

RRBP1 is highly expressed in prostate cancer and correlates with prognosis

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Objective: Recently, ribosome binding protein 1 (RRBP1) is reported to be involved in tumorigenesis. However, the expression and clinical significance of RRBP1 in prostate cancer (PCa) remains unknown. This study is aimed to investigate the expression and clinical significance of RRBP1 in PCa.

Materials and methods: RRBP1 expression was firstly detected in 6 cases of PCa and matched adjacent non-cancerous prostate tissues by reverse transcription-quantitative PCR (RT-qPCR) and Western blot. Then, RRBP1 expression was further detected in 127 cases of PCa and 40 cases of non-cancerous prostate tissues by immunohistochemistry (IHC). The relationship of RRBP1 with clinical-pathological characters and patients' prognosis was analyzed in PCa.

Results: RT-qPCR and Western blot analysis showed that RRBP1 expression levels in PCa tissues were significantly higher compared with those in matched adjacent non-cancerous prostate tissues. IHC results shown that the high-expression rate of RRBP1 in PCa was 69.3%, which was significantly greater than those in non-cancerous prostate tissues (15.0%, $P < 0.001$). RRBP1 expression was significantly associated with T stage, lymph node metastasis, PSA and Gleason score in PCa. Survival analysis indicated that patients with RRBP1 low-expression presented longer survival time compared with those with RRBP1 high-expression. Moreover, RRBP1 as well as T stage, lymph node metastasis and Gleason score could serve as independent prognostic factors in PCa.

Conclusion: RRBP1 is highly expressed in PCa and correlates with prognosis, which may serve as a potential biomarker in PCa.

Keywords: prostate cancer, RRBP1, prognosis, PSA, Gleason score

Introduction

Prostate cancer (PCa) is considered as one of the most common urinary tumors among men in the world, which accounts for the second leading cause of cancer-related mortality.¹⁻³ It is reported that the 5-year survival rate of locoregional PCa is nearly 99%, while about one-third of those patients may progress to metastatic PCa.⁴⁻⁶ Metastatic PCa is the major cause of cancer death. Locoregional PCa can be cured by radical prostatectomy (RP) or radiation therapy, but only palliative treatments can be used to metastatic PCa.^{7,8} Therefore, early detection of PCa is important. However, available diagnostic and prognostic tools for PCa are still insufficient.^{9,10} Identifying novel diagnostic and prognostic biomarker of PCa is required.

Ribosome binding protein 1 (RRBP1), an important endoplasmic reticulum membrane protein, is composed of 1,410 amino acid including a transmembrane domain, an acidic coiled-coil COOH-terminal domain and a ribosome-binding

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domain.¹¹ RRBPI is crucial for the transportation and secretion of nascent proteins.^{11,12} Moreover, RRBPI plays a key role in ribosome binding and the terminal differentiation of secretory cells and tissues.^{13–15} RRBPI is mainly localized on the endoplasmic reticulum and can be detected in nucleus and cytoplasm.¹⁶ Recent studies reported that RRBPI was highly expressed in esophageal carcinoma, breast cancer, lung cancer and colorectal cancer.^{15,17–20} Furthermore, RRBPI is confirmed to be a potential prognostic biomarker in esophageal carcinoma, breast cancer and colorectal cancer.^{15,17,21} Thus, current data indicates that RRBPI is an oncogene and may be involved in tumor formation and progression. However, association between RRBPI and PCa has never been reported.

In this study, RRBPI expression was detected in PCa and matched adjacent non-cancerous prostate tissues. Meanwhile, the association between RRBPI expression and clinical-pathological characters and prognosis was evaluated in PCa.

Material and methods

Patients and samples

All tissue samples were collected from Hunan Provincial People's Hospital, the first affiliated hospital of Hunan Normal University, between January 2012 and December 2014. A total of 127 PCa patients were enrolled in this study. Before puncture biopsy, no patient received radiotherapy, chemotherapy or immunotherapy. Pathological diagnosis was performed by the pathologists in Hunan Provincial People's Hospital. Based on the pathological diagnosis, patients with stage T1–T2 received radical surgery resection. Patients with stage T3–T4 received radiotherapy, chemotherapy, endocrine therapy or immunotherapy. Clinicopathological characters including age, smoke history, T stage, lymph node metastasis, PSA level and Gleason score were obtained from hospital records. A total of 127 cases of PCa and 40 cases of matched adjacent non-cancerous prostate tissues were collected and stored as paraffin embedding tissues. In 127 cases of PCa patients, only 6 cases of fresh PCa tissues and matched adjacent non-cancerous prostate tissues were collected and stored at liquid nitrogen. All patients signed informed consent and completed follow-up. The mean survival time was 49.1 months (range 10–76 months). This study was supported by the Medical Ethics Committee of Hunan Provincial People's Hospital, first affiliated hospital of Hunan Normal University and all patients.

