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Prognostic Value of Protocadherin10 (PCDH10) Methylation in Serum of Prostate Cancer Patients

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

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Background: Prostate cancer is a heterogeneous malignancy with outcome difficult to predict. Currently, there is an urgent need to identify novel biomarkers that can accurately predict patient outcome and improve the treatment strategy. The aim of this study was to investigate the methylation status of PCDH10 in serum of prostate cancer patients and its potential relevance to clinicopathological features and prognosis.

Material/Methods: The methylation status of PCDH10 in serum of 171 primary prostate cancer patients and 65 controls was evaluated by methylation-specific PCR (MSP), after which the relationship between PCDH10 methylation and clinicopathologic features was evaluated. Kaplan-Meier survival analysis and Cox analysis were used to evaluate the correlation between PCDH10 methylation and prognosis.

Results: PCDH10 methylation occurred frequently in serum of prostate cancer patients. Moreover, PCDH10 methylation was significantly associated with higher preoperative PSA level, advanced clinical stage, higher Gleason score, lymph node metastasis, and biochemical recurrence (BCR). In addition, patients with methylated PCDH10 had shorter BCR-free survival and overall survival than patients with unmethylated PCDH10. Univariate and multivariate Cox proportional hazards model analysis indicated that PCDH10 methylation in serum is an independent predictor of worse BCR-free survival and overall survival.

Conclusions: PCDH10 methylation in serum is a potential prognostic biomarker for prostate cancer.

MeSH Keywords: Cadherins • Methylation • Prostatic Neoplasms • Tumor Markers, Biological

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Background

Prostate cancer is the most common malignancy in men, with an estimated 220 800 new cases and 27 540 deaths in the USA in 2015 [1]. Prostate cancer is a molecularly heterogeneous disease; varied clinical outcomes and prognosis are found even among patients with the same tumor/node/metastasis (TNM) classification. Although surgical resection for localized prostate cancer is the best treatment for cure, some patients eventually relapse and progress after surgery [2–4]. Currently, there is no accurately predictive marker of risk assessment for the outcome of prostate cancer patients and it is a major challenge to distinguish aggressive tumors from indolent ones [5–7]. Thus, novel predictive biomarkers are urgently needed.

Recently, cumulative evidence indicates that the initiation and progression of prostate cancer results from accumulation of genetic and epigenetic changes [8–10]. In addition, aberrant methylation of certain tumor-suppressor genes (TSGs) is regarded as the most frequent alteration in human cancers. Thus, aberrant DNA methylation is a promising candidate for potential biomarker [11–13]. Moreover, DNA methylation not only exists in tumor samples, but also in body fluids, especially in serum. Current studies verified that circulating DNA has methylation status similar to that in tumor samples [14–16]. Thus, the detection of serum tumor-related methylated genes may be used as a potential biomarker in human cancers.

In recent years, more and more studies have focused on the aberrant methylation of cadherin family members in human cancer. Cadherins are transmembrane glycoproteins of a large superfamily that includes classic cadherins, protocadherins, desmosomal cadherins, atypical cadherins, and cadherin-related neuronal receptors. These members play important roles in homophilic cell-cell adhesion, establishment of cell polarity, cell proliferation, migration, and differentiation [17–19]. Protocadherin10 (PCDH10), a member of protocadherin gene subfamily, is a recently identified putative TSG in several human malignancies [20–23]. Previous studies have shown that PCDH10 is down-regulated and hypermethylated in prostate cancer [23–25]. However, the clinical significance of PCDH10 methylation in serum of prostate cancer patients remains unclear.

In this study we examined the methylation status of PCDH10 in serum samples of patients with prostate cancer, and correlated PCDH10 methylation status with clinicopathological parameters, as well as patient outcome. The ultimate goal of this study was to determine whether PCDH10 methylation in serum can be used as a potential predictive biomarker in prostate cancer.

