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Original Article

Expression levels and diagnostic values of miR-106b and miR-122 in different stages of laryngeal carcinoma

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Abstract: Objective: To explore the expression levels and diagnostic values of miR-106b and miR-122 in different stages of laryngeal carcinoma (LC). Methods: One hundred and fifty-four cases diagnosed as LC in Maternity and Child Health Care of Zaozhuang from February 2013 to April 2016 were selected as LC group, and one hundred healthy volunteers were selected as control group in the same period. The expression levels of miR-106 and miR-122 in carcinoma tissues and sera of all included subjects were detected using qRT-PCR technique. Then the relationship between expression levels of the two miRNAs and the clinical stages of LC was analyzed using Spearman correlation analysis, and the diagnostic values of miR-106b and miR-122 in LC were analyzed using receiver operating characteristic curve (ROC curve). Results: The expression levels of miR-106b and miR-122 in the LC tissues were higher than those in sera of the LC group ($P<0.05$). The expression levels of miR-106b and miR-122 in LC tissue were higher than those in the sera of the control group, and so were the expression levels of the two miRNAs in sera of the LC group (all $P<0.05$). The expression levels of miR-106b and miR-122 in the LC tissues and sera of LC group raised with increase of clinical stage. And there were differences in the expression levels of the two miRNAs between any two stages ($P<0.05$); Spearman correlation analysis showed that the expression levels of miR-106b and miR-122 were positively correlated with the clinical stages of LC ($r=0.812$, $P=0.014$; $r=0.836$, $P=0.011$). The sensitivity, specificity, and AUC of miR-106b, miR-122 or miR-106b combined with miR-122 in the sera were all lower than those in tissues. The value of the combined in diagnosing LC was higher than that of a separate one. Conclusion: The expression levels of miR-106 and miR-122 in patients with LC was increased. The higher the clinical stage, the higher the expression levels of miR-106 and miR-122. Both miR-106b and miR-122 have different levels of expression in tissues and sera of patients with LC. The expression levels of the two miRNAs in patients with LC rose with the increase of clinical stage. Our study suggests that miR-106b and miR-122 might be valuable in the diagnosis of LC.

Keywords: miR-106b, miR-122, laryngeal carcinoma, staging, diagnostic value

Introduction

Laryngeal carcinoma is one of the most common primary malignant tumors in otolaryngology. And its incidence, next to nasopharyngeal carcinoma and nasal carcinoma, accounts for about five percent of all malignant tumors in human [1, 2]. In recent years, the incidence of LC is increasing with the rise in the proportion of smoking population and the increase of carcinogenic factors such as chemical contaminants and dust [3, 4]. Surgery combined with radiotherapy and chemotherapy is currently the main treatment for patients with LC. Although medical conditions have greatly improved in recent years, the survival rate of patients with LC is still not high, and the five-year survival rate of patients with advanced LC is only about fifty percent, which are mainly due to delay of diagnosis and failure of timely treatment [5, 6].

MicroRNAs (miRNAs) are widely expressed in eukaryotes and represent a very important regulatory network that regulates proliferation, differentiation, and apoptosis of cells, while abnormal changes in miRNA biosynthesis are involved in varieties of pathologic and physiological processes [7, 8]. Many studies have reported that miRNAs are closely related to the biological behaviors of tumor cells such as proliferation

Table 1. The sequences of primers for qRT-PCR

	Upstream primer	Downstream primer
miR-106b	5'-TTTTCGCCCTTAGCGTGAAGA-3'	5'-GAGGCAGTCGAAGCTCTCG-3'
miR-122	5'-TTGAATTCTAACACCTTCGTGGCTACAGAG-3'	5'-TTAGATCTCATTTATCGAGGGAAGGATTG-3'
U6	5'-CGCTTCGGCAGCACATATAC-3'	5'-TTCACGAATTTGCGTGTCAT-3'

and invasion [9, 10]. Studies have found that miR-106b is abnormally expressed in LC [11, 12]. MiR-122 in hepatocellular carcinoma and renal clear cell carcinoma is abnormally expressed [13, 14], but its abnormal expression in LC is rarely reported. At present, the diagnosis of a tumor depends more on pathological diagnosis and ultrasound imaging, but the diagnosis is strongly affected by subjective factors [15, 16]. Screening and early diagnosis of a tumor by serological examination has always been the researchers' direction, which might have lots of advantages such as high sensibility, high specificity, little trauma, good reproducibility, and high patient compliance. As a result, time-consuming and complicated pathologically examination with big trauma is avoided [17, 18].

