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Original Article

Clinical significance of PTBP1 in renal carcinoma and a biological study on promoting proliferation of renal carcinoma

Guoying Zhang, Yu Bai, Ruiqian Li, Bin Zhao, Chen Hu, Jun Li

Department of Urology, The Third Affiliated Hospital of Kunming Medical University, Kunming 650018, Yunnan, China

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Abstract: This study aimed to investigate the clinical value and mechanism of polypyrimidine tract-binding protein 1 (PTBP1) in renal cell carcinoma (RCC). Fifty-six cases of cancer tissues and 56 cases of adjacent normal tissues were collected from patients undergoing RCC surgery. RCC cells were purchased and PTBP1 expression was detected by Western blot (WB), and the clinical value of PTBP1 for renal cancer was analyzed. Cells with the greatest difference in PTBP1 expression (SGC-7901) were selected from the purchased RCC cells for PTBP1 inhibition treatment. Cell proliferation, invasion and apoptosis were observed by CCK-8, Transwell and flow cytometry, respectively. Changes of PTEN/Akt pathway markers (p-Akt, PTEN) in cells after WB treatment were observed. PTBP1 was up-regulated in RCC tissues and cells and correlated with tumor diameter, degree of differentiation, TNM and lymph node metastasis. High expression of PTBP1 indicates a poor prognosis of patients. SGC-7901 inhibited proliferation and invasion after transfecting si-PTBP1, but increased apoptosis rate, increased p-Akt in cells and decreased PTEN. PTBP1 is up-regulated in RCC, and its high expression indicates a poor prognosis of patients. PTBP1 can promote RCC cell proliferation and invasion through PTEN/Akt pathway, and PTBP1 is expected to be a therapeutic target for RCC.

Keywords: PTBP1, renal carcinoma, cell biological function, prognosis

Introduction

Renal carcinoma is a common fatal urological malignancy. It was estimated that in 2018, there were about 400,000 new renal carcinoma cases and 170,000 related deaths [1]. Renal cell carcinoma (RCC) is the most common renal carcinoma, accounting for about 80% of all renal carcinomas [2]. At present, surgery is the only recommended treatment for RCC, but 20-30% of patients will relapse after surgery, resulting in poor prognosis [3]. In addition, since there are no typical disease features in the early stage, and it has high metastasis and invasion, and as such most RCC patients are not qualified for surgery by the time they are diagnosed [4]. Therefore, it is urgent to find new drug therapeutic targets. Polypyrimidine tract-binding protein 1 (PTBP1) is an RNA binding protein that can control the splicing, translation, stability and location of mRNA [5]. PTBP1 can participate in various cellular biological events, such as cell growth, apoptosis and cycle [6-8]. PTBP1 is considered to be a cancer-promoting factor; first reported in glioblastomas and then found to play a cancer-promoting role in other cancers such as colon cancer, lung cancer, liver cancer and breast cancer [9-13]. Previous studies have found that PTBP1 is also elevated in RCC, but the mechanism is not fully elucidated [14]. Since the mechanism of PTBP1 in RCC has not been fully clarified, this article explores the role of PTBP1 in RCC, aiming at finding therapeutic targets for RCC.

Materials and methods

Source of RCC tissue

This research was approved by the Medical Ethics Association of Gongan Hospital of Traditional Chinese Medicine. The subjects were 56 RCC patients treated in Gongan Hospital of traditional Chinese Medicine from November

2013 to June 2015. Inclusion criteria: patients were more than 18 years old; RCC was confirmed by pathological examination; patients met the TNM staging diagnostic criteria issued by AJCC in 2017 [15], patients and their family had signed an informed consent form; and they had complete clinical data. Exclusion criteria are as follows: patients complicated with other malignancies; patients with heart and liver function diseases; patients with infection before admission; patients who were not treated with surgery, chemotherapy or radiotherapy; expected survival time was less than 3 months.

Cancer tissues and adjacent normal tissues were collected during the operation, all tissues were frozen in liquid nitrogen, and then stored at -80°C for further use. The patients were followed up for 3 years, and the overall survival rate (OS) and relapse-free survival rate (RFS) were recorded by telephone calls and outpatient follow-up, with follow-up duration being every month.

