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Upregulation of *CXCR7* Is Associated with Poor Prognosis of Prostate Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CDE 1 **Jihua Yang***
ABC 2 **Hao Tang***
CDE 3 **Jingyu Huang***
ABFG 4 **Huaijie An**

1 Department of Oncology, Naval General Hospital, Beijing, P.R. China
2 Department of Urology, Jinling Hospital, Nanjing, Jiangsu, P.R. China
3 Department of Thoracic and Cardiovascular Surgery, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, P.R. China
4 Central Laboratory, Naval General Hospital, Beijing, P.R. China

* Co-first authors; Jihua Yang, Hao Tang, Jingyu Huang

Corresponding Author: Huaijie An, e-mail: j990jsg@126.com
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Background: Prostate cancer (PCa) is a prevalent cancer in males. *CXCR7* exhibits oncogenic actions in various cancers. The aim of our study was to explore the clinical significance of *CXCR7* in patients with PCa.

Material/Methods: QRT-PCR was used to detect the expression level of *CXCR7* in PCa tissues. The relationship between *CXCR7* expression and clinicopathologic parameters was evaluated by chi-square test. Kaplan-Meier survival curve was used for the survival analysis of patients. Cox regression analyses were performed to assess the potential of *CXCR7* as a prognosis biomarker for PCa patients. We performed MTT and Transwell assays to determine the effect of *CXCR7* on proliferative and migratory abilities of PCa cells, respectively.

Results: *CXCR7* was upregulated in PCa tissues ($P<0.05$) and was correlated with PSA ($P=0.023$), differentiation ($P=0.022$), and lymph node metastasis ($P=0.018$). The results of MTT and Transwell assays demonstrated that inhibition of *CXCR7* suppressed PCa cells growth and migration. Additionally, high *CXCR7* level predicted poor overall survival (log rank test, $P=0.019$). *CXCR7* was a valuable prognostic biomarker for PCa patients (HR=2.271, 95%CI=1.093–4.719, $P=0.028$).

Conclusions: *CXCR7* is an oncogene in PCa that can promote aggressive progression of PCa through enhancing proliferation and migration of the tumor cells. *CXCR7* is an independent biomarker for the prognosis of PCa.

MeSH Keywords: **Genes, vif • Prognosis • Prostatic Neoplasms**

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Background

Prostate cancer (PCa) is a malignant tumor among men and is a leading cause of cancer-related deaths worldwide [1,2]. The traditional treatments for PCa include surgery, chemoradiotherapy, and biotherapy. The therapeutic effects are satisfactory for localized PCa; however, a subgroup of patients develop to recurrence or metastasis, resulting in therapy failures and dismal prognosis [3]. Effective biomarkers are pivotal for early diagnosis and appropriate treatments. The commonly used biomarker for PCa is PSA (prostate-specific antigen), but its low specificity may contribute to over-diagnosis and over-treatment [4]. Thus, it is urgent to find novel and effective biomarkers to predict prognosis and guide therapy for PCa patients.

Chemokines are low molecular weight proteins secreted by bone marrow stromal cells and other related mesothelial and epithelial cells. According to their conserved cysteine, chemokines can be divided into 4 groups: CXC, CC, C, and CX3C family [5]. Cooperating with corresponding receptors, chemokines exert proinflammatory properties and play important roles in chemotaxis and metabolism of leukocytes [6]. Abnormal expression of chemokines can contribute to various diseases and cancers through regulating development, angiogenesis, and atherosclerosis [7,8]. *CXCR7* is newly identified as a receptor of *CSCL12*. *CXCR7* belongs to the G-protein-coupled receptor family and consists of 362 amino acids. *CXCR7* gene is located in the human chromosome 2q37. Growing evidence shows that *CXCR7* plays an important role in the development of tumors. Upregulation of *CXCR7* serves as an oncogene in various of cancers, such as breast cancer, lung cancer, and glioma [9,10]. The oncogenetic action of *CXCR7* in PCa was also reported in previous research. Singh et al. reported that inducing *CXCR7* high expression in normal PCa cells can enhance its proliferative ability [11]. However, the predictive role of *CXCR7* in PCa prognosis remains unclear.