In this study, the expression levels and diagnostic values of miR-106b and miR-122 in LC tissues and sera of patients were explored to further understand the mechanism of development of LC, hoping to provide a reference for diagnosis of LC.

Materials and methods

Patients selection

The study was approved by the Medical Ethics Committee of Maternity and Child Health Care of Zaozhuang, and informed consents were obtained from all the patients or their families. One hundred and fifty-four cases diagnosed as LC in the Medical Ethics Committee of Maternity and Child Health Care of Zaozhuang from February 2013 to April 2016 were selected as LC group. Inclusion criteria: all patients were pathologically diagnosed as LC; all patients had no previous history of any other tumors, no dysfunction in organs such as liver and kidney, no abnormal bleeding or coagulation disorder dysfunction, and no genetic disorders or immunodeficiency. Exclusion criteria: patients who had been treated with radiotherapy and chemotherapy; patients with large tumors; patients who had other diseases in lung or chest wall; patients with physical defects; and patients who had died of other diseases. At the same time, one hundred healthy volunteers were selected as control group.

Samples collection

The samples of LC tissues in all patients were collected through surgeries underwent in Maternity and Child Health Care of Zaozhuang. The sera of volunteers were obtained from the fasting venous blood (5 mL) collected by nurses of our hospital in the early morning.

The qRT-PCR detection

Extraction of total RNA: After grinding, 100 mg of LC tissue was mixed with 1 mL of TRIzol (He Peng (Shanghai) Biotechnology Co., Ltd.), followed by incubation for 6-8 minutes. Then the tissue was precipitated, washed and dissolved after organic extraction with chloroform. About 1 mL of serum was added with 1 mL of TRIzol reagent, and the remaining steps were the same as above. The concentration and purity of the extracted RNA were analyzed by the trace UV spectrophotometer MD1000 (Guangzhou Whiga Technology Co., Ltd.), and the A260/A280 ratio fluctuated between 1.8 and 2.0 was considered to meet the experimental requirement. The integrity of RNA was analyzed through 3% agarose gel electrophoresis (SDS-PAGE Gel Parparation Kit for gel electrophoresis was purchased from Shanghai Jack Chemical Co., Ltd.). Detailed steps referred to the manufacturer's instructions.

The qRT-PCR reaction: the above-described extracted total RNA was reverse transcribed into complementary DNA (cDNA) referring to the instructions carried in the fluorescence qPCR kit (Thermo Fisher Scientific (China) Inc.). Reverse transcription reaction system was as follows: the total RNA (2 μg) was carried out with 1 μL of 2.5 U/μL poly a polymerase, 1 μL of RTase Mix, 5 μL of 5 × Reaction Buffer and

Table 2. Baseline characteristics

		LC group (n=154)	Control group (n=100)	Statistical value	P
Sex (n, %)	Male	104 (67.5)	68 (68.0)	0.006	0.938
	Female	50 (32.5)	32 (32.0)		
Age (year)		48.4±12.5	46.9±9.7	10.170	0.310
Differentiation grade (n, %)	Poorly differentiation	42 (27.3)			
	Moderately differentiation	43 (27.9)			
	Well-differentiation	69 (44.8)			
Clinical stage (n, %)	I	29 (18.8)			
	II	48 (31.2)			
	III	32 (20.8)			
	IV	45 (29.2)			
Lymph node metastasis (n, %)	Yes	60 (39.0)			
	No	94 (61.0)			

Note: LC, laryngeal carcinoma.

Table 3. The expression levels of miR-106b and miR-122

		miR-106b	miR-122
LC group	Tissue	1.324±0.325	1.256±0.334
	Serum	1.125±0.301	1.014±0.298
Control group	Serum	0.917±0.311	0.811±0.317
t_1		5.575	6.709
P_1		<0.001	<0.001
t_2		9.917	10.582
P_2		<0.001	<0.001
t_3		5.311	5.172
P_3		<0.001	<0.001

Note: LC, laryngeal carcinoma; t_1, P_1: tissue of LC group vs. serum of LC group; t_2, P_2: tissue of LC group vs. serum of control group; t_3, P_3: serum of LC group vs. serum of control group.