Cell source and treatment

Cell source and culture: renal cell cancer cell lines ACHN, A498, A704, 786-0 and GES-1 were all purchased from human renal epithelial cells HK-2 in ATCC database. The above five cell lines were grown in RPMI 1640 medium (Gibco Company, USA) containing 10% bovine fetal serum, and then cultured in 37°C incubator (5% CO_2). Cell transfection: cells were adjusted to 2×10^5/well and inoculated into a 6-well plates in an incubator at 37°C overnight. Cells were transfected with Lipofectamine™ 2000 kit (Thermo Fisher Scientific, USA), and PTBP1 (si-PTBP1) inhibition and blank vector (si-NC) transfection were established using pcDNA 3.1 plasmid as vector, respectively, and then they were transferred to normal (10% bovine fetal serum DMEM) culture medium 6 h after transfection.

PTBP1 detection

PTBP1 in tissues and cells was detected by Western blot (WB). The total protein in cultured cells and pulverized tissues was extracted by RIPA lysis, and then protein concentration was detected by BCA method and adjusted to 4 μg/μL. The proteins were separated by 12% SDS-PAGE electrophoresis and then transferred to a PVDF membrane. The membrane was blocked for 2 h with 5% skim milk powder, and then PTBP1 (1:500), p-Akt (1:500), PTEN (1:500), β-Actin (1:2000) (Abcam, USA) primary antibodies were added to incubate overnight at 4°C. The membrane was washed with PBST to remove excess primary antibody, the horseradish peroxidase labeled goat anti-rabbit secondary antibody (1:2000) (Abcam, USA) was added for a one-hour incubation at 37°C, and then it was rinsed 3 times with PBS, each time for 5 min. The protein bands on the membrane developed in a dark room using the enhanced chemiluminescence reagent, and the excess liquid on the membrane was absorbed with filter paper. The protein bands were scanned and the gray value was analyzed using Quantity One. The relative expression level of each protein = the gray value of the target protein band/the gray value of the β-Actin protein band.

Cell proliferation detection

Cells were collected 24 h after transfection, adjusted toa concentration of 4×10^6 cells, inoculated in 96-well plates, and then cultured for 0 h, 24 h, 48 h, 72 h. Altogether 10 μL CCK solution and 90 μL basic medium (DMEM) were added to each well, cultured 2 h at 37°C, and then OD values of cells in each group were measured under 450 nm absorbance using an enzyme reader.

Cell invasion detection

Cells transfected for 24 h were collected, and they were adjusted to 5×10^4 and inoculated on a 6-well plate. They were washed with PBS twice and then inoculated on the upper chamber. A total of 200 μL DMEM culture solution was added to the upper chamber, and 500 mL DMEM (containing 20% FBS) was added to the lower chamber; they were cultured at 37°C for 48 h. Then the matrix was wiped clear of those cells in the upper chamber that did not pass through the membrane surface, washed with PBS for 3 times, fixed 10 min with paraformaldehyde, washed 3 times with double distilled water, and stained with 0.5% crystal violet after it was dried; the cell invasion was observed with a microscope.

Cell apoptosis detection

Transfected cells were digested with 0.25% trypsin, washed twice with PBS after digestion, mixed with 100 μL of binding buffer, prepared into 1×10^6/mL suspension, sequentially added