In the present study, we aimed to explore the expression profile of *CXCR7* in PCa tissues, as well as its association with clinicopathologic characteristics of patients. MTT and Transwell assays were carried out to investigate the functions of *CXCR7* on biological behaviors of PCa cells. In addition, we evaluated the prognostic significance of *CXCR7* in PCa patients. Our results may provide a novel indicator for PCa.

Material and Methods

PCa tissue samples collection

We obtained 152 pairs of PCa tissues and adjacent normal tissue samples during curative resection of PCa patients at Naval General Hospital. None of the patients enrolled in our study had received chemo- or radiotherapy before surgery. After collection, all tissue samples were immediately frozen in liquid nitrogen and then kept at –80°C for further use. The PCa tissues were confirmed by 2 clinical pathologists based on immunohistochemical analysis results. The adjacent normal tissues were defined as those >3 cm away from the cancer tissues. The extent of PCa aggressiveness was evaluated according to the TNM staging system (AJCC Cancer Staging Manual) [12]. The differentiation is the mature degree of tumor tissue. The differentiation degrees of the PCa tissues were estimated using Gleason score. Patients with Gleason score less than 7 were defined as high differentiation, Gleason score 7 was defined as moderate differentiation, while Gleason score >7 was defined as low differentiation [13]. The study was approved by the hospital Ethics Committee and we obtained the written informed consent from all patients in advance.

All the PCa patients in our study had participated in a postoperative 5-year follow-up investigation. The PCa patients were followed up every 3 months for the first year and then every 6 months for the subsequent 2 years, and annually for the last 2 years. The clinicopathological features are listed in Table 1, including age, tumor size, PSA, TNM stage, differentiation, and lymph node metastasis.

Real time PCR

Total RNA was extracted from the tissues using Trizol reagent (Invitrogen). RNA concentration and purity were measured using a Nano-Drop ND-1000 spectrophotometer (NanoDrop Technologies, Houston, TX, USA). cDNA was synthesized from total RNA using the ReverTra Ace-α First-Strand cDNA Synthesis Kit (Toyobo (Shanghai) Biotech Co., Ltd., Shanghai, China). qRT-PCR was performed using the ABI Prism 7900 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) with SYBR Green Premix Ex Taq (Takara, Dalian, China). β-actin served as internal control. The primer sequences of *CXCR7* and β-*actin* were as follows: *CXCR7*: 5'-CTATGACACGCACTGCTACATC-3' (forward), 5'-CTGCACGAGACTGACCACC-3' (reverse); β-*actin* 5'-ATGGAGGGGAATACAGCCC-3' (forward), 5'-TTCTTTGCA GCTCCTTCGTT-3' (reverse) [14]. We measured the relative expression of *CXCR7* by normalizing with β-*actin* and using the $2^{-\Delta\Delta Ct}$ method. Each measurement was performed in triplicate.

Cell culture and transfection

Human PCa cell line PC3 was purchased from the Central Laboratory of the Affiliated Hospital of Qingdao University (Qingdao, Shandong Province, China). DMEM medium was used to culture the PC3 cell lines and the medium was supplemented with 10% FBS (fetal bovine serum), 1% glutamine, 100 U/ml of penicillin, and 100 μg/ml of streptomycin, at 37°C with 5% CO_2.

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Table 1. Association of *CXCR7* expression with clinicopathological features of prostate cancer patients.

