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Original Article

Expression of miR-92a, miR-224 and miR-25 in non-small cell lung cancer and their correlation with clinical characteristics

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Abstract: Objective: To analyze the correlation of the expression of microRNA-92a (miR-92a), microRNA-224 (miR-224), and microRNA-25 (miR-25) in non-small cell lung cancer with its clinical characteristics. Methods: This prospective study was performed in 125 non-small cell lung cancer patients admitted to our hospital between January 2019 and January 2020. All patients' cancer and adjacent tissue were collected and the expression of miR-92a, miR-224, and miR-25 were detected using real-time fluorescence quantitative RT-PCR. Data were analyzed using SPSS statistical software (version 20.0). Correlation analysis was conducted using Pearson correlation coefficient. Results: Compared with adjacent tissue, the relative expression of miR-92a, miR-224, and miR-25 in cancer tissue were increased (all P<0.001). There was no correlation between the expression of miR-92a, miR-224, and miR-25 and baseline data like gender, age, smoking history, and tumor size (all P>0.05). The relative expression of miR-92a, miR-224 and miR-25 in differentiated cancer patients were higher than those in highly and moderately differentiated cancer patients (all P<0.05). The relative expression of miR-92a, miR-224 and miR-25 in patients with lymph node metastasis (LNM) were increased when compared with those had no LNM (all P<0.001). Compared with stage I and II patients, the relative expression of miR-92a, miR-224 and miR-25 in stage III and IV patients were increased (all P<0.001). The relative expression of miR-92a, miR-224, and miR-25 were positively correlated to each other (all P<0.01). Conclusion: miR-92a, miR-224, and miR-25 are overexpressed in non-small cell lung cancer and the expressions are related to the degree of differentiation, presence or absence of LNM, and TNM staging. In addition, the expression of miR-92a, miR-224 and miR-25 are positively correlated to each other. This suggests that miR-92a, miR-224, and miR-25 cooperatively participated in the occurrence and development of non-small cell lung cancer.

Keywords: MicroRNA-92a, MicroRNA-224, MicroRNA-25, non-small cell lung cancer, clinical characteristics

Introduction

Lung cancer is most commonly observed clinical malignant tumor of the respiratory system, with characteristics of high morbidity and mortality [1]. There are numerous kinds of lung cancer. Among them, non-small cell lung cancer (NSCLC) is the most common one, accounting for about 80% [2, 3]. The data of relevant epidemiological surveys show that a high incidence and death rate are characteristics of NSCLC. In addition, the incidence has been increasing year after year [4, 5]. MicroRNAs (miRNAs) are abundant in most organisms. A large number of experimental studies have displayed that miRNAs are closely related to physiologic processes, like cell differentiation, cell apoptosis, neuron development, and fat metabolism. Tissue specificity, stability, and conservation are characteristics of miRNAs. There is an intimate relationship between the occurrence and development of tumor and miRNAs. During the development of cancer, miRNAs, which could be a cancer suppressor or promoter, are commonly applied clinical diagnostic markers of tumor [6-8].

Oncogenes are genes that are abnormally overexpressed and can promote the occurrence and development of cancer. In miRNA family,

the microRNA-17-92 (miR-17-92) cluster is cancer-promoting. In other words, they play a role in accelerating the occurrence and development of many malignant tumors. microRNA-92a (miR-92a) is an important member of the miR-17-92 cluster, and its expression is intimately correlated with the migration ability of cancer cells [9]. Studies have displayed that miR-92a can be used as a biomarker in the diagnosis and prognosis of colorectal cancer. Its expression is also related tovarious diseases [10-12].

MicroRNA-224 (miR-224) is also an important oncogene. A large number of experimental studies have displayed that miR-224 plays a critical role in the occurrence and development of malignant tumors like gastric cancer and colorectal cancer [13]. It was reported that miR-224 was abnormally overexpressed in malignant tumors. Moreover, miR-224 can combine with its target gene Bim. miR-224 could thus regulate the proliferation and apoptosis of cancer cells through the adjusting Bim expression. Therefore, it could be speculated that the inhibition of miR-224 expression could suppress cancer cell proliferation while accelerating its apoptosis. In short, miR-224 may be a marker and therapeutic target of cancer cells [14, 15].