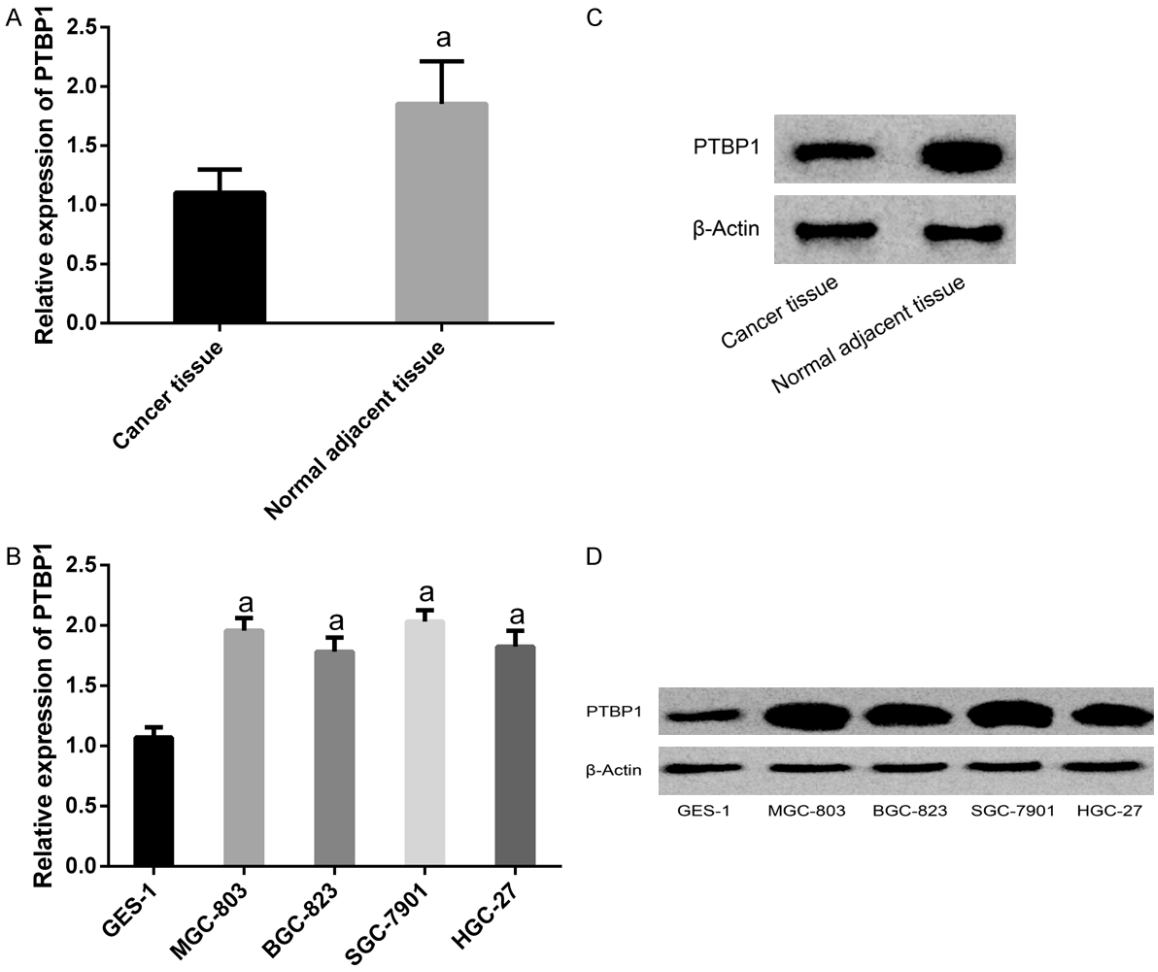

Figure 1. PTBP1 expressed in RCC tissues and cells. A. PTBP1 was elevated in cancer tissues. B. PTBP1 was elevated in the four RCC cells. C, D. WB diagram 'a' stands for $P < 0.05$.

with AnnexinV-FITC and PI, incubated 5 min in the dark at room temperature, and detected with FC500MCL flow cytometer. The experiment was repeated 3 times and results were averaged.

Statistical methods

The data collected in this paper were statistically analyzed by SPSS 20.0, and the required figures were made with GraphPad 7. The intergroup comparison was analyzed by independent-samples T test, and the multi-group comparison was assessed by one-way analysis of variance (ANOVA) and expressed by F; LSD-t test was used for post hoc pairwise comparison, and repeated measures ANOVA was used for multi-time point expression, expressed by F. Bonferroni was used for back testing, OS and RFS for 3 years were drawn by K-M survival curve, Log-rank test was used for analysis, and Cox regression equation test was used for independent prognostic factors of RCC. A *p* value lower than 0.05 indicated that data were statistically different.