Material and Methods

Patients and sample collection

This study was performed according to the Declaration of Helsinki and was approved by the review board of the Third Hospital of Hebei Medical University (no. HMU20040504E). Written informed consent was received form each participant. A total of 236 patients were recruited in our study, including 171 consecutive patients with primary prostate cancer undergoing laparoscopic radical prostatectomy, and 65 patients with benign prostatic hyperplasia (BPH) undergoing transurethral resection of prostate in the Department of Urology of our hospital between 2005 and 2009. None of these prostate cancer patients had received preoperative radiotherapy, chemotherapy, or hormonal treatment. The prostate tissues were reviewed by 2 senior pathologists to confirm the diagnosis and Gleason score. Whole peripheral blood samples (10 ml) were collected before surgery from all the participants. Clotting of serum samples was allowed for 60 min before centrifugation at 1800 g per min for 10 min, and the supernatants were stored at –80°C.

Relevant clinical and pathologic information – age, clinical stage, Gleason score, lymph node metastasis, surgical margin, and preoperative prostate-specific antigen (PSA) – was collected from all the prostate cancer patients (Table 1). The time to biochemical recurrence (BCR) was defined as the period between radical prostatectomy and the measurement of 2 successive values of serum PSA level ≥0.2 ng/ml [26]. The follow-up was conducted from the date of surgery until death or the December 2014 deadline. The BCR-free survival was defined as the time from the initial surgery to the date of BCR, and the overall survival was defined as the time from the date of surgery to the date of death resulting from any cause.

DNA extraction, bisulfite treatment, and methylation-specific PCR (MSP)

DNA was extracted from 0.8 ml archived serum from each patient using the QIAmp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA), according to the manufacturer's instructions. The isolated DNA was modified with bisulfite using the EpiTect Bisulfite Kit (Qiagen, Valencia, CA, USA) and standard protocol as described previously [27,28]. The methylation status of PCDH10 was detected using MSP, as previously described [24,28]. The following PCDH10 MSP primers were used: methylated: forward 5'-TCG TTA AAT AGA TAC GTT ACG C-3' and reverse 5'-TAA AAA CTA AAA ACT TTC CGC G-3'; unmethylated: forward 5'-GTT GTT AAA TAG ATA TGT TAT GT-3' and reverse 5'-CTA AAA ACT AAA AAC TTT CCA CA-3'. The PCR amplification was carried out as reported previously [24,28]. *In vitro* methylated DNA and unmethylated DNA (New England Biolabs, Beverly, MA, USA) were used as methylation and unmethylation positive control,

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Table 1. The correlations between PCDH10 methylation in serum and clinicopathologic features of patients with prostate cancer (n=171).

Features	Variables	No.	M (%)	U (%)	P
Age (years)	≤70	90	41 (45.6)	49 (54.4)	0.103
	>70	81	47 (58.0)	34 (42.0)	
Preoperative PSA (ng/ml)	≤10	58	20 (34.5)	38 (65.5)	0.001
	<10	113	68 (60.2)	45 (39.8)	
Clinical T stage	T1	83	38 (45.8)	45 (54.2)	0.035
	T2	61	30 (49.2)	31 (50.8)	
	T3	27	20 (74.1)	7 (25.9)	
Gleason score	≤6	44	16 (36.4)	28 (63.6)	<0.001
	7	74	33 (44.6)	41 (55.4)	
	≥8	53	39 (73.6)	14 (26.4)	
Lymph node status	N0	146	70 (47.9)	76 (52.1)	0.026
	N1	25	18 (72.0)	7 (28.0)	
Surgical margin status	Negative	156	79 (50.6)	77 (49.4)	0.488
	Positive	15	9 (60.0)	6 (40.0)	
BCR	No	122	49 (40.2)	73 (59.8)	<0.001
	Yes	49	39 (79.6)	10 (20.4)a	

M – methylation; U – unmethylation; BCR – biochemical recurrence.

