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Original Article

Relationship between miR-223 and miR-152 expression and prostate cancer prognosis

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Abstract: Objective: The goal of this study was to determine miR-223 and miR-152 expression in serum and tissues of patients with prostate cancer (PCa) and the significance in clinical practice. Methods: Serum and tissue specimens and normal adjacent tissue specimens from 90 patients and serum from 80 healthy individuals were collected. qRT-PCR was used to detect miR-223 and miR-152 expression in serum and tissue samples. The relationship between miR-223 and miR-152 expression and clinicopathological parameters was analyzed. Results: miR-223 expression in PCa serum was significantly higher than in controls ($P = 0.004$, while miR-152 expression in PCa serum was significantly lower ($P = 0.017$). Compared to the control group, relative miR-223 expression, tumor differentiation, TNM staging, prostate-specific antigen, lymph node metastasis, and Gleason score significantly differed from the PCa group (All $P < 0.05$). A significant correlation was observed between miR-152 relative expression and differentiation, lymph node metastasis, and Gleason score (All $P < 0.05$). Pearson correlation analysis showed that miR-223 and miR-152 expression in the PCa serum was positively correlated with expression in PCa tissue. Multivariate analysis showed that pathological stage, TNM staging, lymph node metastasis, and miR-223 and miR-152 expression levels were independent prognostic factors affecting the overall survival time of patients ($P = 0.005$ and 0.008, respectively). Conclusion: miR-223 and miR-152 expression may be involved in PCa occurrence and development and related to the degree of tumor differentiation and lymph node metastasis. These expression levels may be independent prognostic indicators for PCa.

Keywords: Prostate cancer, miR-223, miR-152, prognosis

Introduction

Prostate cancer (PCa) is the most common malignancy in male patients and second leading cause of death in male patients in Western countries [1]. Statistics show that approximately 900,000 PCa patients were newly diagnosed and 250,000 PCa deaths occurred worldwide in 2008 [2]. Because society is aging, there will be an estimated 1.7 million new diagnoses and 500,000 deaths by 2030. Thus, novel early diagnostic methods are needed to reduce the physiological, psychological, and economic burdens on patients and their families [3]. Treatment of PCa is mostly based on surgery. However, most patients are admitted with advanced disease such that they can no longer undergo surgery and the cancer can only be suppressed through radiation therapy. Patients also develop tolerance following long-term radiation therapy, which has a great adverse effects on the patient's treatment [4]. Therefore, early diagnosis of PCa is particularly important.

microRNAs (miRNAs) are small non-coding RNAs present in eukaryotes with highly conserved sequences and lengths of 19-22 base pairs [5]. By binding of the miRNAs to the 3'-untranslated region of the target gene, expression and translation of the target gene can be promoted or inhibited after transcription, thus post-transcriptionally regulating gene expression [6]. Studies have shown that differential expression of miRNAs can also regulate a variety of biological processes such as infections, cardiovascular diseases, and tumors [8]. A large body of literature shows that miRNAs play a key role in the occurrence and development of tumors, such as promoting tumor cell proliferation, invasion, and apoptosis [9, 10]. The miRNAs miR-223 and miR-152 have been

Table 1. PCR primer sequences

Gene	Forward primer	Reverse primer
miR-223	5'-CAGAAAGCCCAATTCCATCT-3'	5'-GGGCAAATGGATACCATACC-3'
miR-152	5'-ACTCTCGAGGCTTCTAAGCTGGGAACTTTGTC-3'	5'-ACTGAATTCCGCTTGTCTTGGACATATGGCACT-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'

reported to have many biological functions in PCa. However, whether they can be used as markers for PCa diagnosis remains unclear.

Therefore, in this study we examined the expression of miR-223 and miR-152 in tissues and serum samples from patients with PCa, and further validated the expression of miR-223 and miR-152 in patients with PCa as new clinical diagnostic indicators.

Material and methods

Patient clinical data

Serum, tumor tissue specimens, and normal adjacent tissue specimens (≥ 5 cm away from lesions) from 90 patients with PCa and serum from 80 healthy individuals present in our hospital during the same period were collected. The ages of PCa patients ranged from 55 to 70 years and the average age was 65.54 ± 5.84 years. During the same period, the age of healthy examinees was 57-68 years old and the average age was 64.84 ± 6.24 years. All 90 patients with PCa were diagnosed by biopsy. Histological grading was performed according to the American Joint Committee on Cancer version 7 [11]. PCa pathological grade was classified according to the 2003 WHO PCa Gleason scores [12]. The study was approved by the Medical Ethics Committee of the hospital, and patients' family members provided informed consent. There was no significant difference in clinical data between the two groups.