Results

PTBP1 expression in RCC tissues and cells

In this paper, 56 cases of RCC patients' cancer tissues and adjacent tissues were investigated by WB, and PTBP1 was found to be elevated in cancer tissues ($P < 0.05$). Subsequently, the PTBP1 expression levels in RCC cell lines MGC-803, BGC-823, SGC-7901, HGC-27 and normal gastric mucosa cell GES-1 were detected, and PTBP1 was also found to be elevated in the above four RCC cell lines ($P < 0.05$). More details were shown **Figure 1**.

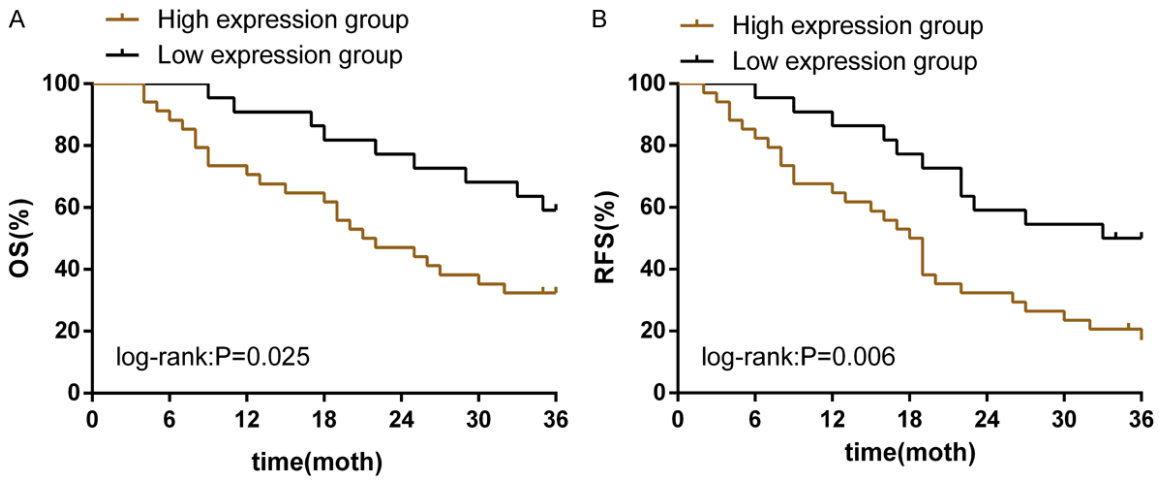

Figure 2. Relationship between PTBP1 and patients' 3-year relapse-free survival and overall survival rate. A. The 3-year overall survival rate in the high expression group was lower than that in the low expression group (log-rank: P=0.025). B. The 3-year relapse-free survival time of high expression group was lower than that of low expression group (log-rank: P=0.006).

Table 1. Relationship between PTBP1 and clinicopathological parameters of patients (x ± sd)

Group	PTBP1	t	P
Age		0.798	0.429
< 60 years old (n=24)	1.765±0.245		
≥ 60 years old (n=32)	1.823±0.286		
Gender		0.686	0.496
Male (n=36)	1.811±0.289		
Female (n=20)	1.759±0.237		
Tumor diameter		2.492	0.016
≤ 5 cm (n=21)	1.705±0.238		
> 5 cm (n=35)	1.887±0.279		
Degree of differentiation		2.614	0.012
High, moderate (n=31)	1.713±0.241		
Low (n=25)	1.892±0.271		
TNM staging		2.426	0.019
I, II (n=26)	1.760±0.262		
III, IV (n=30)	1.936±0.278		
Lymph node metastasis		2.566	0.013
Yes (n=27)	1.911±0.271		
No (n=29)	1.727±0.265		

Relationship between PTBP1 and patients' 3-year relapse-free survival and overall survival rate

According to the median of PTBP1 expression, patients were divided into high expression group (n=34) and low expression group (n=22). The 3-year relapse-free survival and overall survival curves of the two groups were plotted. The 3-year overall survival rate of the high expression group was 32.35% (11/34) lower than that of the low expression group (59.09% (13/22), (Log-rank: P=0.025)). The 3-year relapse-free survival rate in the high expression group was 17.65% (6/34) lower than that in the low expression group (50.00% (11/22), (log-rank: P=0.006)). More details were shown **Figure 2**.

