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Original Article

Serum miR-26a/b expression correlates with pathological features in patients with gastric cancer

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Abstract: Objective: To explore the correlation between miR-26a and miR-26b expression and severity of gastric cancer pathology. Methods: The data of 88 gastric cancer patients were collected as observation group and 80 healthy persons as control group. The serum levels of miR-26a and miR-26b were detected and analyzed retrospectively. Results: The expression of miR-26a and miR-26b in gastric cancer patients was lower than that in healthy controls (both P<0.001). The higher the T-staging, the lower the relative expression of miR-26a and miR-26b, with statistical differences between groups (P<0.01). According to the comparison of different N-staging and M-staging, the relative expression of miR-26a and miR-26b in N1-staging group with peripheral lymphatic metastasis was lower than that in N0-staging group without metastasis (P<0.001), and the relative expression in M1-staging group with distant metastasis was lower than that in M0-staging group without distant metastasis (P<0.001). The relative expression of miR-26a and miR-26b in patients with advanced gastric cancer was significantly lower than that in patients with early gastric cancer (P<0.001). The relative expression of miR-26a and miR-26b in infiltration-ulcerative and infiltrative gastric cancers was significantly lower than that in protuberant and local-ulcerative gastric cancers (P<0.05), and the relative expression in local-ulcerative gastric cancer was lower than that in protuberant one (P<0.001). Conclusion: The expression of miR-26a/b is decreased in patients with gastric cancer, especially in advanced one, and the decrease was related to the tumor malignancy.

Keywords: miR-26a/b, gastric cancer, diagnosis, pathological features, correlation

Introduction

Gastric cancer, as a common malignant tumor in clinic, is the third leading cause of death in the world, with 1.3 million cases in 2015 [1]. In East Asia region, there is a high-risk of gastric cancer in China, with its incidence rate ranking second in tumors [2]. The treatment effect of gastric cancer is poor, and the 5-year survival rate is lower than 10% [3]. At present, surgery is the main treatment for gastric cancer [4]. However, for advanced gastric cancer, the resection rate and the 5-year survival rate are low due to easy recurrence and metastasis after surgery, and the treatment effect by surgery alone is unsatisfactory [5]. Therefore, early diagnosis and treatment for gastric cancer are of great significance to the prognosis of patients.

Detection of the commonly used tumor markers is usually performed for early diagnosis of gastric cancer, but a study in China has found that the detection results are poor, and the prognosis is still not optimistic [6]. In recent years, increasing studies have shown that micro RNA (miRNA) is closely related to the occurrence and development of tumors [7, 8]. Moreover, a study has shown that miR-26 is involved in the occurrence and development of various tumors, and can not only become an effective target for treatment but also be used as a prognostic indicator of tumors [9]. MiR-26a and miR-26b are both important members of miR-26, and it is found that miR-26a is abnormally expressed in various tumors, while there is few study on the relationship between miR-26a and gastric cancer in China [10, 11]. MiR-26b was firstly found to be related to differenti-

ation of adipocytes and stem cells, but in recent years it has been found to be related to differentiation of malignant tumor cells [12, 13]. Previous study has shown that miR-26b increases the invasiveness of cancer cells by regulating the expression of Foxf2 in breast cancer patients, and it also increases the chemosensitivity of liver cancer by acting on EphA2 receptor [14, 15]. Another study has found that miR-26a/b both can inhibit the invasion of colon cancer cells by regulating FUT4 transferase [16]. This study aimed to provide new biomarkers for early diagnosis of gastric cancer by detecting the expression of miR-26a and miR-26b in peripheral blood and studying their correlation with pathological features of gastric cancer patients.

Materials and methods

General data

A retrospective study was conducted on 88 patients with gastric cancer admitted to the Digestive Department of Weinan Central Hospital from January 2016 to December 2018, aged 46-72 years with an average age of 62.9±8.6 years. Whereas 80 health people examined in Weinan Central Hospital were selected as the control, with an average age of 38.4±6.8 years. All the above patients signed informed consent forms, and this study was approved by the Ethics Committee.

Inclusion and exclusion criteria

Inclusion criteria: Patients (1) accorded with the diagnostic criteria for gastric cancer of the Ministry of Health of the People's Republic of China in 2010 [17]; (2) aged 18-75 years old. Exclusion criteria: Patients with (1) incomplete clinical data; (2) serious heart, liver, kidney and other diseases; (3) mental diseases or cerebrovascular diseases; (4) other cancers or non-primary gastric cancer.

