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ORIGINAL ARTICLE

Associations between the expressions of MiR-135 and MiR-92a and pathogenesis of prostate cancer and analysis of their clinical significance

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Summary

Purpose: *To explore the associations between the expressions of micro ribonucleic acid (miR)-135 and miR-92a and the pathogenesis of prostate cancer, as well as their clinical significance.*

Methods: *A total of 40 prostate cancer patients were studied. The associations of expressions of miR-135 and miR-92a with the pathological Gleason score and expression of prostate specific antigen (PSA) were assessed, the sensitivity and specificity of miR-135 and miR-92a in the diagnosis of prostate cancer were compared, and the associations between the expressions of miR-135 and miR-92a and the prognosis of prostate cancer patients were evaluated.*

Results: *In patients with pathological Gleason score ≥8 points the expression level of miR-135 was significantly lower, while that of miR-92a was significantly higher than those in patients with pathological Gleason score <8 points. In patients with PSA expression >10 ng/mL the expression level of miR-135 was obviously lower, while that of miR-92a was obviously higher than those in patients with PSA expression ≤10 ng/mL. The expression of miR-135 was negatively correlated with the pathological Gleason score and PSA expression, while the expression of miR-92a was positively correlated with the pathological Gleason score and PSA expression. In miR-135-positive patients, the mean survival time was longer and the 2-year survival rate was higher than those in miR-135-negative patients.*

Conclusions: *The expressions of miR-135 and miR-92a are of certain value in screening prostate cancer. The prognosis and survival of patients are positively correlated with the miR-135 expression and negatively correlated with the miR-92a expression.*

Key words: *miR-135, miR-92a, expression, prostate cancer, pathogenesis*

Introduction

Prostate cancer is the most clinically common malignant tumor of the male reproductive system, and its morbidity rate has significantly increased in recent years. It frequently occurs in the middle-aged and elderly people aged above 50 years, recently showing a trend for younger ages [1]. Digital rectal examination with low sensitivity and serum PSA with low specificity were often adopted previously in the preliminary screening, but they are not suitable for clinical popularization [2]. Increasingly more studies have demonstrated that during the occurrence, development and metastasis of malignant tumors, tumor cells will release endogenous micro ribonucleic acids (miRs) associated with the primary lesions, which can be detected in the peripheral circulation. Therefore, detection of miRs in the peripheral circulation has certain value in the early diagnosis and prognostic evaluation of tumors [3].

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Among them, miR-135 inhibits the acute promyelocytic leukemia (APL) gene expression in acute promyelocytic leukemia through suppressing the Wnt signal transduction, thereby promoting apoptosis and inhibiting the proliferation of tumor cells, which is a relatively common cancer suppressor gene [4]. In addition, miR-92a is stably expressed in peripheral blood in patients with malignant tumors, and it is currently recognized as a common protooncogene that promotes proliferation, invasion and metastasis and inhibits apoptosis of malignant tumor cells [5]. The associations of miR-135 and miR-92a with the pathogenesis of prostate cancer and their clinical significance are rarely studied. Therefore, the present study was undertaken to analyze the associations between the expressions of miR-135 and miR-92a and the pathogenesis of prostate cancer, as well as their clinical significance.

Methods

General data

A total of 40 prostate cancer patients treated in our hospital from February 2014 to August 2017 were selected. All of them were diagnosed *via* biopsy. Their age was 53-75 years (mean 62.3±1.8). All of the patients signed the informed consent when enrolled, and this study was approved by the Ethics Committee of Ruijin Hospital. The patients had normal neurological condition, and the pathological specimens obtained were sent for gene detection of miR-135 and miR-92a. *Exclusion criteria:* patients with cardiopulmonary, hepatic or renal dysfunction, myocardial infarction, ischemic or hemorrhagic stroke within 6 months before enrollment, those with the Karnofsky performance scale score ≤60 points, immune dysfunction or blood system infection, those who used immunosuppressors and/or glucocorticoids in the last 3 months, or those with distant metastasis or expected survival time less than 3 months. Among the patients enrolled, the Gleason score was ≥8 points in 18 cases and <8 points in 22 cases, and the PSA expression was ≤10 ng/mL in 21 cases and >10 ng/mL in 19 cases.

