably overexpressed in SN12C, Caki-1, and ACHN cell lines (Fig. 2D) and overexpressing PTPN3 effectively suppressed cell proliferation (Fig. 2E) and decreased colony formation ability (Fig. 2F). In addition, the overexpression of PTPN3 significantly inhibited tumor growth in nude mice (Fig. 2G and F). Taken together, these results suggested that PTPN3 can act as a tumor suppressor in the development of RCC.
PTPN3 Inhibits the Growth and Metastasis of ccRCC

Figure 2.
Suppression of PTPN3 promotes RCC cell growth in vitro and in vivo. A, Suppression of PTPN3 in RCC cells were determined by real-time quantitative PCR, normalized to β-actin. B, Suppression of PTPN3 in RCC cells were determined by immunoblotting analysis, GAPDH was used as a loading control. C, Suppression of PTPN3 promotes cells proliferation was determined by the MTS assay; ***P < 0.001, results of Student t test for each paired samples on day 4 or day 5 from three independent experiments. D, Overexpression of PTPN3 in RCC cells were determined by immunoblotting analysis, GAPDH was used as a loading control. E, Overexpression of PTPN3 inhibits cells proliferation was determined by the MTS assay; ***P < 0.001, results of Student t test for each paired samples on day 4 or day 5 from three independent experiments. F, Overexpression of PTPN3 promotes cells proliferation was determined by the MTS assay; ***P < 0.001, results of Student t test for each paired samples on day 4 or day 5 from three independent experiments. G, Overexpression of PTPN3 in SN12C cells and the vector control cells were subcutaneously injected into nude mice. H, The terminal tumor weights are decreased compared with the control group (***, P < 0.001, result of Student t test).
Figure A shows images of cell migration and invasion from 1932 and SN12C cell lines under different conditions. Figure B displays bar graphs comparing the migration and invasion rates of these cell lines. Figure C illustrates the effects of Vector and PTPN3 on ACHN and SN12C cells. Figure D presents a bar graph showing the comparison of Vector and PTPN3 in terms of migration and invasion. Figure E and F depict the cell morphology under different conditions over time. Figure G shows images of SN12C cells transfected with Vector and PTPN3. Figure H is a scatter plot showing the lung metastases per mouse for SN12C-Vector and SN12C-PTPN3 groups, with a statistical significance of P = 0.0367.
PTPN3 inhibits ccRCC cell migration, invasion, and metastasis

We performed wound-healing, transwell migration, and invasion assays to examine whether PTPN3 influences renal cell carcinoma cellular mobility. Findings from these assays revealed that the knockdown of PTPN3 with siPTPN3 increased the migration and invasion of renal cell carcinoma cells transfected (Fig. 3A, B, and E). Accordingly, the overexpression of PTPN3 significantly decreased the migration and invasion of ACHN and SN12C cells (Fig. 3C, D, and F). Furthermore, the tail veins and lung metastatic in vivo experiments in nude mice showed that the number of lung metastatic tumors were significantly fewer in the SN12C-PTPN3 group than the control group (P < 0.05; Fig. 3G and H). Taken together, these results showed an important inhibitory role of PTPN3 in the migration, invasion, and metastasis of ccRCC cells.

Figure 4.
PTPN3 inhibits RCC cellular growth, migration, and invasion through suppression of the PI3K/AKT signaling. A, Western blot analysis of AKT, P-AKTThr308, and P-AKTSer473 expression levels after overexpression of PTPN3 and silencing of PTPN3 from independent experiments. B, The expression of the PI3K/AKT signaling in PTPN3 silencing 1932 and SN12C cells after MK-2206 treatment was detected by immunoblotting from independent experiments. After treatment with 1 μmol/L of MK-2206 or PBS for 24 hours, cell lysates were harvested for Western blot detection. Relative gradation corrected by GAPDH is shown below each band.

PTPN3 inhibits ccRCC cell migration, invasion, and metastasis

Protein kinase B (also named AKT) is an important mediator of cell proliferation, apoptosis, autophagy, and metastasis. Here, we found that silencing PTPN3 in the 1932 and SN12C cells could enhance the expression of phospho-AKTThr308 and phospho-AKTSer473 (Fig. 4A). Conversely, the expression of phospho-AKTThr308 and phospho-AKTSer473 in 1932 and SN12C cells were decreased by overexpressing PTPN3 (Fig. 4A). Furthermore, we found that treatment with MK-2206 decreased phospho-AKTThr308 and phospho-AKTSer473 in SN12C-siPTPN3 and 1932-1-siPTPN3 cells (Fig. 4B). These results suggest that PTPN3 had some negative effects on the PI3K/AKT signaling pathway in RCC cells. PTPN3 seemed increased by the treatment of AKT inhibition for 1932 cell line, while this experimental
Phenomenon could not be repeated for SN12C cell line. In addition, we found that AKT inhibition by MK-2206 impaired the migration and invasion of SN12C-siPTPN3 and 1932-siPTPN3 cells (Fig. 5A and B), as well as the proliferation of SN12C-siPTPN3 and 1932-siAKT cells (Fig. 5C and D). These results illustrate that the knockdown of PTPN3 stimulated RCC cells’ growth, migration, and invasion through the activation of the AKT pathway.

**Discussion**

Although metastases cause the most death in patients with ccRCC, the detailed mechanisms of metastasis remain unclear (6, 7). In this study, we revealed that the expression of PTPN3 was downregulated in ccRCC cell lines and tissue samples. Also, the overexpression of PTPN3 inhibited renal cell carcinoma cell growth, migration, and invasion, and resulted smaller subcutaneous tumors and fewer metastases.
PTPN3 inhibits the growth and metastasis of ccRCC

PTPN3 Inhibits the Growth and Metastasis of ccRCC

PTPN3 was actually an inhibitor for AKT pathway in ccRCC upon controlling cellular proliferation and motility.

Conclusions

PTPN3 inhibits RCC cells’ growth, migration, and invasion via downregulation of the AKT pathway.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: X.-S. Peng, C.-N. Qian
Development of methodology: X.-S. Peng, J.-P. Yang, Y.-Y. Qiang, M.-D. Wang, C.-N. Qian
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X.-S. Peng, J.-P. Yang, Y.-Y. Qiang, L.-S. Zheng, L.-X. Peng, Y. Mei, D.-F. Meng, Z.-J. Liu, F.-J. Zhou, C.-N. Qian
Writing, review, and/or revision of the manuscript: X.-S. Peng, J.-P. Yang, Y. Mei, D.-F. Meng, C.-N. Qian
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): X.-S. Peng, J.-P. Yang, Y.-Y. Qiang, R. Sun, Y. Cao, L.-S. Zheng, L.-X. Peng, Y.-H. Lang, Y. Mei, D.-F. Meng, C.-N. Qian
Other (contributed reagents/materials/analysis tools): C.-Z. Li

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References


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