Characteristics	N=152	*CXCR7* expression		χ^2	*P* values
		Low (n=61)	High (n=91)		
Age (years)					
≥65	88	35	53	0.011	0.916
<65	64	26	38		
Tumor size (cm)					
≥3	79	30	49	0.319	0.573
<3	73	31	42		
PSA (ng/ml)					
≤20	112	51	61	5.173	0.023
>20	40	10	30		
Differentiation					
Well+moderate	109	50	59	5.284	0.022
Poor	43	11	32		
TNM stage					
I+II	81	37	44	2.221	0.136
III+IV	71	24	47		
Lymph node metastasis					
Negative	87	42	45	5.617	0.018
Positive	65	19	46		

PC3 cells at logarithmic growth phase were inoculated in a 96-well plate until the attachment efficiency reached 40–60%. Then, the cells were transfected with *CXCR7-siRNA* using Lipofectamine 2000 Reagent according to the manufacturer's instructions. At 6 h after transfection, we continued to incubate the cells in 10% FBS DMEM medium. Then, cells were harvested for proliferation and migration analyses after culturing for 48 h. The cells transfected with *CXCR7-NC* (Applied Shanghai GenePharma Co., Ltd) were used as controls.

MTT assay

To determine the effect of *CXCR7* on the proliferation of PC3 cells, MTT assay was performed. The transfected cells were seeded into 96-well plates with 200 µl per well (about 10^4 cells/well) and cultured for 3–5 days at 37°C in a 5% CO_2 incubator. MTT assay was performed at 24 h, 48 h, and 72 h. We added 20 µl MTT (Sigma, St. Louis, MO, USA) to each well at a final concentration of 0.2 mg/ml, and incubated for 4 h continuously, and then resolved with 150 µl DMSO (Sigma) with low-speed shock for 10 min. The OD values were measured at 490 nm using a Thermo Scientific Microplate Absorbance Reader (Thermo Biotechnology, USA). Each detection was performed in triplicate.

Transwell migration assay

We used Transwell assay to detect the migratory ability of PC3 cells transfected with *CXCR7* siRNA. The cells (about 10^4 cells/well) were re-suspended in 200 µl serum-free medium and seeded on the top chamber of a Transwell® device (6.5-mm Transwell filter with 8.0-µm pore polycarbonate membrane). Then, we added 600 µl medium containing 10% FBS on the bottom chamber. After incubation for 24 h at 37°C with 5% CO_2, we fixed the cells attached to the lower surface of the membrane with 4% paraformaldehyde at room temperature for 30 min and stained them with crystal violet (Beyotime Institute of Biotechnology, China). The number migrating cells was calculated from photomicrographs. Each group was assessed at least 3 times.

Statistical analysis

SPSS 19.0 software was used for data analysis and GraphPad Prism 5 was used for plotting graphs. All data are expressed as mean ±SD. The difference of *CXCR7* expression between groups was analyzed by *t* test. The relationship between *CXCR7* expression and clinical features of PCa patients was analyzed with the chi-square test. Survival curves were constructed using Kaplan-Meier method and compared by log rank test. Cox