Inclusion/exclusion criteria

Inclusion criteria: The patient's age was > 18 years old; there was no kinship among the patients; the patient had no familial inherited disease or congenital defects memory impairment, autism, or hearing impairment; and the patient's limbs were healthy.

Exclusion criteria: Patients with malignant tumor history, surgery in the past 3 years, uncooperative patients, patient who did not follow-up, and patients for whom incomplete clinical information was available were excluded.

Instruments and reagents

The mirVana PARIS RNA isolation kit was purchased from Ambion (Foster City, CA, USA). Trizol extraction reagent was purchased from Invitrogen (Carlsbad, CA, USA). The TaqMan MicroRNA reverse transcription kit was purchased from Applied Biosystems (Foster City, CA, USA). The TaqMan 2X Universal PCR Master Mix was purchased from Thermo Fisher Scientific (Waltham, MA, USA). The ABI7900-PCR amplification apparatus was purchased from Applied Biosystems. PCR primers were designed and synthesized by Shanghai Shenggong Biological Co., Ltd. (Shanghai, China) (**Table 1**).

Specimen collection and biochemical detection

Cancer tissue collection: During surgery, resected cancer tissue and normal adjacent tissue that was at least 5 cm away from the cancer tissue were collected at the same time. Samples were stored in liquid nitrogen and sent to the laboratory for analysis within 5-10 days.

Patients' venous blood collection: Fasting venous blood was collected from patients one day before surgery into an EDTA tube. The first 3 mL was discarded to prevent contamination of small RNA during puncture. After centrifugation at 3000 g for 10 min, 1.5 mL of the supernatant was removed using a de-enzymed EP tube and a portion of the excess serum was removed and stored at -80°C for further use. Prostate-specific antigen (PSA) was detected using an Axsym automatic immunoassay analyzer (Abbott Laboratories, Lake Bluff, IL, USA).

RNA isolation and qRT-PCR

RNA was extracted from all sera using the mirVana PARIS RNA isolation kit. Next, 250 μL of serum was thawed on ice and the supernatant

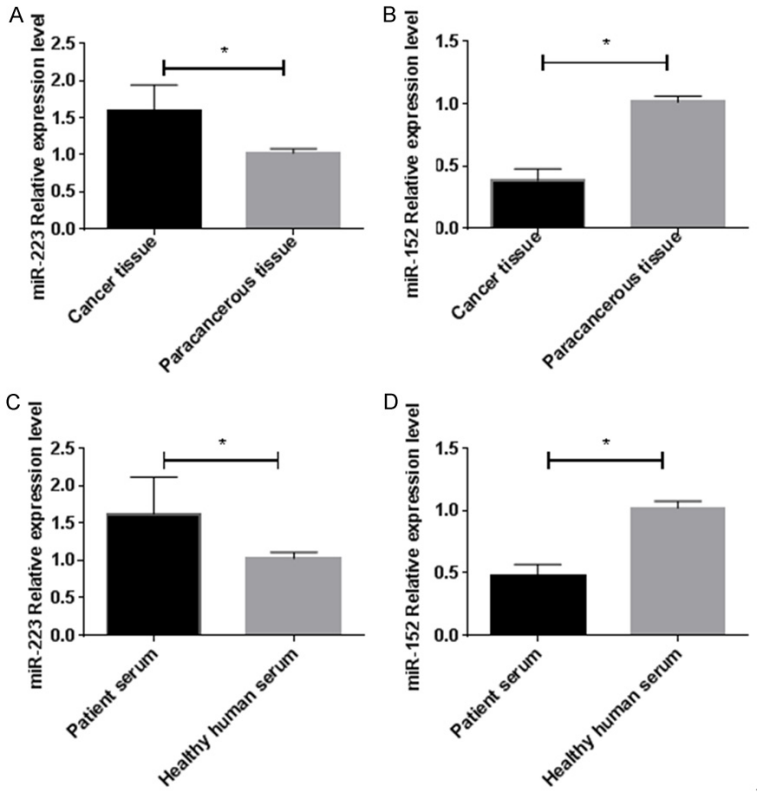

Figure 1. Expression of miR-223 and miR-152 in tissue and serum samples. Relative expression levels of (A) miR-223 and (B) miR-152 in cancer tissue compared to normal tissue in PCa patients, measured by qRT-PCR. Expression of (C) miR-223 and (D) miR-152 in serum from PCa patients compared to serum from healthy controls. *indicate significant differences between groups ($P < 0.05$).