RNase Free Water up to 25 μL of final volume. Reverse transcription reaction condition: the total RNA was transcribed at 37°C for 60 minutes and 85°C for 5 minutes. The cDNA amplification reaction system was as follows: the samples were carried out with 10 μL of 2 × All-in-One qPCR Mix, 0.4 μL of 50 × ROX Reference Dye, 2 μL of Forward Primer, 2 μL of Universal Adaptor PCR Primer and DNase Free Water up to 20 μL of final volume. Cycling steps and conditions were after initial denaturation for 10 min at 95°C, the samples were run for 40 cycles of denaturation for 10 s at 95°C, annealing for 20 s at 60°C, extension for 10 s at 72°C, then extension for 5 min at 72°C. U6 was taken as the internal reference. All samples were replicated in three wells and the results were analyzed using the $2^{-\Delta\Delta ct}$ method. The qRT-PCR primers were designed and synthesized by GENEWIZ (China). The primer sequences are as follows (**Table 1**).

Statistical analysis

Analysis was performed by using SPSS 19.0 (Asia Analytics Formerly SPSS China). The enumeration data were expressed as rate, and χ^2 test was used for intergroup comparison. The measurement data were expressed as $\bar{x} \pm$ sd. And the K-S test was used to analyze whether the measurement data conformed to the normal distribution. Data with normal distribution were compared by independent t-test, and data with non-normal distribution were compared by rank sum test. The measurement data in multiple groups were analyzed by analysis of variance, followed by LSD test for subsequent comparisons between two groups. The relationship between expression levels of the two miRNAs and the clinical stage of LC was analyzed using Spearman correlation analysis. And the diagnostic values of miR-106b and miR-122 in LC were analyzed using ROC curve. $P<0.05$ is considered statistically significant.

Results

Baseline characteristics

Tissue samples of LC were obtained from 154 cases. The patients included 104 males and 50 females with an average age of 58.4, and

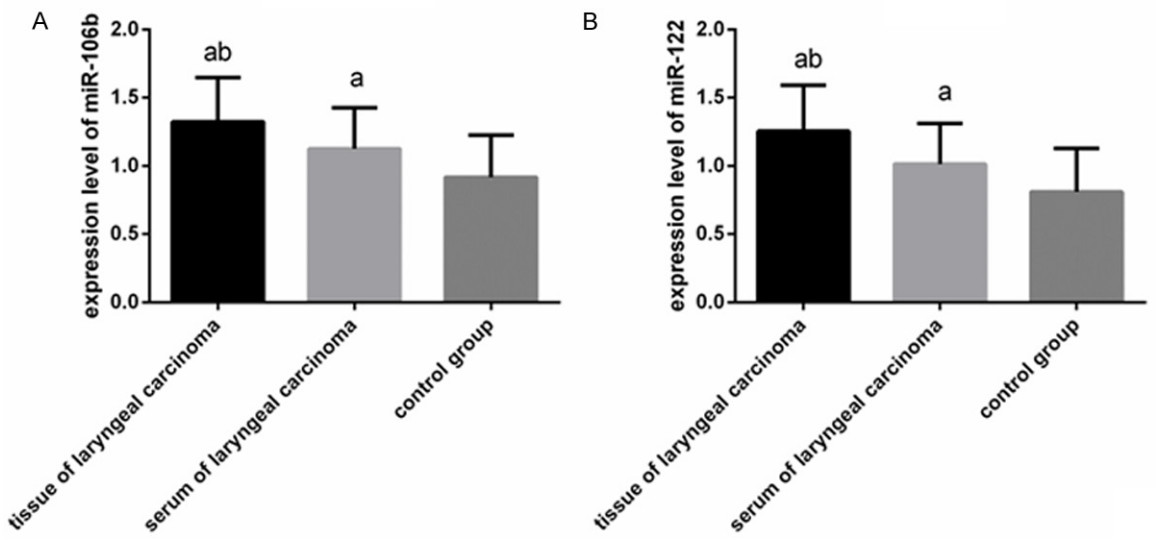

Figure 1. The expression levels of miR-106b and miR-122 for patients in different clinical stages. A. P<0.05 compared with control group; B. P<0.05 compared with those detected in the serum.

Table 4. The expression levels of miR-106b and miR-122 in all clinical stages

Clinical stage	miR-106b of LC group (n=154)		miR-122 of LC group (n=154)	
	Tissue	Serum	Tissue	Serum
I	1.126±0.298	0.917±0.244	1.098±0.256	0.818±0.214
II	1.214±0.276[a]	1.067±0.236[a]	1.169±0.284[a]	0.921±0.252[a]
III	1.438±0.301[a,b]	1.220±0.278[a,b]	1.342±0.293[a,b]	1.111±0.273[a,b]
IV	1.518±0.327[a,b,c]	1.296±0.315[a,b,c]	1.415±0.315[a,b,c]	1.206±0.165[a,b,c]
F	57.739	59.750	40.223	90.808
P	<0.001	<0.001	<0.001	<0.001