Reverse transcription-quantitative PCR (RT-qPCR)

All the manipulation was performed as previously described.²² Total RNA was extracted from fresh tissues using Trizol reagents (Invitrogen, Waltham, MA, USA) according to manufacturer's protocol (Invitrogen). Then, RNA was reversely transcribed to cDNA by using a reverse transcription kit (Takara Biotechnology, Japan). Finally, the levels of mRNA were tested according to the manufacturer's instructions. The sequences of the primers of RRBPI were 5'-TTCAAC-GAGGGCGAGGCCAG-3' (F) and 5'-CGTGCCTGCACAGCCGTGATCT-3' (R). The primer sequences of GAPDH were 5'-GCATCCTGCACCACCAACTG-3' and 5'-GCCTGCTTACCACCTTCTT-3'. Reaction conditions were recorded as follow: 95°C for 30 s, followed by 40 cycles of 95°C for 5 s and 60°C for 30 s. The levels of mRNA were compared by the $2^{-\Delta\Delta C_t}$ method. The expression of GAPDH was used as an internal control gene for standardizing the expression of target genes. Experiments were repeated in triplicate.

Western blot

All the manipulation was performed as previously described.²² Total proteins were extracted from fresh tissues by RIPA lysis buffer (KeyGEN, China) and measured by BCA Protein Assay Kit (KeyGEN). A total of 50 µg of protein was separated on 10% SDS-polyacrylamide gels (SDS-PAGE) and then transferred onto polyvinylidene fluoride (PVDF) membranes. After blocked with 5% nonfat milk PBST solution for 1 hr at room temperature, membranes were incubated with polyclonal RRBPI antibody (1:1,000) (Proteintech, China) and β-actin antibody (1:2,000) (Abcam, USA) at 4 °C overnight, respectively. Then, membranes were washed with PBST and incubated with secondary antibodies (ZhongshanJingqiao, China) for 1 hr at room temperature. Protein band was visualized by ECL Plus Kit (Beyotime, China). Relative protein expression levels were statistically analyzed by measuring the gray density of each protein band. The expression of β-actin was used as an internal control protein for standardizing the expression of target protein. Experiments were repeated in triplicate.

Immunohistochemistry (IHC)

All manipulation was performed as previously described.²³ Tissue sections were dewaxed with xylene and rehydrated with alcohol. Antigen retrieval was performed by 0.01 mol/L citrate buffer (pH 6.0). Then, sections were blocked with

hydrogen peroxide and fetal bovine serum, and incubated with polyclonal RRBPI antibody (1:200) (Proteintech). After incubated with biotinylated secondary antibody, sections were developed by 3,3'-diaminobenzidine (DAB) and stained with hematoxylin. According to the staining intensity and percentage of positive cells, total scores of each sample were calculated by multiplying the two scores. The scores of staining intensity and positive cells percentage were recorded as follow: blank (0), weak (1), moderate (2) and strong (3): <5% (0), ≥5% to <25% (1), 25–50% (2), >50% (3). Total scores of each sample ranged from 0 to 9. RRBPI expression was divided into high-expression (≥4) and low-expression (<4).

Statistical analysis

SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All data were presented as mean ± SD. The difference between two groups was compared by independent sample *t*-test. When the data was not normally distributed, the difference was compared by a non-parametric test. Association between RRBPI expression and clinicopathological characters was analyzed by Pearson chi-square test (χ^2). Kaplan–Meier method and Cox's regression model were used for survival analysis. $P < 0.05$ was considered as a statistical difference.

Results

RRBPI is highly expressed in PCa

To investigate the correlation between RRBPI and PCa, RRBPI expression was firstly detected in 6 cases of fresh

PCa tissues and matched adjacent non-cancer prostate tissues by RT-qPCR and Western blot assays. Results showed RRBPI mRNA levels were significantly higher in PCa tissues compared with those in matched adjacent non-cancer prostate tissues (Figure 1A, $P < 0.001$). Meanwhile, significantly higher levels of RRBPI protein were observed in PCa tissues (Figure 1B, $P < 0.05$). Subsequently, RRBPI expression was further detected in 127 cases of PCa and 40 cases of matched adjacent non-cancer prostate tissues by IHC. As shown in Figure 2, positive expression of RRBPI was mainly observed in cell cytoplasm as brown. Statistical analysis has shown that the high-expression rate of RRBPI in PCa tissues was 69.3%, which was significantly higher than those in non-cancer prostate tissues (15.0%, Table 1, $P < 0.001$). These data indicated that RRBPI was highly expressed in PCa.