was separated by centrifugation at 14,000 rpm for 10 minutes. Then 150 μL of the supernatant was lysed with an equal volume of 2X denaturation solution. RNA was purified according to the kit instructions and eluted with 45 μL of preheated nuclease-free water. Total RNA was isolated from PCa tissues using the standard Trizol method (Invitrogen). The purity and concentration of the extracted RNA were measured using the ultra-micro full spectrum spectrophotometer One Drop 1000 (Wins Technology, Nanjing, China). cDNA reverse transcription was conducted for the samples using the TaqMan MicroRNA Reverse Transcription Kit according to the kit instructions. The ABI7900 was used for amplification. The reaction system consisted of: 10 μL TaqMan® Universal PCR Master Mix (2X), 0.4 μL of each of the upstream and downstream primers, 2 μL cDNA, 2 μL 50X ROX Reference Dye, and 20 μL double-distilled water. The two-step amplification reaction conditions were: preheating at 95°C for 10 minutes, 95°C for 15 seconds, and 60°C for 1 minute. A total of 40 cycles using U6 as an internal reference gene were performed. The relative changes in RNA expression were calculated by the $2^{-\Delta\Delta Ct}$ method using the 7900 Sequence Detection System 2.3 (Applied Biosystems) software, with 95% confidence intervals determined as the default.

Statistical analysis

In this study, SPSS20.0 software (SPSS, Inc., Chicago, IL, USA) was used to analyze the study data, GraphPad Prism 6.0 software (GraphPad, Inc., La Jolla, CA, USA) was used to draw the figures, Pearson correlation was conducted to analyze the relative expression of miRNAs in the tissues and serum, and enumeration data were expressed as a rate (%) and analyzed by Chi-square analysis. The measurement data are expressed as the mean plus or minus standard deviation (mean ± SD), and univariate and multivariate Cox regression analysis were used to analyze their independent prognostic indicators. Data were considered statistically significant when $P < 0.05$.

Results

Expression of miR-223 and miR-152 in cancer tissues

By detecting the relative expression of microRNAs in the tissues of PCa patients by qRT-PCR, we found that the relative expression of miR-223 in cancer tissues was significantly higher ($t = 14.623$, $P = 0.006$) than that in adjacent tissues (**Figure 1A**). In contrast, the relative expression of miR-152 in the tumor tissue was significantly lower ($t = 56.761$, $P = 0.009$) than that in adjacent tissues (**Figure 1B**).

Expression of miR-223 and miR-152 in patient's serum

Measurement of microRNA expression levels in PCa patient serum samples by qRT-PCR

Table 2. Clinical data of two groups of patients

Group	miR-223			miR-152		
	High expression (n = 50)	Low expression (n = 40)	*P* value	High expression (n = 43)	Low expression (n = 47)	*P* value
Age			0.203			0.135
< 55 year (n = 38)	18	20		22	16	
≥ 55 year (n = 52)	32	20		21	31	
Smoking history			0.448			0.109
Yes (n = 82)	7	8		10	5	
No (n = 8)	43	32		33	42	
Exercise habit			0.187			0.192
Yes (n = 33)	15	18		19	14	
No (n = 57)	35	22		24	33	
History of alcoholism			0.232			0.372
Yes (n = 13)	5	8		8	5	
No (n = 77)	45	32		35	42	
Diabetes history			0.647			0.501
Yes (n = 62)	33	29		28	34	
No (n = 28)	17	11		15	13	
Gleason score			0.009			0.001
≤ 6 (n = 52)	36	16		17	35	
7 (n = 23)	9	14		13	10	
≥ 8 (n = 15)	5	10		13	2	
TNM staging			0.005			0.004
I/II (n = 65)	42	23		25	40	
III/IV (n = 25)	8	17		18	7	
lymphatic metastasis			0.001			0.001
Transform (n = 36)	11	25		26	10	
Untransferred (n = 54)	39	15		17	37	
Initial PSA (ng/mL)			0.006			0.003
< 10	8	10		13	5	
10-20	22	26		25	23	
> 20	20	4		5	19	

showed that the relative expression of miR-223 in the serum was significantly higher (t = 11.142, P = 0.004) than that in healthy patients (**Figure 1C**). The relative expression of miR-152 was significantly lower (t = 49.366, P = 0.017) than that in healthy patients (**Figure 1D**).