Methods

The primers of miR-135 and miR-92a were synthesized, and all primers could be queried in PrimerBank, and the mature sequences of miR-135 and miR-92a were determined using the miRNA public database miR-Base. The reagents were provided by Shanghai GenePharma Co., Ltd. (Shanghai, China) and Suzhou GENEWIZ Co., Ltd. (Suzhou, China). The primer sequences were as follows: miR-135 forward (5'-3'): CCUACUTTUCCCCATC, reverse (5'-3'): CCCAAUCTTUUACCUCAUCACCTATCT; miR-92a forward (5'-3'): TATTGCACTTGTCCCGGC, reverse (5'-3'): TTACCTAGCGTATCGTTGAC. The fluorescence quantitative polymerase chain reaction (qPCR) was performed as follows: 1 μg of target RNA was extracted and reversely transcribed into cDNA strictly according to the instructions of kit, followed by quantitative analysis of miR-135 and miR-92a using the fluorescence qPCR instrument: 95°C for 5 min, 95°C for 30 s, 55°C for 30 s, and 72°C for 20 s. All operations were performed in the laboratory with more than 5 years of experience in strict accordance with the instructions, and the quantitative level was measured 3 times and averaged.

Observation indexes

The associations of expressions of miR-135 and miR-92a with the pathological Gleason score and expression of PSA were detected, the sensitivity and specificity of miR-135 and miR-92a in the diagnosis of prostate cancer were compared, and the associations between the expressions of miR-135 and miR-92a and the prognosis of prostate cancer patients were clarified.

Evaluation criteria

The Gleason score (grade 1-5) was given according to the degree of differentiation of tumor tissues, and the structure of adenocarcinoma at different sites of prostate lesions was also scored in primary and secondary orders. Then, the two scores were added up: the total score of 2-4 points (high differentiation), 5-7 points (moderate differentiation) and >8 points (poor and/or no differentiation), and the score was negatively correlated with the prognosis of patients. In terms of the PSA level, the normal value was <4 ng/mL, while >10 ng/mL indicated high likelihood of prostate cancer.

Statistics

SPSS 20.0 (IBM, Armonk, NY, USA) was used for statistical processing. Measurement data were expressed as mean±standard deviation (x±s). T-test was performed for the comparison of means between the two groups, and x^2 test for the comparison of rates between the two groups. The survival curves were plotted using the Kaplan-Meier method and compared using log-rank test. P<0.05 suggested statistically significant differences.

Table 1. Associations of miR-135 and miR-92a expressions with the pathological Gleason score (x±s)

Gleason score	*miR-135*	*miR-92a*
≥8 points	15.2±1.0	7.3±0.3
<8 points	20.1±1.9	4.1±0.2
t	14.434	56.132
p	<0.001	<0.001

Table 2. Associations of miR-135 and miR-92a expressions with PSA (x±s)

PSA expression (ng/mL)	*miR-135*	*miR-92a*
>10	14.8±0.9	7.5±0.4
≤10	21.4±1.9	4.0±0.2
t	19.855	49.497
p	<0.001	<0.001

Results

Associations of miR-135 and miR-92a expressions with the pathological Gleason score

In patients with Gleason score ≥8 points, the expression level of miR-135 was significantly lower (p<0.05), while that of miR-92a was significantly higher than those in patients with Gleason score <8 points (p<0.05). (Table 1).

Associations of miR-135 and miR-92a expressions with PSA

In patients with PSA >10 ng/mL, the expression level of miR-135 was obviously lower (p<0.05), while that of miR-92a was obviously higher than in patients with PSA ≤10 ng/mL (p<0.05). (Table 2).

Correlation analysis between miR-135 expression and serum PSA and pathological Gleason score

The expression of miR-135 was negatively correlated with the PSA and Gleason score (p<0.05). (Figures 1 and 2).

Correlation analysis between miR-92a expression and serum PSA and pathological Gleason score

The expression of miR-92a was positively correlated with the PSA expression and Gleason score (p<0.05). (Figures 3 and 4).

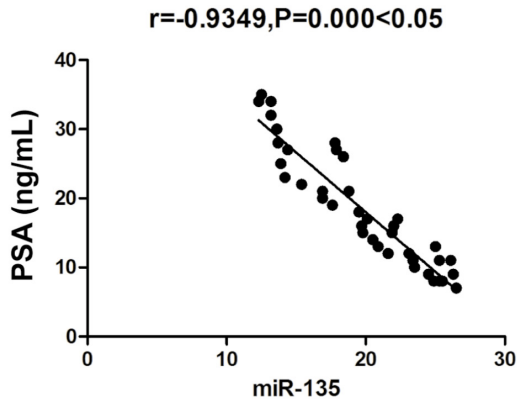

Figure 1. Correlation between miR-135 expression and serum PSA.