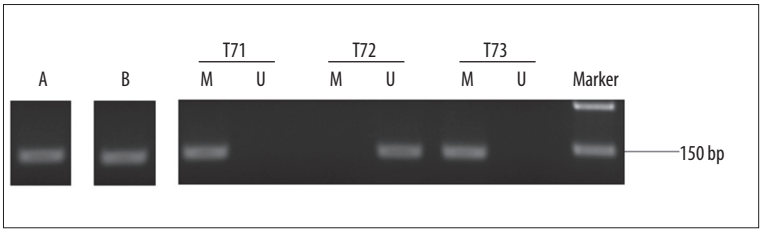

Figure 1. Representative MSP results for PCDH10 methylation in serum of patients with prostate cancer. A – methylation-positive control; B – unmethylation-positive control; T – prostate cancer patients; T71 and 73 – exhibited methylated PCDH10; T72 – exhibited unmethylated PCDH10.

respectively. The MSP products were separated in 2% agarose gel, stained with ethidium bromide, and visualized under ultraviolet illumination for analysis. The product was defined as methylation-positive when methylated allele was present in the methylated DNA lane or both in the methylated and unmethylated DNA lanes, and the product was defined as methylation-negative when a band was present only in the unmethylated DNA lane, as reported previously [24,27,28].

Statistical analysis

The difference in PCDH10 methylation between prostate cancer patients and controls was evaluated using Fisher's exact test. The association between PCDH10 methylation and clinicopathologic parameters was evaluated by chi square test. Kaplan-Meier survival analysis and log-rank test were used for survival analysis. Univariate and multivariate Cox proportional hazards model analysis was used to evaluate the predictive effect of PCDH10 methylation in serum on prostate cancer. The statistical analysis was performed using SPSS 13.0 software. P<0.05 was considered to be statistically significant.

Results

The methylation status of PCDH10 in serum

In the current study, we first examined the methylation status of PCDH10 in serum of prostate cancer patients (n=171) and in patients with BPH (n=65). Interestingly, PCDH10 methylation was found in 88 (51.5%) patients with prostate cancer, but no PCDH10 methylation was detected in patients with BPH (Figure 1). The difference between these 2 groups was statistically significant (P<0.001).

Association between PCDH10 methylation in serum and clinicopathologic parameters

To clarify the clinical significance of PCDH10 methylation in serum of prostate cancer patients, the correlation between PCDH10 methylation and clinicopathologic parameters was conducted. We found that PCDH10 methylation was significantly associated with higher preoperative PSA level (P=0.001), advanced

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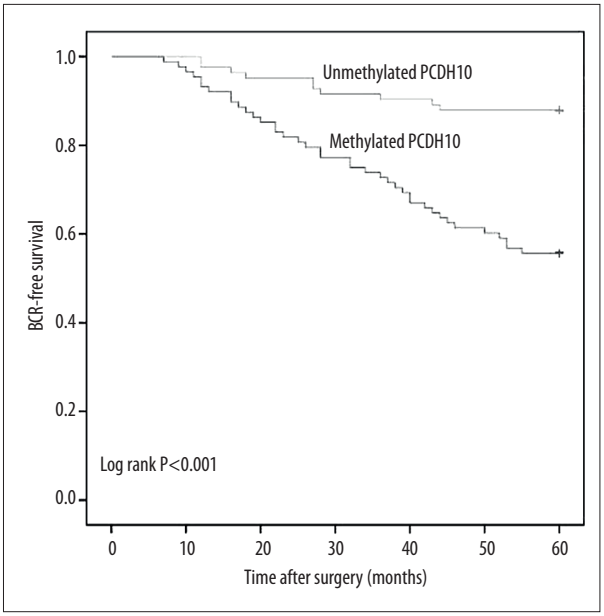

Figure 2. Associations between PCDH10 methylation and BCR-free survival of patients after radical prostatectomy. Patients with methylated PCDH10 showed significantly shorter BCR-free survival than those with unmethylated PCDH10. (P<0.001, log-rank test)

