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ORIGINAL ARTICLE

Increased Expression of ProBDNF/Sortilin in Localized Prostate Cancer Tissues Compared to Adjacent Non-Cancerous Tissues

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SUMMARY

Background: **The unprocessed precursor of brain-derived neurotrophic factor (BDNF), proBDNF, has emerged as a potential determinant of therapeutic response in prostate cancer. Upon secretion, proBDNF preferentially binds to the co-receptors sortilin and p75NTR, triggering pro-apoptotic or pro-survival cascades, depending on cellular context. ProBDNF engages sortilin/p75NTR to drive castration resistance and metastasis in prostate cancer. High proBDNF/sortilin predicts poor therapy outcome, yet their tissue expression in prostate cancer (PCa) remains unclear.**

Methods: **To evaluate the protein expression levels of proBDNF, sortilin, and p75NTR, we performed immunohistochemical analyses on 18 formalin-fixed paraffin-embedded (FFPE) PCa tissues obtained at radical prostatectomy between 2024 and 2025, together with matched para-carcinoma tissues.**

Results: **Compared with para-carcinoma tissues, immunohistochemistry in 18 paired specimens showed that proBDNF was significantly upregulated in PCa tissues (median IHC score 60.5 (range 57 - 65) vs. 41.5 (40 - 45), $p < 0.05$). Sortilin expression was also higher in PCa (median 37.0 (35 - 39) vs. 16.5 (15 - 18), $p < 0.01$); P75 expression remained relatively low in both prostate cancer and adjacent non-cancerous tissues (18.5 (17 - 20) vs. 6.5 (5 - 8), $p < 0.05$).**

Conclusions: **These findings suggest a correlation between the expression levels of proBDNF, sortilin, and p75-NTR and the characteristics of PCa. Further investigation into the mechanisms underlying these interactions may provide valuable insights for the development of targeted therapies for PCa.**

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INTRODUCTION

PCa is the second most common cancer among men globally [1]. While the involvement of pro-BDNF, sortilin, and p75NTR in PCa has not been extensively studied, their potential roles in the development of this disease are increasingly recognized. However, the impact of PCa on the expression and function of pro-BDNF,

sortilin, and p75NTR remains a subject of ongoing debate. In the central nervous system (CNS), BDNF exists in two forms: mature BDNF and proBDNF, the latter being the precursor to mature BDNF [2]. The prodomain of BDNF plays a crucial role in the secretion and anterograde transport of proBDNF [3]. Research on proBDNF is less extensive compared to that on mature BDNF, but emerging evidence suggests functional differences between the two [4]. The p75NTR neurotrophin receptor is a specific type of nerve growth factor (NGF) receptor [5]. In the CNS, proBDNF can interact with p75NTR, exhibiting contrasting biological effects compared to mature BDNF [6]. Recently, an increasing number of studies have highlighted the significant role of the proBDNF/p75NTR axis in cancer biology [7]. For instance, p75NTR has been reported to contribute to drug resistance, thereby promoting tumor progression. Studies have demonstrated that p75NTR is a crucial regulator of glioma invasion and is naturally expressed in patient tumors [8,9]. Additionally, p75NTR has been found to be significantly expressed in clear cell renal cell carcinoma, melanoma, and laryngeal cancer [10-12]. In contrast, in prostate and gastric cancer, activation of p75NTR can trigger apoptosis in tumor cells, while its downregulation promotes tumor growth [13, 14]. Furthermore, pro-BDNF interacts with the p75NTR receptor, and its ability to induce apoptosis relies on the collaborative action of sortilin, another receptor [15]. Several studies have confirmed the expression of p75-NTR and sortilin in the majority of nevi and melanomas, with no significant differences in their expression levels [16]. However, the functions of these three receptors in PCa have been rarely reported. This study aimed to fill this knowledge gap by investigating the expression and potential roles of pro-BDNF, sortilin, and p75-NTR in PCa. Our findings provide a foundation for clinical diagnosis and the identification of potential therapeutic targets, contributing to a deeper understanding of the molecular mechanisms underlying PCa progression.

MATERIALS AND METHODS

Tissue sample collection and study design

Tissue specimens were collected and stored at Yancheng First People's Hospital, following protocols approved by the Institutional Review Board. The study encompassed a total of 18 laparoscopic radical prostatectomy specimens from patients with PCa between 2024 and 2025. All procedures were in compliance with the management standards and ethical guidelines established by the Ethics Committee of Yancheng First People's Hospital.