Note: a, II vs. I, P<0.05; b, III vs. II, P<0.05; c, IV vs. III, P<0.05; LC, laryngeal carcinoma.

they ranged in ages from 40 to 76 years old. In these cases, there were 42 patients with poor differentiation, 43 with moderate differentiation, and 69 with good-differentiation of tumors. The clinical stages were classified as stage I in 29 patients, stage II in 48, stage III in 32, and stage IV in 45. Lymph node metastases occurred in 60 patients. There was no statistical difference in gender and age between the LC patients and control (both P>0.05) (**Table 2**).

Results of qRT-PCR

In LC group, the relative expression level of miR-106b was 1.324±0.325 in the LC tissues, 1.125±0.301 in the sera. And the relative expression level of miR-106b was 0.917±0.311 in the sera of control group. In LC group, the relative expression levels of miR-122 in the LC tissues and the sera were 1.256±0.334 and 1.014±0.298, respectively. And the relative expression level of miR-122 in the sera of control group was 0.811±0.317. The relative expression levels of miR-106b and miR-122 in LC tissues of LC group were higher than those in the sera of LC group (P<0.05). The relative expression levels of miR-106b and miR-122 in the LC tissues and the sera of LC group were higher than those in the sera of control group (all P<0.05) (**Table 3**, **Figure 1**).

The analysis of the relative expression levels of miR-106b and miR-122 in all clinical stages showed that the relative expression levels of both in the LC tissues and sera of LC group rose with the increase of clinical stage. There were differences in the relative expression levels of miR-106b and miR-122 between any two stages (P<0.05), and the Spearman correlation analysis showed that the relative expression levels of miR-106b and miR-122 were positively correlated with the clinical stage of LC (r=0.812, P=0.014; r=0.836, P=0.011) (**Table 4**).

Table 5. Diagnostic values of miR-106b and miR-122 in LC

	miR-106b		miR-122		miR-106b & miR-122	
	Serum	Tissue	Serum	Tissue	Serum	Tissue
AUC	0.661	0.815	0.614	0.805	0.741	0.895
95% confidence interval	0.586-0.736	0.755-0.875	0.586-0.736	0.745-0.864	0.673-0.809	0.851-0.939
Diagnostic level	1.070	1.112	0.975	1.045		
Sensitivity	73.0%	77.0%	67.0%	77.0%	66.0%	83.0%
Specificity	62.0%	79.0%	74.0%	74.0%	73.0%	85.0%

Note: LC, laryngeal carcinoma.

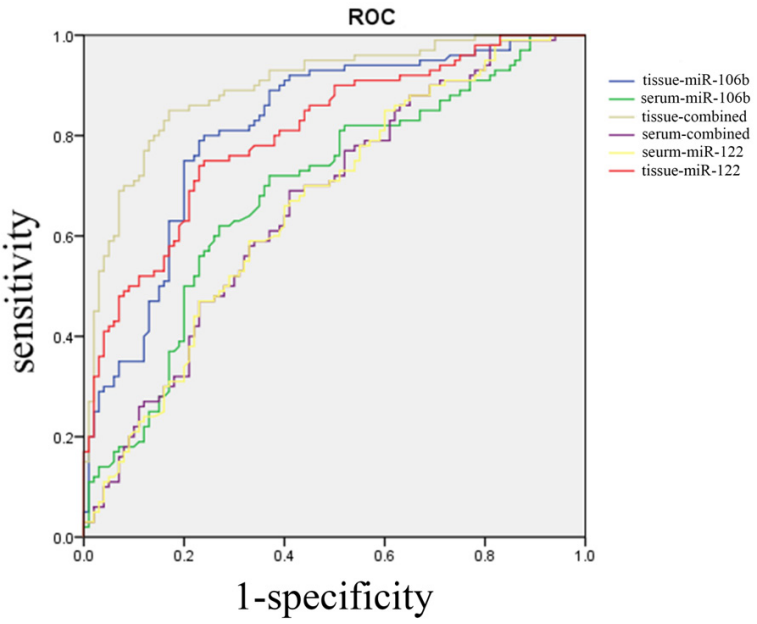

Figure 2. ROC of diagnosis of LC using miR-106b and miR-122 ROC, receiver operating characteristic; LC, laryngeal carcinoma.