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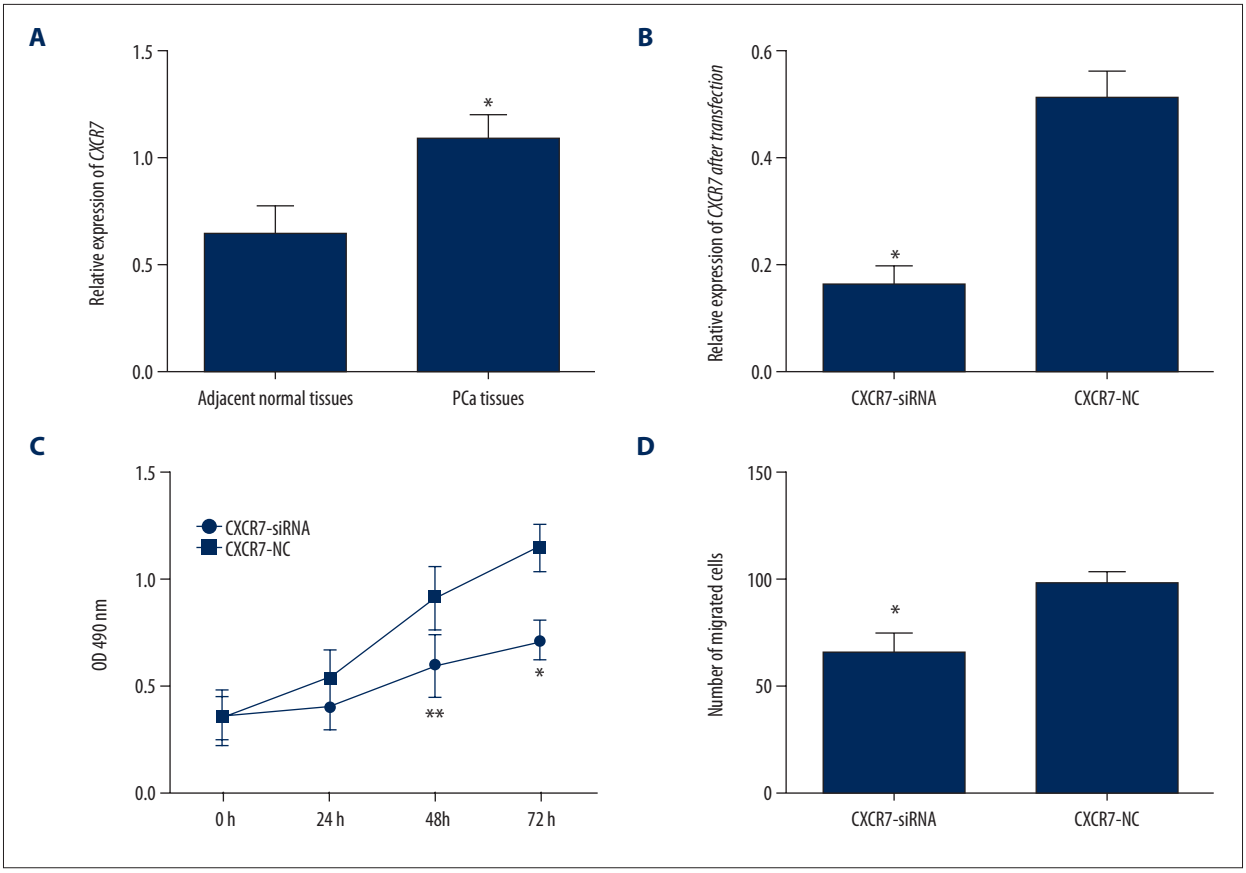

Figure 1. The expression pattern of *CXCR7* in tissues specimens, and its effects on the proliferation and migration of PCa cells *in vitro*. (**A**) Expression level of *CXCR7* between PCa tissues and adjacent normal tissues. The results suggested that *CXCR7* appeared to be highly expressed in PCa tissues compared with non-cancerous tissues ($P<0.05$). (**B**) *CXCR7* expression after transfected with *CXCR7*-siRNA and *CXCR7*-NC. *CXCR7*-siRNA successfully inhibited the expression of *CXCR7* in PC3 cells ($P<0.05$). (**C**) The proliferation of PC3 cell line after transfection. Inhibition of *CXCR7* expression suppressed the proliferative ability of PC3 cells. (**D**) The migration ability of PC3 cell line after transfection. Analysis indicated that PC3 cells transfected with *CXCR7*-siRNA had decreased migratory ability compared with those transfected with empty vector ($P<0.05$).

regression analysis was used for the univariate and multivariate analyses. Differences were considered statistically significant at $P<0.05$.

Results

High expression of *CXCR7* in PCa

We used qRT-PCR to examine the expression of *CXCR7* in 152 pairs of PCa tissues and adjacent normal tissues. The results showed that *CXCR7* expression in PCa tissues was significantly higher than that in adjacent normal tissues ($P<0.05$) (Figure 1A).