Clinical and pathological stage

Clinical stage and pathological grade were evaluated with reference to diagnostic criteria of UICC/AJCC Seventh Version [18].

MiRNA extraction methods

Trizol kit (Molecular Research Center, Inc., USA) was applied in this study. The upstream and downstream primers were provided by Guangzhou Ruibo Biotechnology Company. After that, RT-PCR technology was used to reverse transcribe miRNA into cDNA using reverse transcription kit (Canada Fernentas Company), which was then amplified as template. Finally, the expression of miRNA-26a/b in serum samples was determined by fluorescence probe-PCR detection. Specific operation methods: (1) Two tubes of peripheral venous blood, each about 2 mL, were collected from all the included patients in the early morning who were fasted for solids and liquids at 10 pm the day before. EDTA anticoagulant was added to the tubes to keep the integrity of the cells, and then the blood was shaken gently and evenly so that the blood cells were in full contact with the anticoagulant. (2) The tubes were put into a 4°C refrigerator, and plasma was separated from the collected venous blood within 2 hours. (3) The plasma was centrifuged with a high-speed centrifuge (Shanghai Sangon Biotech Company) for 10 min. Then the supernatant was sucked out into the Eppendorf tube, without the middle white layer. (4) The supernatant was centrifuged for another 10 min. (5) The separated plasma was stored at -80°C refrigerator and divided into a volume of 500 μL. (6) MiRNA-26 was extracted and purified by Trizol kit. The sequences of the upstream primer and the downstream primer were as follows: 5'-GTGGTTTCATATATATATATATAACGACG-3' and 5'-GACGAAGACGTCAAACTCATTT-3' (miR-26a), 5'-GAAGATTATGGCCCATCTGA-3' and 5'-CCAAGCTTAAACACCC-3' (miR-26b), compared with the reference primer 5'-TCGCTTCGGCCACA3' (U6). Circulation System (Shanghai Biotech Well Co., Ltd., China) 25 μL: SYBR premix (2×) (Shanghai Haoran Biotechnology Co., Ltd., China) 12.5 μL, upstream and downstream primers of the target gene 0.5 μL each, cDNA template 2.0 μL, and ddH_2O 9.5 μL. Reaction conditions: predenaturation at 94°C for 4 min, 95°C for 40 s, 60°C for 30 s, 72°C for 30 s, for a total of 35 cycles, then extension at 72°C for 1 min. Agarose electrophoresis was applied to detect PCR amplification products. The relative expression was analyzed with $2^{-\Delta\Delta C(T)}$ based on the expression of U6 snRNA. Finally, the relative expression of miRNA-26a/b was determined.

Statistical indicators

The SPSS 17.0 statistical software was used to statistically analyze the collected data. The continuous variables were expressed as the

Table 1. The general information of 88 patients with gastric cancer

Item	Case (n, %)
Age	
≥65 years old	32 (36.4)
<65 years old	56 (63.6)
Gender	
Male	42 (47.7)
Female	46 (52.3)
Diameter of tumor	
≤5 mm	15 (17.1)
5.1-10 mm	31 (35.2)
>10 mm	42 (47.7)
T staging	
T1	22 (25.0)
T2	21 (23.9)
T3	29 (32.9)
T4	16 (18.2)
N staging	
N0	62 (70.4)
N1	26 (29.6)
M staging	
M0	71 (80.7)
M1	17 (19.3)
The stage of the disease	
Early gastric cancer	28 (31.8)
Advanced gastric cancer	60 (68.2)

mean ± standard deviation ($\bar{x}$ ± sd). Data accorded with normal distribution and homogeneity of variance within group were compared by independent sample t-test or paired t-test, otherwise, by rank sum test. One-way analysis of variance was used for multiple-group comparison, and least significant difference test as post hoc test. Pearson product-moment correlation method was applied to analyze the linear correlation between two variables. The difference was statistically significant with P<0.05.

Results

General data

The general data of 88 gastric cancer patients included in this study were shown in **Table 1**.

Comparison of relative expression of miR-26a/b

MiR-26a and miR-26b in the observation group were significantly lower than those in the control group (P<0.001). See **Table 2**.

Correlation between relative expression of miR-26a, miR-26b and age and gender

The relative expression of miR-26a and miR-26b was 1.78±1.43 and 1.82±1.59 in 32 patients with gastric cancer over 65 years old, and 1.76±1.07 and 1.80±1.19 in 56 patients under 65 years old. The relative expression was 1.89±1.09 and 1.95±1.21 in 42 males, and 1.66±1.31 and 1.68±1.45 in 46 females. Therefore, there was no difference in the relative expressions of miR-26a and miR-26b among gastric cancer patients with different ages and genders (P>0.05).