RRBPI expression correlates with clinicopathological characters and patients' prognosis

Then, the correlation between RRBPI expression and clinicopathological characters and patients' prognosis was further analyzed in 127 cases of PCa. Results have shown that RRBPI expression significantly correlated with T stage, lymph node metastasis, PSA level and Gleason score (Table 2, $P < 0.05$), but was not significantly connected with age and smoke history (Table 2, $P > 0.05$). RRBPI expression levels were significantly higher in patients with T3–T4 stage or lymph node metastasis. Patients with more higher PSA level (>20 ng/ml) or Gleason score (≥8) presented more higher levels of RRBPI. Kaplan–Meier survival analysis has shown

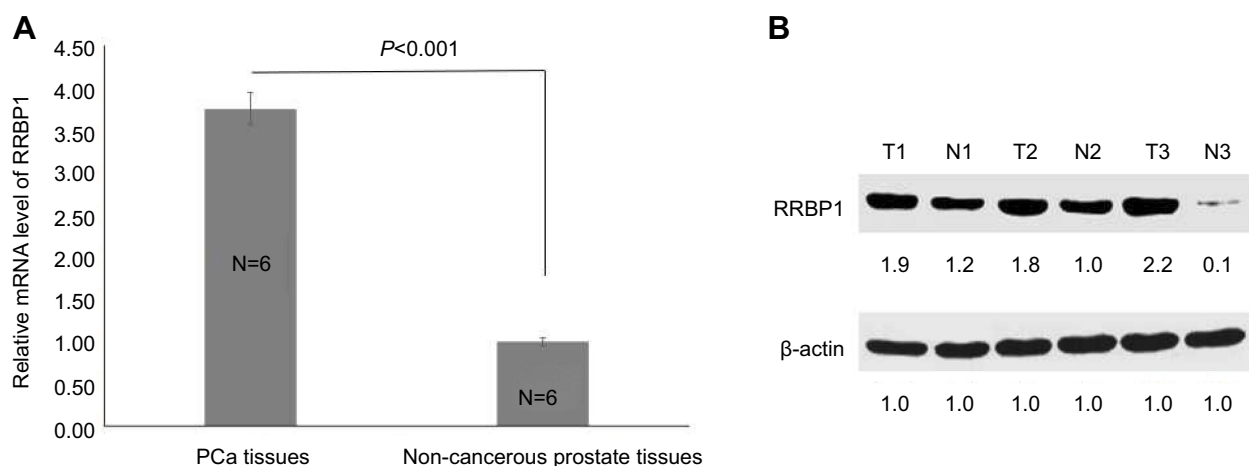


Figure 1 RRBPI was highly expressed in PCa. **(A)** Relative mRNA level of RRBPI was detected in PCa and non-cancerous prostate tissues by RT-qPCR, and mean ± SD represented three independent experiments. **(B)** RRBPI protein expression level was detected in PCa and non-cancerous prostate tissues by Western blot, and the gray density of each protein band was recorded.

Abbreviations: T, tumor; N, non-cancerous prostate tissues; RRBPI, ribosome binding protein I; PCa, prostate cancer; RT-qPCR, reverse transcription-quantitative PCR.

