Relationship of Common Variants in PRL-3 Gene With Susceptibility and Prognosis of Prostate Cancer

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Abstract

Background: Phosphatase of regenerating liver-3 (*PRL-3*) was involved in a variety of malignancies. In this study, we investigated the expression pattern of *PRL-3* and its prognostic significance in prostate cancer (PCa).

Methods: The expression profiles of *PRL-3* in 126 pairs PCa tissues and adjacent normal specimens were analyzed by quantitative real-time polymerase chain reaction (qRT-PCR). Chi-square test was used to estimate the association of *PRL-3* level with clinicopathological factors. Survival analysis was performed by Kaplan-Meier method with log rank test. Prognosis analysis was carried out using Cox proportional hazard models.

Results: *PRL-3* expression was significantly up-regulated in PCa tissues compared to that in normal controls ($P<0.001$). Moreover, the expression of *PRL-3* was positively associated with lymph node metastasis ($P=0.038$), Gleason score ($P=0.003$) and lymphovascular invasion ($P=0.013$). High *PRL-3* expression predicted poor overall survival (OS) (log rank test, $P=0.019$) and dismal BCR-free survival (log rank test, $P=0.021$) for PCa patients. *PRL-3* was an independent prognostic factor for OS (HR=2.619, 95%CI=1.129-6.076, $P=0.025$) and BCR-free survival (HR=2.120, 95%CI=1.095-4.105, $P=0.026$) in PCa.

Conclusions: *PRL-3* expression is elevated in PCa, and exhibits positive association with malignant tumor progression. *PRL-3* may serve as a prognostic biomarker for patients with PCa.

Background

Prostate cancer (PCa) is one of the most frequently diagnosed malignancies in males, representing a leading cause of cancer-associated deaths worldwide [1, 2]. In China, the incidence and mortality of PCa are rapidly increasing, posing a big threat to human health [3]. Radical prostatectomy (RP) and radiotherapy are effective treatments for patients with PCa, however, many patients will develop postoperative recurrence, leading to high mortality [4]. Tumor progression evaluation remains a major challenge for PCa patients. Currently, the clinicopathological variables, such as Gleason score (GS), clinical tumor-node-metastasis (TNM) stage and pathological T (pT) staging are frequently used to guide treatments for PCa patients [5, 6]. However, the prognostic significance of these parameters can not meet the clinical needs. In addition, serum prostate-specific antigen (PSA) level is a main biomarker for risk stratification in PCa patients, but its low specificity may lead to over-diagnosis and treatments [7, 8]. Thus, novel and effective biomarkers are in urgent needs to improve the treatments and outcomes of PCa patients. The etiology PCa is a multi-steps process which is implicated in accumulation of genetic and epigenetic changes [9]. Therefore, the altered molecules during tumorigenesis of PCa may provide reliable information for prognosis and individual treatments in PCa.

Phosphatase of regenerating liver-3 (*PRL-3*, also known as *PTP4A3*) belongs to the *PRL* family, holds the potential to dephosphorylate tyrosine and serine/threonine residues [10]. *PRL-3* mainly exists in plasma membrane, and the early endosomes with a small unprenylated proteins fraction in nucleus [11].

Accumulating evidences suggest that *PRL-3* is involved in multiple steps in tumorigenesis, including cell proliferation, motility, metastasis, and invasion [12, 13]. High expression of *PRL-3* may enhance the malignant potential of the cancer cell through various pathways, such as Ras/MAPK, PI3K/Akt and SRC [14–16]. The oncogenic roles of *PRL-3* has been reported in colon cancer [17], gastric cancer [12], breast cancer [18], etc. In PCa, the expression of *PRL-3* showed increased in diseased tissues, and was positively correlated with proliferative and athletic abilities of the cancer cells [19]. Based on the related researches, we deduced that *PRL-3* might be a credible biomarker for prognosis prediction in PCa.

In this study, the expression pattern of *PRL-3* mRNA in PCa tissue specimen was detected, as well as its association with clinical characteristics. In addition, we evaluated the effects of *PRL-3* expression on overall survival of PCa patients, and its prognostic value in the disease.