The diagnostic value of miR-106b and miR-122 in LC

The sensitivity, specificity, and AUC of miR-106b, miR-122, and the combined as the diagnostic criteria for LC in the tissues of patients were all higher than those in the sera. The value of miR-106b combined with miR-122 in diagnosing LC was higher than that of miR-106b or miR-122 alone (**Table 5**, **Figure 2**).

Discussion

The occurrence and development of carcinoma is a multi-step process of multiple genetic lesions, and tumor cells in the process will be accompanied with abnormal expressions of miRNAs. Relevant miRNAs, as markers for the early diagnosis of malignant tumors, are currently hot topics in tumor researches around the world [19, 20]. This study tried to understand more about the mechanism of development of LC by detecting the expression levels of miR-106b and miR-122 in the LC tissues and sera of patients, hoping to provide references for the diagnosis of LC.

The results of this study showed that the expression levels of miR-106b and miR-122 in the sera of patients with LC were higher than those of normal ones, and the expression levels of miR-106b and miR-122 in the LC tissues of patients were higher than those in the sera, which were similar to the reports related to miR-106b. Yu et al. reported in 2014 that miR-106b was a novel marker of laryngeal squamous cell carcinoma [11]. And then Yu et al.'s study on miRNA microarray screening for LC in 2015 showed that miR-106b was up-regulated in LC [12]. In 2016, Li et al. reported that miR-106b promoted the proliferation of LC cells by targeting the Rb gene, and the Rb gene was the earliest tumor suppressor gene discovered [21]. There were few reports about the roles of miR-122 in LC. Many studies reported that miR-122 is abnormally expressed in hepatocellular carcinoma, colorectal carcinoma, and non-small cell lung carcinoma [22-24]. Lou et al. found that miR-122 was able to increase the sensitivity of hepatocellular carcinoma cells to chemotherapeutic drugs [22]. The survival rate of patients with LC is not high, and the five-year survival rate of patients with

advanced LC is less than fifty percent, which is related to the low sensitivity of LC to chemotherapeutic agents currently [5, 6]. Qin et al. also reported that miR-122 could inhibit the metastasis of cells and epithelial-mesenchymal transition in non-small cell lung carcinoma [24]. These studies showed that miR-106b and miR-122 were abnormally expressed in some tumors and were closely related to the biological behavior of tumor cells. In this paper, the experiments were not conducted in vitro. Therefore, the effect of miR-122 on the biological behavior of LC cells was an inference. Further study will be conducted to provide experimental evidences for clinical treatment of LC.

Failure to detect an early-stage tumor has always been one of the important reasons for the low survival rate of a patient with tumor, and it is also true for patients with LC [25, 26]. Therefore, we evaluated the diagnostic values of miR-106b and miR-122 in LC. From the previous analyses, we found that the expression levels of miR-106b and miR-122 in the tissues of LC were higher than those in the sera. The ROC analysis also showed that AUCs of the expression levels of miR-106b and miR-122 as the diagnostic criteria in the tissues were significantly higher than those in the sera (both AUCs of the expression levels of miR-106b and miR-122 were less than 0.7 in the sera), and the specificity and sensitivity were the same. We then analyzed the diagnostic value of miR-106b combined with miR-122 for LC. We performed a binary logistic regression analysis of miR-106b and miR-122, and then performed a ROC analysis on combining predictors, which revealed that AUC of miR-106b combined with miR-122 as the diagnostic criteria in the LC tissues and the sera of patients was elevated. Nevertheless, AUC of miR-106b combined with miR-122 as the diagnostic criteria in the sera of patients was still not satisfied (just 0.741), while the specificity and sensitivity were only 73.0% and 66.0% respectively, which were a little far from the expectation. Shi et al. in their study found that the AUC of miR-106b in the diagnosis of hepatic carcinoma was 0.855, and the sensitivity was 90.0% with a specificity of 66.7% [25]. Tang et al. reported that miR-122 had high sensitivity and specificity for the diagnosis of gliomas, with a sensitivity of 91.9% and specificity of 81.1%, and AUC of 0.939 [26]. We speculated that these might be due to the difference between our study subjects.

To sum up, miR-106b and miR-122 have different levels of expression in LC tissues and sera in patients with LC. The expression levels of miR-106 and miR-122 in patients with LC was increased. The higher the clinical stage, the higher the expression levels of miR-106 and miR-122. Therefore, both miRNAs might be more valuable than any one of them and be a helpful choice to the diagnosis of LC. Indeed, miR-106b and miR-122 have a certain value in the diagnosis of LC, but whether it can be applied to serological diagnosis of LC still remains to be further explored.

Disclosure of conflict of interest

None.

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