Most members of the miRNA family are abnormally expressed in malignant tumors. However, only a few members' expression changes are detected in blood. Moreover, only miRNA, whose alteration can be detected in both the cancer tissue and blood of patients with malignant tumors, can be implemented as a diagnostic indicator for malignant tumors. It was reported that microRNA-25 (miR-25) was abnormally expressed in the cancer tissue and serum of patients with malignant tumors. Combined with the detection of miR-25 expression, the diagnosis of malignant tumors was more accurate [16-18].

However, there are only rare reports on the correlation between the expression changes of miR-92a, miR-224, and miR-25 and the occurrence and development of NSCLC. Here, we collected the surgical resection specimens of patients with NSCLC and detected the expression of miR-92a, miR-224, and miR-25, hoping to explore the expression of miR-92a, miR-224, and miR-25 in NSCLC and their correlation with clinical characteristics.

Materials and methods

Materials

The prospective study was performed in 125 NSCLC patients admitted to our hospital from January 2019 to January 2020. Among them, 71 were males and 54 were females. They aged 52-69 years, with an average age of 60.5±6.8 years. TNM staging were divided into 4 levels, stage I (23 patients), stage II (35 patients), stage III (41 patients), and stage IV (26 patients). As for the degree of cancer tissue differentiation, 39 patients had highly differentiated cancer, 52 patients had moderately differentiated cancer, and 34 patients had poorly differentiated cancer. Informed consent was signed by the patients or their family members. This study was approved by the Ethics Committee of our hospital.

Inclusion criteria: Patients met the diagnostic criteria of NSCLC defined in the Chinese Medical Association Guidelines for Clinical Diagnosis and Treatment of Lung Cancer (Edition 2018) [19]; patients had complete medical records; patients received surgical treatment.

Exclusion criteria: Patients with incomplete medical records; patients had non-surgical treatment; patients received relevant treatment before enrollment; patients with heart, kidney, liver or other organ dysfunction; patients had another malignant tumor.

Methods

Specimen collection: All patients' surgically removed cancer tissue and adjacent tissue located at more than 5 cm away from the cancer tissue were collected. These specimens were then fixed with 4% neutral formalin (Nanjing Senbeijia Biological Technology Co., Ltd., China). Thereafter, they were dehydrated and embedded in paraffin. After sectioning, 3 μm slices were obtained.

Real-time fluorescent quantitative RT-PCR: An appropriate amount of liquid nitrogen was added into cancer and adjacent tissues, which were frozen in liquid nitrogen, to grind them into powder. Following the instruction of RT-PCR kit (Shanghai Kule Biotech Co., Ltd., China; article number: V003), total RNA was extracted from the specimen to be detected. Thereafter, the

Table 1. Expression of miR-92a, miR-224, and miR-25 in cancer and adjacent tissue ($\bar{x}$ ± sd)

Tissue	miR-92a	miR-224	miR-25
Adjacent Tissue (n=125)	1.19±0.24	1.25±0.26	1.08±0.19
Cancer Tissue (n=125)	1.63±0.32	1.79±0.46	1.61±0.28
t	12.300	11.430	17.510
P	<0.001	<0.001	<0.001

Note: miR-92a: microRNA-92a; miR-224: microRNA-224; miR-25: microRNA-25.

purity and quantity of RNA were tested. The fluorescence quantitative RT-PCR reaction system and parameters were set up in accordance with the RT-PCR kit manual. The fluorescence quantitative RT-PCR was performed and a standard curve was drawn. Here, U6 was used as the internal reference. The expression of miR-92a, miR-224, and miR-25 were relatively quantified using $2^{-\Delta\Delta CT}$. miR-92a primers: 5'-CCTGCAAGGCATAGTCTCATTGAA-3' (forward primer), 5'-GAACTTGGCCACTTGCTAGATCAA-3' (reverse primer). miR-224 primers: 5'-AGTCTCTG-GCTGACTACATCA-CAG-3' (forward primer), 5'-CTACTCACAAAACAG-GAGTGGAATC-3' (reverse primer). miR-25 primers: 5'-CGGCGGCATTG-CACTTGGTCTC-3' (forward primer), 5'-GTGC-AGGGTC-CGAGGT-3' (reverse primer).