CXCR7 promoted the proliferation and migration of PCa cells

To explore the effect of *CXCR7* on behaviors of PCa cells, *CXCR7-siRNA* was constructed. The results shown in Figure 1B demonstrate that the siRNA vector was successfully constructed. MTT analysis indicated that the growth of cells transfected with *CXCR7-siRNA* was significantly decreased compared with the *CXCR7*-NC group ($P<0.05$) (Figure 1C). As shown in Figure 1D, the migratory ability of *CXCR7-siRNA*-transfected cells was reduced compared with the *CXCR7*-NC group ($P<0.05$).

The relationship between *CXCR7* expression and clinicopathologic features of PCa

We also explored the relationship between *CXCR7* expression level and clinicopathologic characteristics in PCa patients. The patients were grouped into high-expression and low-expression

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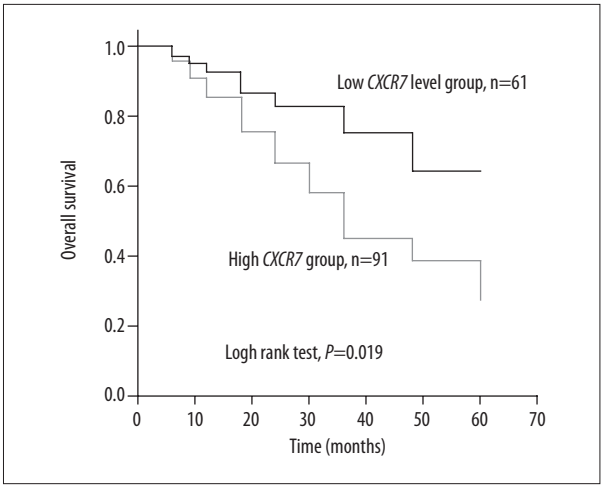

Figure 2. Kaplan-Meier analysis of PCa patients based on their expression of *CXCR7*. The overall survival curve demonstrated that patients with high level of *CXCR7* had a significantly worse survival than those with low level (log rank test, *P*=0.019).

groups according to their median expression value of *CXCR7*. The results in Table 1 show that *CXCR7* expression was obviously associated with PSA (*P*=0.023), differentiation (*P*=0.022), and lymph node metastasis (*P*=0.018). However, no obvious relationship was found between *CXCR7* expression and the age, tumor size, or TNM stage of the patients (all *P*>0.05).

Correlation between *CXCR7* expression and overall survival of PCa patients

The relationship between the expression of *CXCR7* level and survival time of the PCa patients was evaluated by Kaplan-Meier analysis. The 5-year survival rate for PCa patients with high *CXCR7* expression was significantly lower than that for patients with low *CXCR7* expression (*P*=0.019, Figure 2).

Prognostic value of *CXCR7* expression in PCa

Univariate and multivariate Cox regression analyses revealed a significant correlation between overall survival and *CXCR7* expression (HR=2.271, 95%CI=1.093-4.719, *P*=0.003, Table 2). Thus, *CXCR7* is a valuable independent biomarker for predicting the prognosis of PCa patients.

Discussion

PCa is a frequently diagnosed malignancy among men, with increasing morbidity with age [15,16]. PCa has a highly variable natural history. In patients diagnosed with indolent PCa, close surveillance is sufficient, while other patients need active treatments due to aggressive tumor progression [17]. It is challenging to discriminate between low-risk and high-risk PCa patients [18]. Prognostic biomarkers can accurately predict the progression of the cancer and can guide therapy. Conventionally, PCa prognosis evaluation is mainly based on surgical margin status, lymph node status, Gleason score, and PSA. Unfortunately, the prognostic performance of these factors is far from satisfactory [17,19]. Recently, in order to improve the management of PCa, more and more molecular biomarkers have been confirmed for PCa. For examples, Deng et al. showed that serum *PCDH10* is an independent predictor for overall survival of PCa patients [20]. Cui et al. reported that *SIRT1* can promote migration and invasion of PCa cells via epithelial-mesenchymal transition (EMT). *SIRT1* might be a potential therapeutic target for PCa [21]. In addition to genes, the non-coding miRNAs might also take part in regulation of PCa. For instance, *miR-301a* and *miR-301b* were 2 hypoxia-responsive miRNAs that might be involved in radioresistance of PCa [22]. Accumulating evidence demonstrates that the PCa-related genes may provide new insights into the etiology of PCa, which may be of great help in clinical practice.