Comparison of clinical data and pathological data with expression of miR-223 and miR-152

Based on the median of relative expression of miR-223 and miR-152 in the patient's serum, we divided the patients into a high-expression group and low-expression group and compared the clinical and pathological data between these groups. The results revealed no significant difference in age, smoking history, exercise habits, alcoholism history, and diabetes history (P > 0.05) between the two expression groups. There were significant differences between miR-223 high and low expression groups regarding the relative expression of miR-223, PSA expression, differentiation of TNM staging, lymph node metastasis, and Gleason score (P < 0.05). Additionally, the relative expression of miR-152, PSA expression, the degree of lymph node metastasis and differentiation of TNM staging, and Gleason score were significantly different between the miR-152 high and low expression groups (P < 0.05) (**Table 2**).

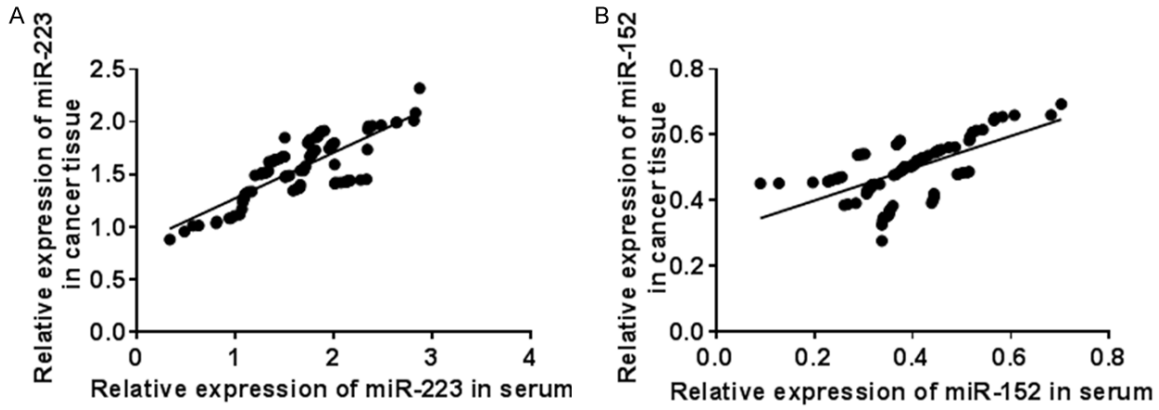

Figure 2. Correlation between cancer tissue and serum levels of miR-223 and miR-152. The correlation between two types of miRNAs in (A) tissue and (B) serum was analyzed by Pearson correlation, and a positive correlation was found between the two types of miRNAs.

Correlation between miR-223 and miR-152 in serum and cancer tissues

The correlation between miR-223 and miR-152 expression was examined in the serum and cancer tissues by Pearson correlation. The results showed that miR-223 and miR-152 expression in cancer tissues was positively correlated with the serum (miR-223: r = 0.769, P = 0.005; miR-152 r = 0.627, P = 0.008) (**Figure 2A**, **2B**).

Multivariate Cox regression model analysis

To determine independent prognostic factors of PCa, a multivariate Cox regression model was used to analyze expression of miR-223 and miR-152 in the serum and the clinical and pathological features of PCa patients. By single-factor Cox analysis, differentiation and expression of miR-223 and miR-152 and TNM staging in serum were determined to be prognostic factors for PCa patients. Subsequently, multivariate Cox analysis showed that miR-223 expression, miR-152 expression, PSA expression, and differentiation of TNM staging in serum were independent prognostic factors of patients with PCa (**Table 3**).

Discussion

Prostate cancer is a common malignancy in males. Studies have shown that PCa has become the most common malignancy in male patients in Europe and the United States followed by lung cancer and rectal cancer [13]. In the global population, annual deaths by PCa account for the second highest death rate among males [14]. As society ages, the incidence of PCa in developing countries is increasing each year. However, PCa has a high propensity for occultation, leading to difficulty in the early detection of the disease. Patients are typically in the middle or late stage of disease when they arrive at the hospital and have missed the most optimal treatment window, which can seriously threaten the patients' survival and quality of life [15]. PSA is currently widely used as the primary screening indicator of PCa for early clinical diagnosis. However, the specificity of PSA is low and various common prostate diseases lead to increased PSA levels, which may result in clinical misdiagnosis [16, 17]. Therefore, more effective diagnostic indicators are needed to improve the diagnosis and prognosis of PCa and provide a scientific theoretical basis for clinical treatment and diagnosis.