Relationship between PTBP1 and clinical pathological parameters of patients

Analysis of the relationship between PTBP1 and clinical pathological parameters of patients showed that PTBP1 had higher expression in tumor diameter lower than 5 cm, low degree of differentiation, TNM stages in III, IV and tissues of patients with lymph node metastasis, which indicated that PTBP1 was closely related to tumor diameter, degree of differentiation, TNM and lymph node metastasis and might participate in RCC development. More details were shown in **Table 1**.

Analysis of factors affecting prognosis of patients

The clinical data and pathological parameters of patients were analyzed by multiple factors, and it was found that degree of differentiation, TNM staging and PTBP1 might be potential factors affecting prognosis. Then, the above three factors were analyzed by Cox regression equa-

Table 2. Univariate analysis on prognosis of patients

Group	Number of cases survived in 3 years	χ^2	P
Age		0.492	0.483
< 60 years old (n=24)	9 (37.50)		
≥ 60 years old (n=32)	15 (46.88)		
Gender		0.784	0.376
Male (n=36)	17 (47.22)		
Female (n=20)	7 (35.00)		
Tumor diameter		2.800	0.094
≤ 5 cm (n=21)	12 (57.14)		
> 5 cm (n=35)	12 (34.29)		
Degree of differentiation		5.419	0.020
High, moderate (n=31)	9 (29.03)		
Low (n=25)	15 (60.00)		
TNM staging		6.916	0.008
I, II (n=26)	16 (61.54)		
III, IV (n=30)	8 (26.67)		
Lymph node metastasis		1.290	0.256
Yes (n=27)	9 (33.33)		
No (n=29)	14 (48.28)		
PTBP1		3.899	0.048
High expression group (n=34)	11 (32.35)		
Low expression group (n=22)	13 (59.09)		

tion. The results showed that TNM staging and PTBP1 were independent prognostic factors affecting the overall survival time of patients ($P < 0.05$). More details were shown in **Tables 2** and **3**.

Inhibition of PTBP1 on biological function of RCC cells

Previously, we found that PTBP1 was not only elevated in RCC patients and cells, but also could be used as a prognostic factor of RCC and was closely related to tumor diameter, degree of differentiation, TNM and lymph node metastasis. Therefore, we suspected that PTBP1 might participate in RCC development. Therefore, we transfected SGC-7901 (PTBP1 had the greatest difference in expression in this cell line) with si-PTBP1, and observed the changes of cell biological function after infection to explore its role in RCC. The results showed that after SGC-7901 transfected si-PTBP1, PTBP1 in SGC-7901 was down-regulated ($P < 0.05$). The proliferation, invasion and apoptosis of SGC-7901 were observed by CCK-8, Transwell and flow cytometry. The results showed that the proliferation and invasion of SGC-7901 transfected with si-PTBP1 were inhibited while the apoptosis rate increased. This revealed that PTBP1 acted as an oncogene in RCC. More details were shown **Figure 3**.

Inhibition of PTBP1 on PTEN/Akt pathway markers

According to Result 2.5, PTBP1 is known to contribute to RCC development, but the specific mechanism is unclear. In order to further explore the mechanism of PTBP1 in RCC, we detected the changes of PTEN/Akt pathway markers after SGC-7901 transfected si-PTBP1, which was a typical growth pathway and activated in various tumor species. The results showed that after SGC-7901 transfected si-PTBP1, p-Akt was down-regulated and PTEN was up-regulated. This showed that PTBP1 could promote RCC progress through PTEN/Akt pathway. More details were shown **Figure 4**.

Discussion

RCC is one of the world's top 10 most common malignancies, threatening people's lives [16]. At present, with the application of targeted drugs in RCC, the survival outcome of advanced patients has been improved to some extent [17]. However, drug resistance will eventually occur, so it is vital to find new therapeutic targets. In this article, we analyzed the role and mechanism of PTBP1 in RCC through clinical and cell experiments. In clinical experiments, we found that PTBP1 was up-regulated in RCC, and its high expression predicted poor prognosis of patients. In cell experiments, we discovered that PTBP1 could promote RCC cell proliferation and invasion, and induce apoptosis. Besides, we also found that PTBP1 promoted cancer in RCC, at least partially through PTEN/Akt axis.