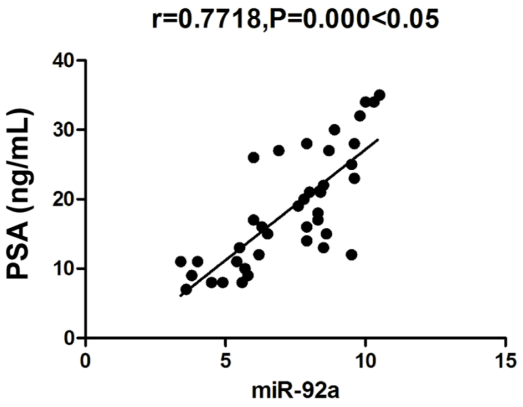

Figure 3. Correlation between miR-92a expression and serum PSA.

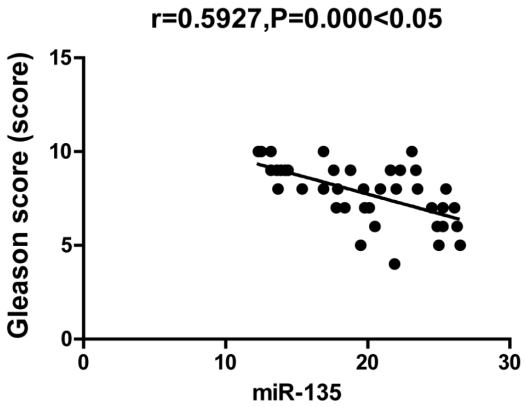

Figure 2. Correlation between miR-135 expression and pathological Gleason score.

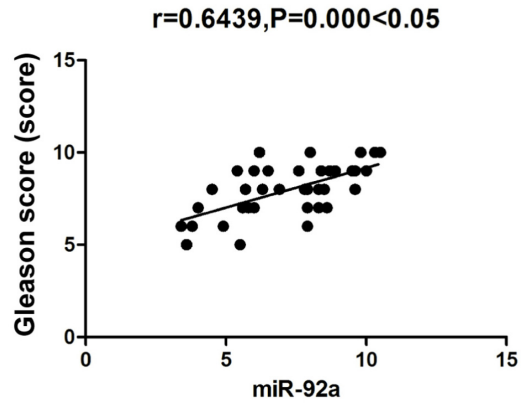

Figure 4. Correlation between miR-92a expression and pathological Gleason score.

Table 3. Associations of miR-135 and miR-92a expressions with PSA and Gleason score

	r	*p*
Association between miR-135 expression and serum PSA	-0.9349	<0.001
Association between miR-135 expression and pathological Gleason score	-0.5927	<0.001
Association between miR-92a expression and serum PSA	0.7718	<0.001
Association between miR-92a expression and pathological Gleason score	0.6290	<0.001

Table 4. Comparison of sensitivity and specificity of miR-135 and miR-92a in the diagnosis of prostate cancer

	Sensitivity (%)	*Specificity (%)*
miR-135	26/31 (83.9)	6/9 (66.7)
miR-92a	28/32 (87.5)	6/8 (75.0)

Table 5. Correlation analysis between miR-135 and miR-92a expressions and prognosis of prostate cancer patients

	Mean survival time (months)	*2-year survival rate (%)*
miR-135 (-)	14.6±2.3	23/40 (57.5)
miR-135 (+)	21.3±1.4	36/40 (90.0)
miR-92a (-)	20.5±1.6	34/40 (85.0)
miR-92a (+)	16.9±2.5	24/40 (60.0)

t=15.738, p=0.000, x^2=9.298, p=0.002 *vs.* miR-135(-); t=7.671, p=0.000, x^2=6.270, p= 0.012 *vs.* miR-92a(-).

Associations of miR-135 and miR-92a expressions with PSA and Gleason score

The expression of miR-135 was negatively associated with the Gleason score and PSA expression ($p<0.05$), while the expression of miR-92a was positively correlated with the Gleason score and PSA expression ($p<0.05$). (Table 3).

Comparison of sensitivity and specificity of miR-135 and miR-92a in the diagnosis of prostate cancer

The sensitivity and specificity of miR-135 and miR-92a in the diagnosis were above 80% and about 70%, respectively (Table 4).

Correlation analysis between miR-135 and miR-92a expressions and prognosis of prostate cancer patients

In miR-135-positive patients, the mean survival time was longer ($p<0.05$) and the 2-year survival rate was higher than those in miR-135-negative patients ($p<0.05$). In miR-92a-positive patients, the mean survival time was shorter ($p<0.05$) and the 2-year survival rate was lower than those in miR-92a-negative patients ($p<0.05$) (Table 5).