Immunohistochemical staining

Immunohistochemical analysis was performed using the following primary antibodies: anti-pro-BDNF (Abcam and Santa Cruz Biotechnology), anti-sortilin (Alomone Labs), and anti-p75NTR (Abcam). The streptavidin-biotin complex (SABC) method was employed for staining. Tissue specimens were initially subjected to a 2-hour baking process at 60°C in an oven to fix the sections. Subsequently, paraffin-embedded tissue sections were processed through standard dewaxing and rehydration protocols as previously described [17]: sections were deparaffinized in three changes of xylene (10 minutes each), followed by rehydration through graded ethanol solutions (100%, 100%, 95%, 70%, each 3 - 5 minutes), and were finally rinsed in running tap water. The sections were then treated with 3% hydrogen peroxide (H_2O_2) for 10 minutes to quench endogenous peroxidase activity and eliminate any unwanted background reactions. Antigen retrieval was achieved by immersing the sections in 0.01 mol/L citrate buffer (pH 6.0) and heating in a microwave at 95°C for 15 minutes. After cooling to room temperature, the sections were washed three times with phosphate-buffered saline (PBS), with each wash lasting 5 minutes. Excess liquid was carefully removed from the sections using filter paper, and the primary antibodies were applied as follows: anti-pro-BDNF (1:500), anti-sortilin (1:500), and anti-p75NTR (1:200). The sections were incubated with the primary antibodies for 2 hours at room temperature on a rocker to ensure even distribution. Following this, the samples were stored overnight at 4°C in a refrigerator to allow for complete antibody binding. On the following day, the sections were incubated with a biotinylated secondary antibody for 30 minutes at room temperature, followed by a 30-minute incubation with the SABC enzyme complex. Staining was visualized using 3,3'-diaminobenzidine (DAB) as the chromogenic substrate. The sections were counterstained with Harris hematoxylin, dehydrated through graded alcohols, cleared in xylene, and coverslipped. Immunostained slides were then evaluated by a board-certified pathologist under a light microscope (Olympus BX53, Tokyo, Japan) in a blinded manner.

Statistical analysis

Statistical analysis was performed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA) and ImageJ software (Image-Pro Plus, Version 7.0). After setting a consistent threshold, the “Analyze Particles” function calculated the percentage of DAB-positive pixels. The same macro was applied to all cores; batch processing minimized user bias. The differences in protein expression levels between para-carcinoma tissues and PCa groups were analyzed using the Mann-Whitney U test. A p-value of less than 0.05 was considered statistically significant. All statistical tests were two-sided.

RESULTS

Pro-BDNF and sortilin expressions are enhanced in PCa

Baseline clinicopathologic characteristics are summarized in Table 1. The expression levels of pro-BDNF,

Table 1. Clinicopathological characteristics of 18 prostate cancer patients.

Characteristic	All patients (n = 18)	Missing
Age, years	68 (62 - 73)	0
Pre-operative PSA, ng/mL	9.6 (6.2 - 14.5)	1
Gleason score		0
- 3 + 3 = 6	3 (16.7%)	
- 3 + 4 = 7	6 (33.3%)	
- 4 + 3 = 7	4 (22.2%)	
- 8	3 (16.7%)	
- 9 - 10	2 (11.1%)	
Pathological T stage		0
- T2	8 (44.4%)	
- T3a	6 (33.3%)	
- T3b/T4	4 (22.2%)	
N stage		1
- N0	15 (88.2%)	
- N1	2 (11.8%)	
M stage		2
- M0	16 (100%)	
- M1	0	

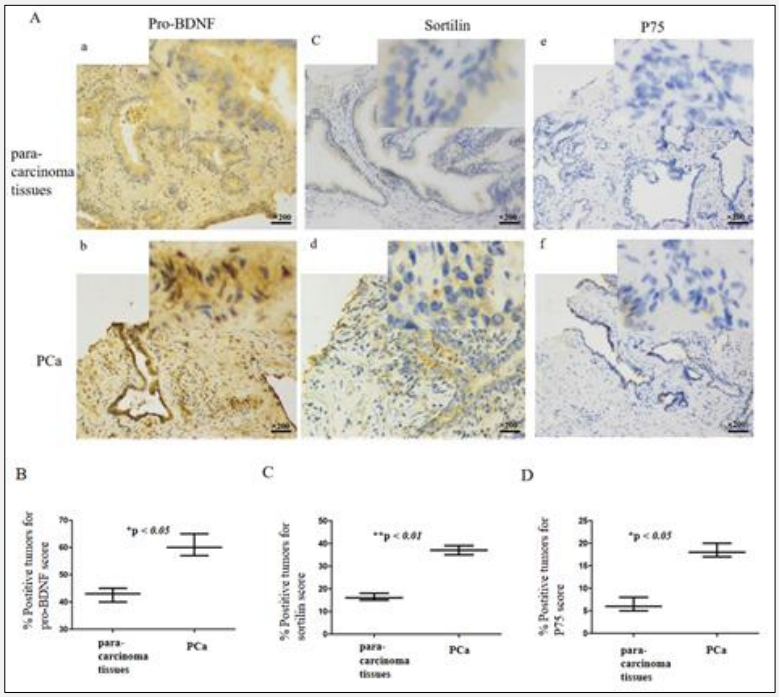

Figure 1. Immunohistochemical staining on para-carcinoma tissues and PCa tissues.