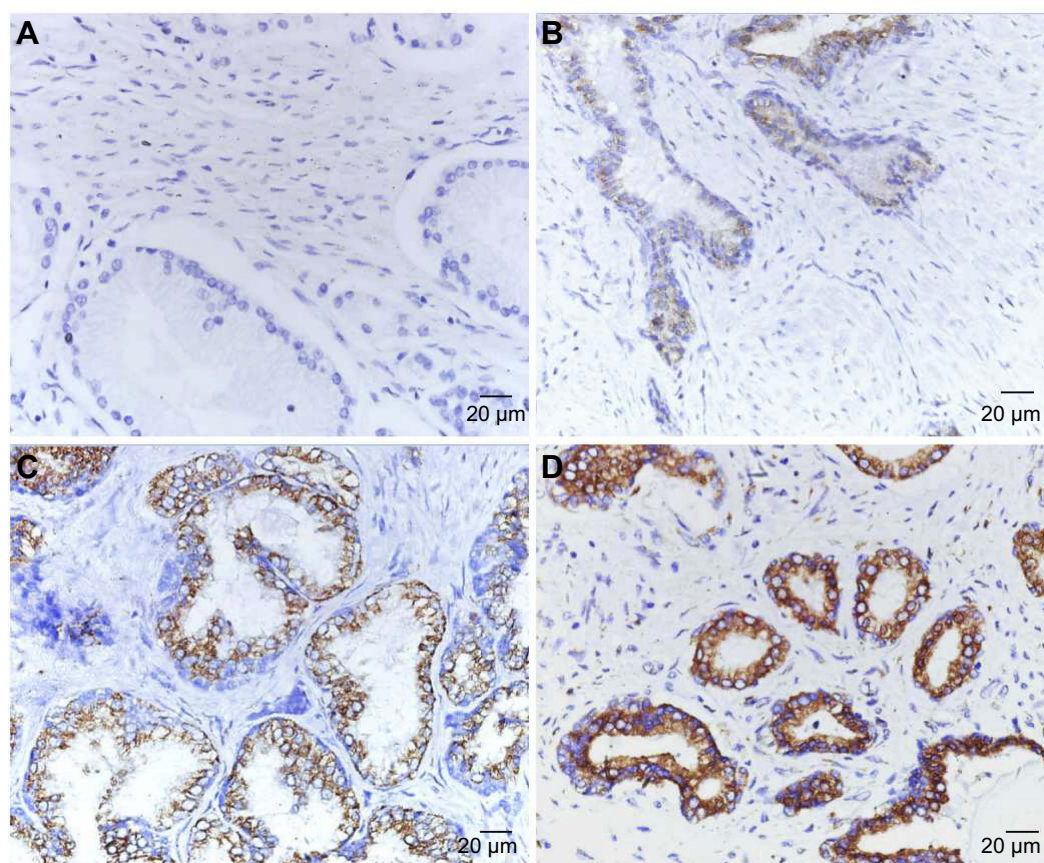


Figure 2 RRBPI expression was detected in PCa by IHC. (A) No positive staining of RRBPI in non-cancerous prostate tissues (Score = 0, $\times 400$). (B) Weak staining of RRBPI in PCa (Score = 1, $\times 400$). (C) Moderate staining of RRBPI in PCa (Score = 4, $\times 400$). (D) Strong staining of RRBPI in PCa (Score = 9, $\times 400$).

Abbreviations: RRBPI, ribosome binding protein I; IHC, immunohistochemistry; PCa, prostate cancer.

Table 1 RRBPI expression was detected in PCa tissues by IHC

Types	N	RRBPI		P-value
		Low-expression	High-expression	
PCa tissues	127	39 (30.7%)	88 (69.3%)	<0.001
Non-cancerous prostate tissues	40	34 (85.0%)	6 (15.0%)	

Abbreviations: RRBPI, ribosome binding protein I; IHC, immunohistochemistry; PCa, prostate cancer.

that patients with RRBPI high-expression presented poorer prognosis. The mean survival time of patients with RRBPI high-expression was 56 months, which was significantly reduced than those with RRBPI low-expression (73 months) (Table 3, Figure 3, $P < 0.001$). Meanwhile, T stage, lymph node metastasis, PSA and Gleason score were associated with patients' prognosis (Table 3, $P < 0.05$). Cox regression analysis showed RRBPI expression, T stage, lymph node metastasis and Gleason score were independent prognostic factors in PCa (Table 4, $P < 0.05$).

Discussion

In this study, to investigate the correlation between RRBPI expression and PCa, we firstly detected RRBPI expression in PCa and matched adjacent non-cancer prostate tissues by RT-qPCR and Western blot assays. Results showed that RRBPI mRNA and protein levels in PCa tissues were significantly greater than those in non-cancer prostate tissues, indicating RRBPI high-expression was associated with the formation of PCa. Meanwhile, IHC assay received the same results that RRBPI was highly expressed in PCa, which further supported that RRBPI high-expression was connected with the formation of PCa. Moreover, IHC results shown that RRBPI was hard to detect in non-cancer prostate tissues, suggesting that RRBPI detection might be helpful for the diagnosis of PCa.