PTBP1 can shuttle back and forth between nucleus and cytoplasm, and it can participate in mRNA biogenesis. mRNA attenuation and translation regulate cell fate [18, 19]. With the exploration of PTBP1 in tumors, it is believed

Table 3. Multivariate analysis on prognosis of patients

Group	P	HR (95 CI%)
TNM staging (phase I + II VS phase III + IV)	0.376	1.621 (0.601-3.861)
Differentiation (low differentiation VS moderate + high differentiation)	0.001	3.694 (1.670-7.684)
PTBP1 (high expression VS low expression)	0.014	2.991 (1.365-6.889)

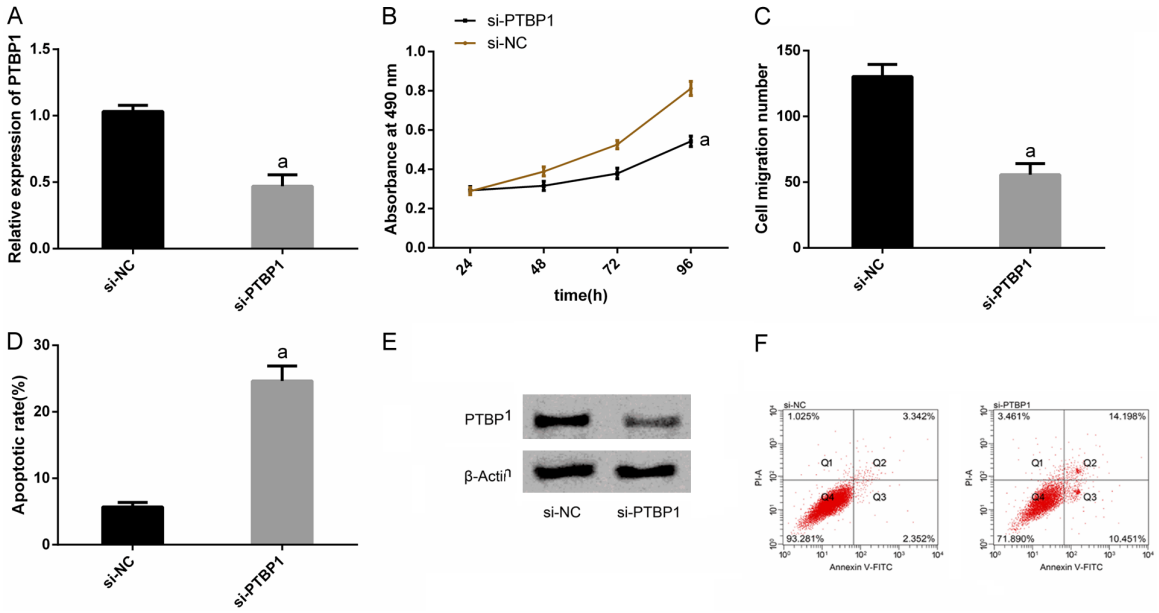

Figure 3. Inhibition of PTBP1 on the biological function of RCC cells. A. After SGC-7901 transfected si-PTBP1, PTBP1 in SGC-7901 was down-regulated. B. CCK-8 experiment found that SGC-7901 transfected si-PTBP1 decreased proliferation ability. C. Transwell experiment found that SGC-7901 transfected with si-PTBP1 decreased the invasive ability. D. Flow cytometry showed that the apoptosis rate increased after SGC-7901 transfected si-PTBP1. E. WB diagram. F. Flow cytometry. 'a' stands for $P < 0.05$.