Discussion

The morbidity rate of prostate cancer is among the top three in the world, especially in developed countries in Europe and America, and prostate cancer is the most common malignant tumor in middle-aged and elderly men [6]. With the aging of population and changes in dietary and living habits in China, the morbidity rate of prostate cancer has also increased year by year, which is, however, lower than in developed countries in Europe and America, but it remains a malignant tumor seriously affecting the reproductive system health and quality of life of middle-aged and elderly men in China [7]. A study has shown that among the patients newly diagnosed with prostate cancer in China, the localized type accounted for less than 30.0%, and most of them have been in the middle-late stage and even complicated with distant metastasis when diagnosed, thus losing the opportunity of surgery and leading to poor prognosis [8]. Therefore, early diagnosis and prompt and effective treatment of prostate cancer has positive significance in improving the prognosis of patients [9]. Screening for high-risk groups is currently the most effective way to improve the early diagnosis rate of prostate cancer. Studies have demonstrated that a large number of endogenous miRs will be released during the occurrence, development and metastasis of prostate cancer cells, which can be detected in the peripheral circulation of patients [10], and they bind to the target gene mRNA to induce degradation of miR target genes. Therefore, detecting free miRs in peripheral blood can reflect the occurrence and development of prostate cancer to some extent, and help the prognostic evaluation [11].

In the present study, the expressions of miR-135 and miR-92a were detected in patients with prostate cancer, and their associations with occurrence and development of prostate cancer and their clinical significance were explored. First, the associations of miR-135 and miR-92a expressions with the Gleason score and PSA expression were detected. It was found that in patients with Gleason score ≥8 points, the expression level of miR-135 was significantly lower, while that of miR-92a was significantly higher than those in patients with Gleason score <8 points. In patients with PSA >10 ng/mL, the expression level of miR-135 was obviously lower, while that of miR-92a was obviously higher than in patients with PSA ≤10 ng/mL, indicating that the lower level of miR-135 and higher level of miR-92a correspond to significantly higher Gleason score and PSA in patients with prostate cancer. In addition, the correlation analysis of miR-135 and miR-92a expressions with serum PSA and Gleason score further revealed that the expression of miR-135 was negatively associated with the Gleason score and PSA level, while the expression of miR-92a was positively correlated with Gleason score and PSA level. At the same time, the sensitivity and specificity of miR-135 and miR-92a in the diagnosis of prostate cancer were compared, and it was observed that the sensitivity and specificity of miR-135 and miR-92a in the diagnosis were above 80% and about 70%, respectively, suggesting that

miR-135 and miR-92a have high sensitivity and specificity for the diagnosis of prostate cancer, and they are also of certain value in clinical screening of prostate cancer.

Finally, the correlation between miR-135 and miR-92a expressions and prognosis of prostate cancer patients was analyzed. The results showed that in miR-135-positive patients, the mean survival time was longer and the 2-year survival rate was higher than those in miR-135-negative patients. In miR-92a-positive patients, the mean survival time was shorter and the 2-year survival rate was lower than those in miR-92a-negative patients, which further suggest that the positive expression of miR-135 is a protective index for prostate cancer, while the positive expression of miR-92a is a risk factor for prostate cancer.

MiR-135, a clinically common gene that promotes apoptosis and inhibits proliferation of tumor cells [12], has been proved to play an important regulatory role in the occurrence and development of various malignant tumors [13]. It is able to regulate the JAK2 pathway and inhibit the binding of STATE to DNA to suppress the expression of STATE protein [14], thereby inhibiting proliferation and facilitating apoptosis of malignant cells [15]. Moreover, miR-135 can promote the transformation of hormone-dependent tumor cells into hormone-independent ones in prostate cancer patients, and it is expressed in peripheral blood, which can obviously inhibit proliferation and promote apoptosis of prostate cancer cells [16]. Besides, the expression level of serum miR-92a in prostate cancer patients obviously rises, playing a certain role in the occurrence and development of prostate cancer [17], and its high expression will enhance the proliferation of prostate cancer cells, thereby altering the biological behaviors of malignant cells whose mechanism may be related to the fact that miR-92a raises the activity of PI3K/Akt signal transduction pathway through binding to PTEN 3'UTR [18], thus promoting proliferation of prostate cancer cells, and that miR-92a suppresses the expression of RAB14 in cells [19]. Therefore, miR-92a plays a similar role as an oncogene, and it is a related gene promoting the occurrence and development of prostate cancer [20].

Conclusions

In conclusion, the expressions of miR-135 and miR-92a are of certain value in screening prostate cancer. The prognosis and survival time of patients are positively correlated with the miR-135 expression and negatively correlated with the miR-92a expression.

Conflict of interests

The authors declare no conflict of interests.

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