It was well known that T stage, lymph node metastasis, PSA level and Gleason score correlated with PCa progression and affected patients' prognosis.^{24–28} Thus, the correlation between RRBPI expression and clinicopathological characters and patients' prognosis was further analyzed in

Table 2 The association between RRBPI expression and clinical-pathological characters was analyzed in PCa

Clinical-pathological characters	N	RRBPI		P-value
		Low-expression	High-expression	
Age (years)				
≤64	67	16	51	0.086
>64	60	23	37	
Smoke history				
Negative	36	9	27	0.522
Positive	91	30	61	
T stage				
T1–T2	75	34	41	<0.001
T3–T4	52	5	47	
Lymph node metastasis				
Negative	106	37	69	0.021
Positive	21	2	19	
PSA (ng/ml)				
≤20	67	30	37	<0.001
>20	60	9	51	
Gleason score				
<8	65	31	34	<0.001
≥8	62	8	54	

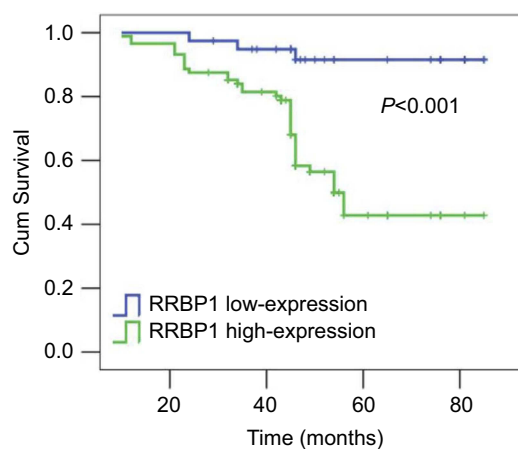
Abbreviations: RRBPI, ribosome binding protein I; PCa, prostate cancer.

PCa. Results showed RRBPI expression significantly correlated with T stage, lymph node metastasis, PSA level and Gleason score, suggesting that RRBPI high-expression was implicated in the progression of PCa. Kaplan–Meier survival analysis showed that RRBPI expression as well as T stage, lymph node metastasis, PSA level and Gleason score were connected with patients' prognosis. Meanwhile, Cox regression analysis showed RRBPI expression as well as T stage, lymph node metastasis and Gleason score were independent prognostic factors in PCa. These data indicated that RRBPI could serve as a novel prognostic biomarker in PCa, which was consistent with the findings in esophageal carcinoma, breast cancer and colorectal cancer.^{15,17,21}

In addition, there are a few limitations in this study. On the one hand, it is inevitable to exclude the selection bias because of the potential differences in specimens collection. On the other hand, it is hard to eliminate the histological differences in adjacent non-cancer prostate tissues. Therefore, further investigations are required to validate our findings.

Table 3 Patients' survival was evaluated by Kaplan–Meier analysis

Variables	N	Mean survival time (month, 95% CI)	P-value
RRBPI			
Low-expression	39	73 (69–76)	<0.001
High-expression	88	56 (51–60)	
Age (years)			
≤64	67	64 (58–69)	0.251
>64	60	60 (55–65)	
Smoke history			
Negative	36	59 (53–66)	0.403
Positive	91	63 (58–67)	
T stage			
T1–T2	75	65 (61–70)	0.011
T3–T4	52	56 (50–62)	
Lymph node metastasis			
Negative	106	64 (60–68)	<0.001
Positive	21	48 (37–58)	
PSA (ng/ml)			
≤20	67	67 (63–71)	0.002
>20	60	55 (49–61)	
Gleason score			
<8	65	69 (65–72)	<0.001
≥8	62	54 (48–60)	

**Figure 3** Kaplan–Meier survival analysis showing RRBPI high-expression that presented poor prognosis in PCa.

Abbreviations: RRBPI, ribosome binding protein I; PCa, prostate cancer.

Conclusion

Our data indicate that RRBPI is highly expressed in PCa, which may be helpful for the diagnosis of PCa. RRBPI high-expression predicts unfavorable prognosis, which may be beneficial for the prediction of prognosis in PCa.

Table 4 Patients' survival was evaluated by Cox regression analysis

Variables	Hazard rate	95% CI	P-value
RRBP1 expression (high-expression vs Low-expression)	6.924	1.995–24.035	0.002
Age (>64 years vs ≤64 years)	1.375	0.692–2.740	0.363
Smoke history (positive vs negative)	1.648	0.738–3.681	0.223
T stage (T3–T4 vs T1–T2)	6.410	1.842–22.222	0.004
Lymph node metastasis (positive vs negative)	4.027	1.691–9.590	0.002
PSA (>20 ng/ml vs ≤20 ng/ml)	1.017	0.419–2.475	0.969
Gleason score (≥8 vs <8)	6.534	1.964–21.737	0.002

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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