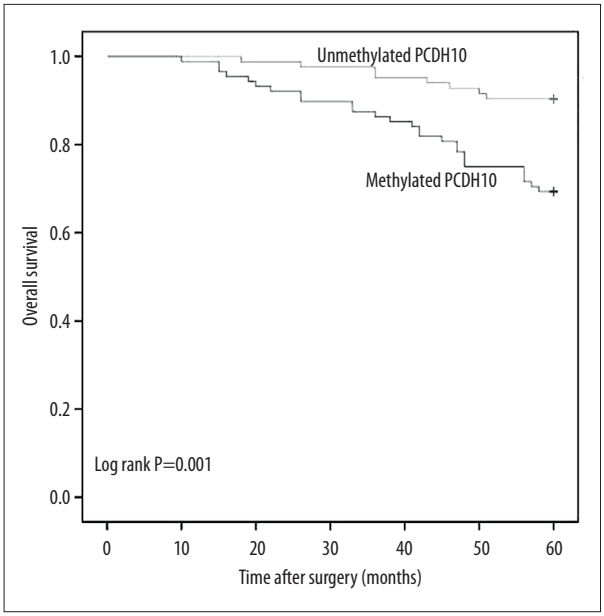

Figure 3. Associations between PCDH10 methylation and overall survival of patients after radical prostatectomy. Patients with methylated PCDH10 showed significantly shorter overall survival than those with unmethylated PCDH10. (P=0.001, log-rank test).

clinical stage (P=0.035), higher Gleason score (P<0.001), lymph node metastasis (P=0.026), and BCR (P<0.001). However, no correlation was found between PCDH10 methylation and age or surgical margin (P>0.05). These findings are shown in Table 1.

The predictive value of PCDH10 methylation for the prognosis of prostate cancer patients

One of the most important challenges in clinical practice for prostate cancer is to find more accurate predictive biomarkers to guide individualized treatment. For this reason, the association between PCDH10 methylation in serum and BCR-free survival/5-year overall survival was evaluated. Kaplan-Meier survival analysis and log-rank test indicated that patients with methylated PCDH10 had shorter BCR-free survival (Figure 2) and overall survival (Figure 3) than patients with unmethylated PCDH10. Moreover, univariate and multivariate Cox proportional hazards model analysis further confirmed that PCDH10 methylation in serum is an independent predictive biomarker of shorter BCR-free survival (Table 2) and overall survival (Table 3).

Discussion

Prostate cancer is a heterogeneous malignancy with outcome difficult to predict. Currently, some clinicopathologic features, such as PSA, Gleason score, and clinical stage, are used to predict patient outcome in clinical practice, but they fail to accurately distinguish aggressive tumors form indolent ones [29]. Thus, there is an urgent need to identify novel biomarkers that can accurately predict patient outcome and improve treatment strategy. Multiple studies indicated that aberrant DNA methylation is a hallmark of prostate cancer and is associated with malignant initiation, as well as progression, and demonstrated that it is possible to use it as a potential biomarker [30].

There are several advantages to using DNA methylation as a prognostic biomarker in human cancers [30,31]. First, genomic DNA is more stable than RNA and protein. Second, DNA can be easily extracted from tissue specimens. Third, DNA methylation can be examined by simple, inexpensive methods, such as MSP, which can be easily implemented into routine clinical practice. Moreover, DNA methylation not only can be detected in tissue samples, but also in body fluids, especially in serum. Serum samples can be obtained through a minimally invasive procedure and provide an ideal substrate for DNA methylation analysis. Li et al. found that PCDH10 gene was inactivated by promoter hypermethylation in human prostate cancer cell lines [24]. Moreover, our previous study indicated that PCDH10 methylation occurred frequently in prostate cancer tissues and was associated with malignant behaviors and poor BCR-free survival [25]. These findings prompted us to further investigate the clinical significance of PCDH10 methylation in serum of prostate cancer patients.

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Table 2. Prognostic value of PCDH10 methylation in serum for the BCR-free survival in univariate and multivariate Cox proportional hazards model analysis.