Methods

Methods

Patients and specimens

All the experiments were performed in accordance with ethical and legal standards, and the approval of this study protocol was obtained from the Ethics Committee of Harrison International Peace Hospital. The PCa tissues and matched adjacent normal specimens were obtained from 126 PCa cases who had underwent radical prostatectomy in Harrison International Peace Hospital. Before surgery, none of the patients had received chemotherapy, radiation therapy or androgen deprivation treatment. After prostatectomy, the tissues samples were immediately frozen in liquid nitrogen and stored at -80°C until use. The follow up was conducted from 2 months to 60 months. Written informed consent was obtained from all patients, and the clinical information of the patients was shown in Table 1.

Table 1
The relationship between *PRL-3* level and the clinicopathological characteristics of PCa patients

Variables	N	<i>PRL-3</i> level		<i>P</i> value
		High (60)	Low (66)	
Age				0.746
≥ 65	67	31	30	
< 65	58	29	36	
Lymph node metastasis				0.038
Negative	77	31	46	
Positive	49	29	20	
Perineural invasion				0.506
Present	57	29	28	
Absent	69	31	38	
Gleason score				0.003
4–6	70	25	45	
7–10	56	35	21	
Lymphovascular invasion				0.013
Present	61	36	25	
Absent	65	24	41	
Surgical margin				0.832
Negative	81	38	43	
Positive	45	22	23	

RNA isolation and quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted from tissues performed with Trizol reagent (Invitrogen, Carlsbad, CA) along with RNase-free DNase according to the manufacturer's instructions. Complementary DNA (cDNA) was synthesized by reverse transcriptase (SuperScript III, Invitrogen, Carlsbad, CA). QRT-PCR was applied to detect the relative expression level of *PRL-3* mRNA. The reaction was carried out using SYBR-Green PCR Master Mix (Applied Biosystems, Foster City, CA, USA) on ABI Prism 7900 Sequence Detection System (Applied Biosystems). *GAPDH* was used as internal control. The sequences of used primers were listed: *PRL-3* forward 5'-AGTTGCCCGCTTTACTTTGGTTGG-3' and reverse 5'-AGGAAGCTGCCCACTGTTTGATA-

3'. *GAPDH* forward 5'-CGGAGTCAACGGATTTGGTCGTAT-3', reverse 5'-AGCCTTCTCCATGGTGGTGAAGAC-3'. The relative expression of *PRL-3* was calculated by $2^{-\Delta\Delta C_t}$. All experiments were in triplicate.

Serum PSA measurements

After prostatectomy, serum prostate-specific antigen (PSA) level of patients were measured by ELISA kit. Moreover, the PSA level > 0.2 ng/ml was defined as biochemical recurrence (BCR).

Statistical analysis

SPSS 18.0 software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad, San Diego, CA, USA) were used for statistical analysis. The expression value of *PRL-3* was expressed as mean $\pm$ SD, and its difference between two groups were compared by Student's t-test. Chi-square test was used to evaluate the association between *PRL-3* expression and clinicopathological variables of the patients. Survival analysis was estimated using the Kaplan-Meier method with the log-rank test, and Cox's regression model was applied for prognosis analysis. $P < 0.05$ was considered statistically significant.

Results

PRL-3 expression is increased in PCa

To determine the potential role of *PRL-3* in the tumorigenesis and progression of PCa, we assessed *PRL-3* mRNA expression in 126 PCa tissues and matched adjacent normal tissues specimens by qRT-PCR. As shown in Fig. 1, the expression of *PRL-3* in PCa samples was significant higher than that in normal controls ($P < 0.001$).