A) Tissue micro array of para-carcinoma tissues (a, c, e) and PCa tissues (b, d, f) with immunostaining for pro-BDNF (a, b), sortilin (c, d), and p75NTR (e, f) (× 200 magnification, scale bar, 50 µm).
Histograms with percentage of positive samples for score of immunostaining intensity (evaluated by image J) for B) pro-BDNF, C) sortilin, and D) $p75^{NTR}$ (n = 3 independent experiments).
Data are presented as mean ± SD.

sortilin, and P75NTR were examined in PCa and para-carcinoma tissues obtained from 18 patients who underwent prostatectomy. Immunohistochemical staining was performed on these tissues to evaluate the expression of pro-BDNF, sortilin, and P75NTR. Comparative analyses were conducted between the para-carcinoma tissues and PCa regions within each patient sample using immunohistochemistry. The intensity of immunostaining was quantified using ImageJ software. The results of the pro-BDNF immunostaining revealed that pro-BDNF was highly expressed in both PCa and para-carcinoma tissues, with significantly higher expression levels observed in PCa samples. In para-carcinoma tissues, pro-BDNF staining was predominantly localized to the cytoplasm (Figure 1A. a). In contrast, in PCa tissues, pro-BDNF was detected in both the cytoplasm and the cell membrane (Figure 1A. b). Sortilin expression was also observed in both para-carcinoma tissues and PCa tissues. In PCa, sortilin staining was mainly localized to the cytoplasm (Figure 1A. c), whereas in para-carcinoma tissues, it was predominantly detected at the cell membrane (Figure 1A. d). Conversely, P75NTR expression was rarely detected in para-carcinoma tissues (Figure 1A. e), with only weak expression observed in PCa tissues (Figure 1A. f). Compared with para-carcinoma tissues, immunohistochemistry in 18 paired specimens showed that proBDNF was significantly upregulated in PCa tissues (median 60.5 vs. 41.5, range 57 - 65 vs. 40 - 45, $p < 0.05$); sortilin expression was also higher in PCa (median 37.0 vs. 16.5, range 35 - 39 vs. 15 - 18, $p < 0.01$). P75NTR expression remained relatively low in both prostate cancer and adjacent non-cancerous tissues (median: 18.5 (17 - 20) vs. 6.5 (5 - 8), $p < 0.05$) (Figure 1B - D). Furthermore, the percentages of high expression of pro-BDNF, sortilin, and P75NTR in prostate cancer were 15/18 (83%), 12/18 (67%), and 2/18 (11%), respectively (Supplementary Table S1). These findings suggest that pro-BDNF and sortilin may play significant roles in the pathogenesis of prostate cancer.

DISCUSSION

Previous studies have identified pro-BDNF, sortilin, and P75NTR as poor prognostic factors and contributors to tumor aggressiveness in various cancers [8,10,18,19]. For instance, it has been confirmed that P75NTR and pro-BDNF promote the survival and migration of clear cell renal cell carcinoma cells [20]. Additionally, studies have demonstrated that BDNF and TrkB influence colorectal cancer cells, highlighting their importance in both *in vitro* cell growth and tumor survival [21]. However, the involvement of these factors in PCa has not been previously reported. Although some studies have examined the association between P75NTR and cancer, and others have focused solely on sortilin and cancer, our study aimed to investigate the expression of pro-BDNF, sortilin, and P75NTR in clinical samples of PCa, with para-carcinoma tissues serving as the control group. Our findings revealed that pro-BDNF levels were significantly elevated in both PCa and para-carcinoma tissues, with the effects being more pronounced in PCa. Furthermore, we observed low expression of sortilin in both PCa and para-carcinoma tissues, with differential expression patterns in distinct tissue sections. P75NTR was not detected in para-carcinoma tissues and exhibited only weak expression in PCa. Furthermore, we observed that pro-BDNF was almost exclusively cytoplasmic in benign para-carcinoma glands, whereas in malignant epithelium it additionally appeared at the plasma membrane. Sortilin displayed the opposite shift: in para-carcinoma tissues its signal outlined the cell membrane, but in PCa it accumulated in the cytoplasm. It is reported that these reciprocal localizations may reflect altered trafficking of the pro-BDNF/sortilin/p75-NTR complex that has been documented in other cancers [22]. These results suggest that pro-BDNF and sortilin may possess a certain degree of specificity and could potentially serve as a supplementary diagnostic tool to enhance the detection of PCa.

Data Availability Statement:
The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Consent to Participate:
Informed consent was obtained from all individual participants included in the study.

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Declaration of Interest:
The authors declare no competing interests.

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