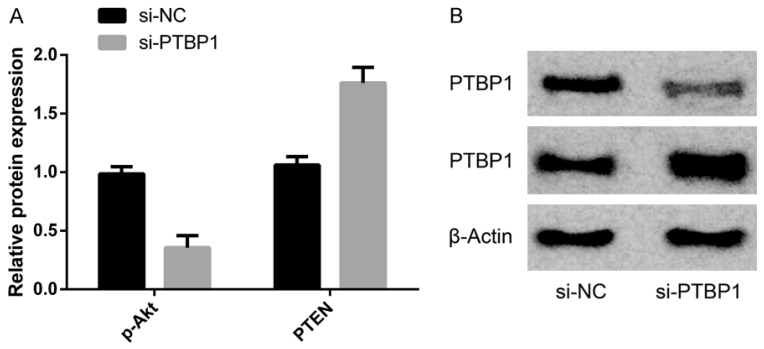

Figure 4. Inhibition of PTBP1 on PTEN/Akt pathway markers. A. After SGC-7901 transfected si-PTBP1, p-Akt was down-regulated and PTEN was up-regulated. B. WB diagram. 'a' stands for $P < 0.05$.

that PTBP1 is closely related to the growth of cancer cells and the occurrence of tumors [20]. In this paper, the expression and function of PTBP1 in RCC have been deeply explored. We found that PTBP1 was up-regulated in RCC tissues and cells, similar to previous research results [14]. Analysis of the relationship between PTBP1 and clinicopathological parameters of patients in this article showed that PTBP1 was strongly linked to tumor diameter, degree of differentiation, TNM and lymph node metastasis. In addition, we also found that PTBP1, which was highly expressed, indicated a poor prognosis for patients. This suggested that it might contribute to RCC development and might be used as a prognostic marker for RCC. Subsequently, *in vitro* experiments were conducted to explore PTBP1's role in RCC and its related mechanisms. After transfecting the RCC cell SGC-7901 with si-PTBP1, we observed the changes

of its biological function. It was found that SGC-7901 was inhibited in proliferation and invasion, but the apoptosis rate increased. This showed that PTBP1 promoted cancer in RCC. In colorectal cancer, high expression of PTBP1 is associated with poor prognosis of patients, and migration and invasion of the disease can be accelerated by alternative splicing of cortical hormones [21]. In gliomas, PTBP1 can promote the development of the disease by activating ADAR1 [22]. In lung cancer, PTBP1 promotes cancer through AXL [9]. This shows that the carcinogenic effect of PTBP1 is extensive.

Although we have proved that PTBP1 can promote RCC development, the specific regulatory mechanism is still unknown. Previous reports have pointed out that PTBP1 can promote breast cancer progression through PTEN/Akt pathway [23]. The PTEN/Akt pathway has been proved to be involved in various biological events such as proliferation, apoptosis and invasion of various tumor cells [24]. Therefore, we suspect that PTBP1 may also promote cancer through the PTEN/Akt pathway in RCC. In order to prove this conjecture, we detected the changes of the pathway markers of SGC-7901 after transfecting si-PTBP1. The results showed that after transfecting si-PTBP1, p-Akt increased and PTEN decreased. This showed that PTBP1 could promote cancer in RCC at least partially through PTEN/Akt pathway.

This article proves that PTBP1 is up-regulated in RCC, its high expression indicates poor prognosis of patients, and it can contribute to RCC progress through the PTEN/Akt pathway, which is believed to be a possible new therapeutic target for RCC in the future. Previous studies have found that PTBP1 can be targeted and regulated by micro RNA, thus participating in disease progression [10]. Therefore, in the following research, we can find the upstream target of PTBP1 and continuously improve understanding of the PTBP1/PTEN/Akt axis. There are some limitations in this study. First, we have not carried out nude mice experiments and do not know whether PTBP1 can affect tumor volume changes. Secondly, the results have certain limitations due to the small sample size in this clinical study. We hope to carry out more basic experiments in future research, collect a larger number of clinical samples for further verification, and enrich the research in future papers.

In general, this article proves that PTBP1 is up-regulated in RCC, and its high expression indicates poor prognosis of patients. PTBP1 can help RCC progress through PTEN/Akt pathway, and it is expected to become a target for RCC treatment.

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Disclosure of conflict of interest

None.

Address correspondence to: Jun Li, Department of Urology, The Third Affiliated Hospital of Kunming Medical University, No. 519, Kunzhou Road, Xishan District, Kunming 650018, Yunnan, China. E-mail: yan285815848141@163.com

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