Associations between *PRL-3* expression and clinicopathological parameters

In this study, the mean expression value of *PRL-3* mRNA in 126 PCa patients was used as the cutoff to divide the cases into high expression ($n = 60$) and low expression ($n = 66$) groups. Chi-square test indicated that the increased expression of *PRL-3* was significantly associated with positive lymph node metastasis ($P = 0.038$), high Gleason score ($P = 0.003$) and lymphovascular invasion ($P = 0.013$). However, no association between expression levels of *PRL-3* with age, perineural invasion or surgical margin (all, $P > 0.05$) was found (Table 1)

The association of *PRL-3* with the overall survival and BCR-free survival

Kaplan-Meier survival curves were constructed to evaluate the effects of *PRL-3* expression on overall survival and BCR-free survival of patients with PCa. The curves suggested that patients with high *PRL-3* expression had shorter overall survival than those with low expression (log rank test, $P = 0.019$; Fig. 2). The BCR-free survival curves demonstrated that high expression of *PRL-3* predicted poor BCR-free survival for patients with the disease (log rank test, $P = 0.021$; Fig. 3).

More importantly, the univariate and multivariate Cox proportional hazards model analysis was applied to evaluate the predictive significance of clinical parameters and PRL-3 expression for overall survival and BCR-free survival. Analysis results revealed that lymph node metastasis ($P = 0.030$), Gleason score ($P = 0.028$) and PRL-3 expression ($P = 0.025$) were significantly correlated with overall survival of PCa patients. Multivariate analysis demonstrated that increased PRL-3 expression was an independent biomarker for poor prognosis in PCa (HR = 2.619, 95%CI = 1.129–6.076, $P = 0.025$) (Table 2). Likewise, cox analysis for BCR-free survival revealed that upregulation of *PRL-3* might be employed as a significant predictor for dismal BCR-free survival (HR = 2.120, 95%CI = 1.095–4.105, $P = 0.026$) (Table 3).

Table 2
Prognostic value of *PRL-3* and clinical parameters for OS in PCa patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age	1.489 (0.673–3.292)	0.326	-	-
Lymph node metastasis	2.407 (1.091–5.313)	0.030	-	-
Perineural invasion	0.999 (0.453–2.205)	0.999	-	-
Gleason score	2.575 (1.110–5.970)	0.028	-	-
Lymphovascular invasion	1.119 (0.508–2.462)	0.781	-	-
Surgical margin	1.214 (0.535–2.751)	0.643	-	-
<i>PRL-3</i> expression	2.619 (1.129–6.076)	0.025	2.619 (1.129–6.076)	0.025
Note: -: indicated no related data.				

Table 3
Prognostic value of *PRL-3* for the BCR-free survival in univariate and multivariate Cox proportional hazards model analysis.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age	1.102 (0.580–2.094)	0.766	-	-
Lymph node metastasis	1.774 (0.935–3.364)	0.079	-	-
Perineural invasion	1.901 (0.990–3.650)	0.054	-	-
Gleason score	1.893 (0.987–3.629)	0.055	-	-
Lymphovascular invasion	1.384 (0.730–2.624)	0.319	-	-
Surgical margin	1.595 (0.836–3.042)	0.157	-	-
<i>PRL-3</i> expression	2.120 (1.095–4.105)	0.026	2.120 (1.095–4.105)	0.026
Note: -: indicated no related data.				

Discussion

Prostate cancer (PCa) is a frequently diagnosed malignancy in males worldwide, with severe mortality [20]. Although the diagnosis and therapies for PCa have been significantly improved, the clinical outcome of the patients is still poor. Recurrence and metastasis are the major reasons for cancer-related deaths in PCa patients [4]. Up to now, serum PSA is the only biomarker for early screening and monitoring of PCa in clinical setting [21]. Despite of the high sensitivity, the low specificity of PSA may lead to over-treatments [22]. Therefore, it is of great importance to develop reliable biomarkers for prognosis estimation and guidance of treatments in PCa. In the present study, our results confirmed that the expression of *PRL-3* was remarkably increased in PCa tissues, and significantly correlated with tumor progression and outcomes of the patients, suggesting its possibility to act as an independent prognostic biomarker for patients with PCa.