Table 2. Univariable Cox analyses for *CXCR7* in 152 PCa patients.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
CXCR7 (high *vs.* low)	2.271	1.093–4.719	0.028	2.271	1.093–4.719	0.028
Age (year) (≥65 *vs.* <650	1.399	0.752–2.602	0.290	–	–	–
Tumor size (cm) (≥3 *vs.* <3)	1.002	0.555–1.809	0.994	—	–	–
PSA (ng/ml) (>20 *vs.* ≤20)	1.311	0.710–2.420	0.386	–	–	–
Differentiation (poor *vs.* well+moderate)	1.712	0.946–3.096	0.075	–	–	–
TNM stage (III+IV *vs.* I+II)	1.306	0.726–2.348	0.373	–	–	–
Lymph node metastasis (positive *vs.* negative)	1.215	0.675–2.188	0.516	–	–	–

'–' – indicated no related data.

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In recent years, *CXCR7* has been identified as a receptor to *CXCL12*, which is a 7-transmembrane span [23]. It was reported that dysregulation of *CXCR7* contributes to formation, invasion, and metastasis of cancers [24]. Elevated expression of *CXCR7* was observed in several cancers, such as lung, liver, brain, and breast cancers [10,25,26]. In this research, we investigated the *CXCR7* expression pattern in PCa. QRT-PCR suggested that PCa tissues exhibited increased expression of *CXCR7* compared with non-cancerous tissues. Moreover, upregulation of *CXCR7* was significantly correlated with high serum level of PSA, poor differentiation, and positive lymph node metastasis. All the data revealed that *CXCR7* was an oncogene in PCa and promoted the malignant progression of PCa.

In order to explore the oncogenic mechanisms of *CXCR7* in PCa, we performed a series of cell experiments. The results indicated that knockdown of *CXCR7* significantly suppressed proliferation and migration of PCa cells. Based on the above results, we deduced that *CXCR7* was involved in the progression of PCa through regulating the proliferative and migratory abilities of the cancer cells. *CXCR7* might be a therapeutic target for PCa. Mir et al. reported that Andrographolide damages PCa cells via targeting the expression of CXCR3 and *CXCR7* [27], supporting the conclusions of the present study. However, the specific molecular mechanisms by which *CXCR7* affects PCa remain unclear and further research is needed.

Given its functional roles in pathogenesis of malignancy, *CXCR7* is a predictive factor for several cancers. Wang et al. found that high expression of *CXCR7* predicted poor survival for patients with renal cell carcinoma [28]. In cervical cancer, upregulation of *CXCR7* was strongly correlated with aggressive clinical characteristics and might be an independent biomarker for disease-specific survival [29]. Yao et al. found that *CXCR7* expression was closely associated with tumor stage, which could serve as an independent biomarker for gallbladder cancer patients [30]. In our study, the clinical prognosis value of *CXCR7* in PCa was evaluated. The results of Kaplan-Meier analysis showed that PCa patients in the high *CXCR7* expression group had poor survival rate. Moreover, Cox regression analysis further suggested that *CXCR7* is a valuable independent biomarker for the prognosis of PCa patients. In this study, we proved that high expression of *CXCR7* predicted poor prognosis for PCa patients. However, the sample size was relatively small in this study, and the utility of *CXCR7* in PCa prognosis should be verified by further investigations.

Conclusions

Upregulation of *CXCR7* in PCa patients is significantly correlated with high concentration of PSA, poor differentiation, and positive metastasis. *CXCR7* may contribute to malignant progression of PCa by regulating the proliferative and migratory abilities of cancer cells, and *CXCR7* may be an independent biomarker for prognosis of PCa patients.

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