Statistical methods

All data were processed by SPSS statistical software version 20.0. The measurement data were calculated as mean ± standard deviation ($\bar{x}$ ± sd); F test was implemented for comparison among multiple groups; LSD-t test was applied for inter-group comparison. Correlation analysis was performed using Pearson correlation coefficient. The difference was significant when *P* value was <0.05.

Results

The expression of miR-92a, miR-224, and miR-25 in cancer and adjacent tissue

The relative expression of miR-92a, miR-224, and miR-25 in cancer tissue were higher than those in adjacent tissue (all P<0.001, **Table 1**).

The relationship between the relative expression of miR-92a, miR-224, and miR-25 and baseline data

As displayed in **Table 2**, there were no significant differences in the relative expression of miR-92a, miR-224, and miR-25 between male and female patients (all P>0.05); there were no significant differences concerning the relative expression of miR-92a, miR-224, and miR-25 between patients aged below 60 years and above 60 years (all P>0.05); there were no significant differences on the relative expression of miR-92a, miR-224, and miR-25 between patients with and without smoking history (all P>0.05); there were no significant differences concerning the relative expression of miR-92a, miR-224, and miR-25 between patients with tumor size above 5 cm^3 and below 5 cm^3 (all P>0.05).

The relationship between the relative expression of miR-92a, miR-224, and miR-25 and the degree of differentiation

As shown in **Table 3**, compared with highly differentiated cancer patients, the relative expression of miR-92a, miR-224, and miR-25 in moderately differentiated cancer patients were increased (all P<0.05); the relative expression of miR-92a, miR-224 and miR-25 in poorly differentiated cancer patients was higher than those in moderately differentiated cancer patients (all P<0.05).

The relationship between the relative expression of miR-92a, miR-224, and miR-25 and the presence or absence of lymph node metastasis (LNM)

The relative expression of miR-92a, miR-224, and miR-25 in patients without LNM were increased when compared with patients who had LNM (all P<0.001, **Table 4**).

Relationship between the relative expression of miR-92a, miR-224, and miR-25 and TNM staging

Compared with stage I and II patients, the relative expression of miR-92a, miR-224 and miR-25 in stage III and IV patients were increased (all P<0.001, **Table 5**).

The correlation among the expression of miR-92a, miR-224, and miR-25

As illustrated in **Figure 1**, correlation analysis was performed among the expression of miR-92a, miR-224, and miR-25. The expressions of miR-92a were positively correlated to the

Table 2. Relationship between the relative expression of miR-92a, miR-224, and miR-25 and baseline data ($\bar{x}$ ± sd)

Baseline data	miR-92a	t	P	miR-224	t	P	miR-25	t	P
Gender									
Male (n=71)	1.61±0.28	1.242	0.217	1.75±0.42	0.721	0.472	1.58±0.31	0.765	0.446
Female (n=54)	1.68±0.35			1.81±0.51			1.62±0.26		
Age									
Above 60 years (n=75)	1.59±0.30	1.038	0.301	1.72±0.40	0.912	0.364	1.57±0.28	1.331	0.186
Below 60 years (n=50)	1.65±0.34			1.79±0.45			1.64±0.30		
Smoking history									
Present (n=62)	1.64±0.33	0.971	0.333	1.76±0.41	0.641	0.523	1.59±0.29	0.745	0.458
Absent (n=63)	1.58±0.36			1.81±0.46			1.63±0.31		
Tumor size									
Below 5 cm^3 (n=66)	1.64±0.37	0.794	0.429	1.78±0.43	0.254	0.800	1.60±0.32	0.547	0.586
Above 5 cm^3 (n=59)	1.59±0.33			1.80±0.45			1.57±0.29		

Note: miR-92a: microRNA-92a; miR-224: microRNA-224; miR-25: microRNA-25.