The PRL family, comprised of PRL-1, PRL-2, and PRL-3, plays an important role in development and metastasis of human malignancies, based on their regulatory roles in cellular processes [23]. The family member of PRL may control cell growth and tumorigenesis through various pathways. For instance, the study carried out by Jin et al. demonstrated that the oncogenic function of *PRL-1* in progression and metastasis of hepatocellular carcinoma might be mediated by PI3K/AKT/GSK3 β signaling pathway. Up-regulation of *PRL-1* predicted poor prognosis for patients with the disease [24]. As a member of PRL subgroup, *PRL-3* also played a promoting role in malignant progression of cancer. Xiong et al. suggested that the expression of PRL-3 showed increased in metastatic gastric cancer tissues, and it might control the aggressive potential of the cancer cell via activating the PI3K/Akt signaling pathway, and up-regulating MMP-2/MMP-9 expression [12]. Besides of gastric cancer, the over-expression of PRL-3 was

also observed in ovarian cancer, breast cancer, esophageal squamous cell carcinoma, cervical carcinoma, and colorectal cancer [25–29]. The dysregulation of PRL-3 in tumorigenesis showed significant association with tumor progression and clinical outcomes of the patients which might be employed as a prognostic biomarker for the cancers. However, the prognostic performance of PRL-3 in PCa remained unclear.

In the current study, we investigated the expression pattern of PRL-3 in PCa tissues specimens, as well as its association with clinical parameters of the patients. Analysis results suggested that PCa tissues exhibited up-regulated expression of PRL-3, compared with non-cancerous tissues. Moreover, the elevated expression of PRL-3 was positively correlated with lymph node metastasis, Gleason score and lymphovascular invasion. The data revealed that PRL-3 served as an oncogene in progression of PCa. The increased expression of PRL-3 might enhance the malignant development and progression of the disease. It was reported that the over-expression of PRL-3 might promote the growth and migration of PCa cell line, thus contributing to the pathogenesis of PCa [19]. However, the molecular mechanisms underlying the oncogenic action of PRL-3 in PCa were poorly known. Further analysis was still required to address the issue.

Growing evidences have reported that *PRL-3* was an useful indicator for patient outcome in several human cancers, including hepatocellular cancer [25], gastric cancer [30] and colorectal cancer [31]. In the present study, survival analysis showed that patients with high *PRL-3* expression had significantly worse OS and BCR-free survival than those with low *PRL-3* expression. More importantly, multivariate analysis demonstrated *PRL-3* could serve as an independent biomarker for clinical outcomes and BCR-free survival for patients with PCa. However, the results might be limited by the single-center study design and relatively small sample size in the current study. The predictive value of PRL-3 for prognosis of PCa was required to be identified by further studies.

Conclusions

In summary, *PRL-3* expression is significantly upregulated in PCa tissues, and positively correlated with aggressive development and progression of the disease. PCa may be an independent prognostic factor for patients with PCa.

Abbreviations

Phosphatase of regenerating liver-3 (*PRL-3*)

prostate cancer (PCa)

quantitative real-time polymerase chain reaction (qRT-PCR)

overall survival (OS)

Radical prostatectomy (RP)

Gleason score (GS)

tumor-node-metastasis (TNM)

pathological T (pT)

prostate-specific antigen (PSA)

biochemical recurrence (BCR)

Declarations

Ethics approval and consent to participate

This study was supported by the Ethics Committee of Harrison International Peace Hospital and also has been carried out in accordance with the World Medical Association Declaration of Helsinki.

The subjects had been informed the objective. Certainly, written consents were signed by every subject in this study.

Consent for publication: We obtaining permission from participants to publish their data.

Availability of data and materials The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

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Authors' contributions S.C., L.Z. design of the work; S.C., L.Z. the acquisition, analysis, S.C., L.Z. interpretation of data; S.C., L.Z. the creation of new software used in the work; S.C., L.Z. have drafted the work or substantively revised it. All authors read and approved the final manuscript.

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Figures

Figure 1

Relative PRL-3 mRNA expression in PCa tissue specimens detected by qRT-PCR method. The PRL-3 level in PCa tissues was significantly higher than in adjacent normal specimens ($P < 0.001$).

Figure 2

Associations between PRL-3 expression and survival of patients after prostatectomy. Patients with high PRL-3 expression showed significantly shorter overall survival than those with low PRL-3 expression (log rank test, $P=0.019$).

Figure 3

The effects of *PRL-3* expression on BCR-free survival of patients with PCa. High *PRL-3* expression indicated significantly poor BCR-free survival in patients with PCa (log rank test, $P=0.021$).