Varivale	Univariate analysis			Multivariate analysis		
	Exp (B)	95% CI	P	Exp (B)	95% CI	P
Age	0.906	0.714–4.834	0.627			
PSA	1.357	0.747–4.692	0.047	1.142	0.861–4.375	0.114
Clinical T stage	1.963	1.286–5.344	0.016	1.273	0.932–4.763	0.075
Gleason score	2.967	1.109–6.284	0.003	1.574	1.043–5.327	0.021
Lymph node status	1.223	0.918–3.545	0.142			
Surgical margin status	1.033	0.785–2.623	0.417			
PCDH10 methylation	3.679	1.542–5.372	<0.001	2.796	1.431–6.763	0.006

Table 3. Prognostic value of PCDH10 methylation in serum for the Overall survival in univariate and multivariate Cox proportional hazards model analysis.

Varivale	Univariate analysis			Multivariate analysis		
	Exp (B)	95% CI	P	Exp (B)	95% CI	P
Age	0.895	0.733–4.845	0.736			
PSA	1.264	1.187–3.562	0.044	0.947	0.783–6.763	0.362
Clinical T stage	1.721	1.313–4.766	0.034	1.147	1.088–4.546	0.047
Gleason score	2.742	1.338–5.467	0.009	1.435	1.253–3.486	0.036
Lymph node status	1.006	0.745–3.468	0.507			
Surgical margin status	1.103	0.804–2.462	0.426			
PCDH10 methylation	3.183	1.562–7.631	0.001	2.271	1.426–6.168	0.013

In this study we first demonstrated that PCDH10 gene was frequently methylated in serum of patients with prostate cancer. Only a few studies have examined the aberrant DNA methylation in serum as a biomarker for prostate cancer [30,31]. Checking serum DNA methylation has the advantages of less invasiveness, low cost, high sensitivity and specificity, and suitability for clinical application [30–34]. Moreover, PCDH10 methylation was only detected in prostate cancer patients, not in controls. This finding suggests that PCDH10 methylation in serum is tumor-specific in prostate cancer. Thus, it is possible to evaluate its clinical significance. Subsequently, we correlated PCDH10 methylation to clinicopathologic features of prostate cancer. Interestingly, PCDH10 methylation in serum was significantly associated with higher preoperative PSA level, advanced clinical stage, higher Gleason score, and lymph node metastasis. These parameters are all risk factors for the relapse and progression of prostate cancer [3]. Moreover, PCDH10 methylation in serum was significantly associated with BCR after surgery. The results indicated that PCDH10 methylation in serum was associated with malignant behaviors of prostate cancer.

Considering that aberrant DNA methylation plays an essential role in tumor initiation and progression [35–38], we further explored the prognostic value of PCDH10 methylation in prostate cancer patients. Kaplan-Meier survival analysis and log-rank test indicated that patients with methylated PCDH10 in serum had worse BCR-free survival and overall survival than patients with unmethylated PCDH10. Moreover, univariate and multivariate Cox proportional hazards model analysis further confirmed that PCDH10 methylation in serum is an independent predictive biomarker of worse BCR-free survival and overall survival in prostate cancer. Similarly, other reports found a significant association between PCDH10 methylation in serum and worse outcome of patients with bladder cancer and colorectal cancer [28,39]. These results suggest that PCDH10 methylation in serum is an independent prognostic biomarker in prostate cancer; patients with methylated PCDH10 in serum have higher risk of BCR and death. Therefore, PCDH10 methylation in serum could constitute a molecular predictive marker for prostate cancer patients, identifying patients who are more likely to have higher risk of BCR and death and who need more aggressive adjuvant therapy after initial curative surgery, so as to achieve better prognosis. Our findings could help establish a more individualized therapy strategy.

Our study also has some limitations. Our cohort consisted of only 65 patients with BPH as control, and this study only used

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1 method. In future studies, more healthy people should be included in the control group, and another method should be used to verify and extend the findings, such as microarray.

Conclusions

In conclusion, our data demonstrated that PCDH10 methylation occurred frequently in serum of patients with prostate cancer, and was associated with higher preoperative PSA level, advanced clinical stage, higher Gleason score, lymph node metastasis, and BCR. Moreover, patients with methylated PCDH10 in serum had worse BCR-free survival and overall survival, and PCDH10 methylation in serum is an independent predictor for BCR-free survival and overall survival. Our findings suggest that PCDH10 methylation is a novel prognostic biomarker for prostate cancer.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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