Table 3. Relationship between the relative expression of miR-92a, miR-224, and miR-25 and the degree of differentiation ($\bar{x}$ ± sd)

Degree of differentiation	miR-92a	miR-224	miR-25
High differentiation (n=39)	1.35±0.21	1.46±0.31	1.39±0.23
Moderate differentiation (n=52)	1.59±0.28*	1.72±0.45*	1.63±0.30*
Poor differentiation (n=34)	1.81±0.35*,#	1.91±0.49*,#	1.80±0.37*,#

Notes: Compared with high differentiation, *P<0.05; compared with moderate differentiation, #P<0.05. miR-92a: microRNA-92a; miR-224: microRNA-224; miR-25: microRNA-25.

Table 4. The relationship between the relative expressions of miR-92a, miR-224, and miR-25 and the presence or absence of lymph node metastasis ($\bar{x}$ ± sd)

Lymph node metastasis	miR-92a	miR-224	miR-25
Absent (n=64)	1.53±0.28	1.62±0.42	1.52±0.25
Present (n=61)	1.74±0.36	1.89±0.49	1.75±0.36
t	3.650	3.313	4.165
P	<0.001	0.001	<0.001

Note: miR-92a: microRNA-92a; miR-224: microRNA-224; miR-25: microRNA-25.

Table 5. The relationship between the relative expression of miR-92a, miR-224, and miR-25 and TNM stage ($\bar{x}$ ± sd)

TNM stage	miR-92a	miR-224	miR-25
Stage I and II (n=58)	1.49±0.26	1.58±0.41	1.46±0.32
Stage III and IV (n=67)	1.76±0.37	1.90±0.57	1.72±0.37
t	4.651	3.553	4.169
P	<0.001	0.001	<0.001

Note: miR-92a: microRNA-92a; miR-224: microRNA-224; miR-25: microRNA-25.

expression of miR-224 (r=0.296, P=0.001, **Figure 1A**); There was a positive correlation between the expression of miR-92a and miR-25 (r=0.283, P=0.001, **Figure 1B**); the expression of miR-224 was positively correlated to the expression of miR-25 (r=0.319, P=0.001, **Figure 1C**).

Discussion

Most NSCLC patients are not diagnosed until their condition has reached to an advanced stage, posing a serious threat to the safety of these patients. Therefore, timely diagnosis and improvement of early diagnosis rate are significant for the clinical treatment and prognosis of patients with NSCLC [20, 21]. At present, the pathogenesis of NSCLC has not been thoroughly studied. Many experts and scholars are devoting themselves to this study. In recent years, scholars have explored the pathogenesis of NSCLC through the application of molecular biology and basic medicine [22, 23].

It was previously reported that the altered expression of miR-92a was involved in the

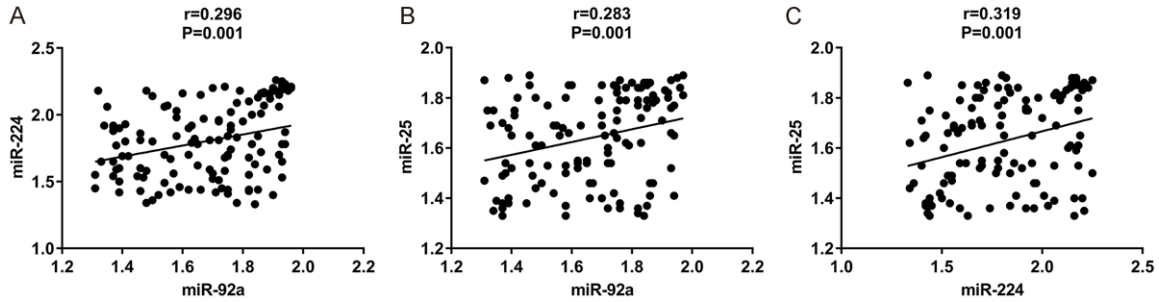

Figure 1. Correlation among the expression of miR-92a, miR-224, and miR-25. A: Correlation between the expression of miR-92a and miR-224; B: The correlation between the expression of miR-92a and miR-25; C: The correlation between the expression of miR-25 and miR-224. miR-92a: microRNA-92a; miR-224: microRNA-224; miR-25: microRNA-25.