miRNAs are small non-coding RNAs that can inhibit the translation of mRNA. Many genes are involved in the inhibition process. These genes regulate biological functions such as cell proliferation, migration, invasion, and apoptosis [18]. Studies have shown that miRNAs are differentially expressed in tumors and are associated with the prognosis and phenotype of tumors, and thus can serve as important tumor-regulating molecules [19]. For example, Chen et al. [20] reported reducing the expression levels of miR-30d-5p in lung cancer cells can inhibit cell proliferation and apoptosis. miR-223 and miR-152 are differentially expressed

Table 3. Cox regression model analysis

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
miR-223 expression	0.846 (0.584~1.054)	0.001	1.484 (1.234~1.864)	0.005
miR-152 expression	1.225 (0.843~1.481)	0.001	1.684 (1.482~1.954)	0.008
Age	1.354 (1.158~1.833)	0.288		
Smoking history	1.157 (0.815~1.402)	0.835		
Exercise habit	1.052 (0.843~1.253)	0.584		
History of alcoholism	1.188 (0.846~1.329)	0.741		
Diabetes history	0.684 (0.459~0.949)	0.684		
PSA	1.641 (1.384~2.168)	0.001	1.692 (1.480~2.033)	0.032
TNM staging	3.203 (1.312~5.652)	0.001	2.254 (1.825~3.625)	0.028
lymphatic metastasis	1.356 (0.859~1.653)	0.084		
Gleason score	2.218 (1.848~2.684)	0.001	1.846 (1.538~2.125)	0.001

in various tumors, including PCa [21, 22]. However, reports of miR-223 and miR-152 expression in the literature are related to cellular biology functions rather than clinical studies. Therefore, we investigated the relationship between the expression of two miRNAs in cancer tissues and serum of PCa patients and disease prognosis.

miR-223 is located on the human X chromosome q12 PT and can be regulated by multiple transcription factors such as PU.1, C/EBPa, C/EBPb, and NFI-A [23]. Studies have shown that miR-223 regulates the body's immune system, inflammatory response, and hematological system functioning in combination with target genes [24]. miR-223 plays an important role in the development of many types of tumors and behaves differently in different tumors. It can be used as a tumor suppressor gene and oncogene. Several studies have shown that miR-152 is down-regulated in many cancers such as colon cancer and ovarian cancer [25, 26]. Matrix metalloprotease-3 can be regulated by miR-152 to inhibit glioma cell invasion and angiogenesis. Endometrial cancer growth can be inhibited by upregulation of miR-152.

In this study, we examined the expression of miR-223 and miR-152 in the tissues and blood of PCa patients by qRT-PCR and found that miR-223 is highly expressed while miR-152 is lowly expressed in the tissue and serum of PCa patients. These data suggest that miRNA expression in cancer tissues is consistent with that in the serum. A study by Zhu et al. [27] also showed that the relative expression of miR-152 was significantly lower than that in PCa adjacent tissues. In a study by Volinia et al. [28], miRNA-223 was highly expressed in PCa based on gene chip screening microarrays of 6 solid tumors. These studies support our results. The association between the relative expression in serum and tissue remains unclear. Therefore, Pearson correlation analysis was conducted, which showed that the relative expression of the two miRNAs in the sera and tissues were positively correlated and showed differences. Subsequently, serum miR-223 and miR-152 levels were compared with clinical data and pathological data between the two groups and found that miR-223 levels, Gleason scores, and PSA expression were related to differentiation degree and lymph node metastasis, while miR-152 expression was related to Gleason scores, PSA expression, TNM staging, and lymph node metastasis. At the end of the study, multivariate Cox regression analysis of the two miRNAs in the serum was performed and it was found that miR-223, miR-152 expression, Gleason score, PSA expression, and TNM staging are prognostic factors for PCa and are independent prognostic factors. Based on this data, miR-223 and miR-152 are potential prognostic indicators of PCa.

However, this study has some limitations. Primarily, the number of samples was small, which may have impacted our results. Additionally, in this study, clinical data was compared with pathological data and conducted corresponding Cox model analysis on the relative expression of miRNAs in the serum. A corresponding analysis of miRNA expression in the

tissues was not conducted. The main reason is that serum is the most common clinical specimen and is easily obtained with little trauma to the patients. Finally, in-depth studies were not performed to validate the prediction ability of the two miRNA target genes. Therefore, to increase the number of subjects and detection variables and to validate these results is a goal of future study.

In summary, miR-223 is up-regulated while miR-152 is downregulated in the serum and tissues of patients with PCa. These expression patterns may be involved in the occurrence and development of PCa and related to the degree of tumor differentiation and lymph node metastasis. Expression levels of miR-223 and miR-152 are expected to be independent prognostic indicators for patients with PCa.

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Disclosure of conflict of interest

None.

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