occurrence and development of tumor. In cancer tissues, it was abnormally overexpressed, and the expression changes were closely related to LNM [24, 25]. Our results revealed that miR-92a was abnormally overexpressed in NSCLC tissue, indicating that miR-92a, an oncogene, plays a critical role in the occurrence and development of NSCLC. Here, we also tested the expression of miR-92a in NSCLC tissue with different clinicopathologic characteristics. Our results displayed that the expression of miR-92a in cancer tissue of patients with poorly differentiated, lymph node metastasized, and stage III and IV NSCLC were relatively high, suggesting that there is certain correlation between the expression of miR-92a and clinical characteristics such as the differentiation of cancer tissue, presence or absence of LNM, and TNM staging. Namely, miR-92a participated in the occurrence and development of NSCLC.

Previous studies have revealed that the expression of miR-224 is abnormal in some diseases. For example, Cecilia et al. found that compared with normal livers, the expression of miR-224 was significantly up-regulated in both peri-tumoral cirrhotic livers and HCC samples [26]. Zhang et al. reported that miR-224 could promote tumorigenesis by down-regulating caspase-9 in triple-negative breast cancer [27]. Our results displayed that miR-224 was abnormally overexpressed in NSCLC, denoting that miR-224 is a cancer promoter in the development of NSCLC. Here, we also detected the expression of miR-224 in NSCLC tissue with different clinicopathologic characteristics. Our results showed that the expression of miR-224 in cancer tissue of patients with poorly differentiated, lymph node metastasized, and stage III and IV NSCLC were relatively high, indicating that there is certain correlation between the expression of miR-224 and clinical characteristics such as the differentiation of cancer tissue, presence or absence of LNM, and TNM staging. Namely, miR-224 participated in the occurrence and development of NSCLC.

Some researchers have reported the role of miR-25 in heart disease [28, 29]. However, miR-25 is also reported to play a role in cancer development. For example, a study reported that SOCS5/miR-18/miR-25 axis contributes to tumorigenesis in liver cancer [30]. Our results showed that miR-25 was abnormally overexpressed in NSCLC tissue, suggesting that miR-25 is a cancer promoter in the development of NSCLC. We also detected the expression of miR-25 in NSCLC tissue with different clinicopathologic characteristics. Our results displayed that the expression of miR-25 in cancer tissue of patients with poorly differentiated, lymph node metastasized, and stage III and IV NSCLC were relatively high, indicating that there is certain correlation between the expression of miR-25 and clinical characteristics such as the differentiation of cancer tissues, presence or absence of LNM, and TNM staging. Namely, miR-25 participated in the occurrence and development of NSCLC.

However, this study is performed in a limited number of patients. In addition, we did not perform a targeted study to analyze the distribution of risk factors for NSCLC. Subsequent study will be conducted in a larger sample to compare the expression of miR-92a, miR-224, and miR-25 on the basis of distribution of risk

factors for NSCLC. Due to funding constraints, we did not detect the level of miR-92a in serum. We will add this into our subsequent studies.

In summary, miR-92a, miR-224, and miR-25 are overexpressed in NSCLC and their expressions are correlated with the degree of differentiation, the presence or absence of LNM, and TNM staging. In addition, the expression of miR-92a, miR-224 and miR-25 are positively correlated to each other. It could be assumed that miR-92a, miR-224, and miR-25 cooperatively participated in the occurrence and development of NSCLC.

Disclosure of conflict of interest

None.

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