Correlation between relative expression of miR-26a, miR-26b and tumor size

The relative expression of miR-26a and miR-26b was different in patients with different tumor sizes. The larger the tumor size was, the lower the relative expression was (P<0.05). By correlation analysis, the relative expression of miR-26a and miR-26b were negatively correlated with tumor size, respectively (r=-0.703, P<0.001; r=-0.687, P<0.001). See **Table 3**.

Correlation between relative expression of miR-26a, miR-26b and TNM stage

The higher the stage of T, N and M was, the lower the relative expression of miR-26a and miR-26b was. There were statistical differences between the groups (P<0.01). The expression of miR-26a and miR-26b was negatively correlated with T stage (r=-0.256, P=0.017; r=-0.356, P=0.004). There was negative correlation between miR-26a and miR-26b and N stage, respectively (r=-0.318, P=0.003; r=-0.456, P<0.001). And the correlation of miR-26a and miR-26b and M stage was negative (r=-0.672, P<0.001; r=-0.743, P<0.001). See **Tables 4**-**6** and **Figure 1**.

Comparison of relative expression of miR-26a and miR-26b in different disease stages

The relative expression of miR-26a and miR-26b in patients with advanced gastric cancer was significantly lower than that in patients of early stage, with statistical difference (P<0.001). See **Table 7**.

Comparison of pathological types and relative expression of miR-26a and miR-26b in 60 cases of advanced gastric cancer

The relative expression of miR-26a and miR-26b in infiltration-ulcerative and infiltrative gas-

Table 2. Comparison of relative expression of miR-26a/b

Group	Control group (n=80)	Observation group (n=88)	t	P
Relative expression of miR-26a	4.12±1.14	1.77±1.21	12.942	<0.001
Relative expression of miR-26b	4.08±0.95	1.81±1.34	12.710	<0.001

Table 3. Correlation between relative expression of miR-26a/b and tumor size

Group	Relative expression of miR-26a	Relative expression of miR-26b
≤5 mm (n=15)	2.92±1.13	3.09±1.25
5.1-10 mm (n=31)	1.62±0.92	1.65±1.02
>10 mm (n=42)	0.68±0.39	0.61±0.43
F	36.628	36.608
P	<0.001	<0.001
P1	<0.001	<0.001
P2	<0.001	<0.001
P3	<0.001	<0.001

Note: P1, compared ≤5 mm group and 5.1-10 mm group; P2, compared ≤5 mm group and >10 mm group; P3, compared 5.1-10 mm group and >10 mm group.

Table 4. Comparison of relative expression of miR-26a/b in T staging

Group	Relative expression of miR-26a	Relative expression of miR-26b
T1 (n=22)	2.98±1.20	3.15±1.33
T2 (n=21)	2.21±0.92	2.30±1.02
T3 (n=29)	1.22±0.56	1.20±0.62
T4 (n=16)	0.51±0.24	0.41±0.27
F	34.762	34.784
P	<0.001	<0.001
P1	0.003	0.003
P2	<0.001	<0.001
P3	<0.001	<0.001
P4	<0.001	<0.001
P5	<0.001	<0.001
P6	0.006	0.006

Note: P1, compared T1 and T2; P2, compared T1 and T3; P3, compared T1 and T4; P4, compared T2 and T3; P5, compared T2 and T4; P6, compared T3 and T4.

tric cancers was significantly lower than that in protuberant and local-ulcerative gastric cancers (P<0.05), and the relative expression in local-ulcerative gastric cancer was lower than that in protuberant gastric cancer, with statistical difference (P<0.001). See **Table 8** and **Figure 2**.

Table 5. Comparison of relative expression of miR-26a/b in N staging

Group	Relative expression of miR-26a	Relative expression of miR-26b
N0 (n=62)	2.19±1.18	2.28±1.30
N1 (n=26)	0.76±0.46	0.69±0.51
t	8.217	8.208
P	<0.001	<0.001

Table 6. Comparison of relative expression of miR-26a/b in M staging

Group	Relative expression of miR-26a	Relative expression of miR-26b
M0 (n=71)	2.05±1.18	2.12±1.30
M1 (n=17)	0.60±0.32	0.52±0.36
t	9.023	9.043
P	<0.001	<0.001

Discussion

The early diagnosis of malignant tumor has been a concern in clinic. It has a positive effect on the prognosis of patients to find reliable and accurate markers in serum for early diagnosis. Clinically, for gastric cancer patients, the diagnosis is often lack of specificity only through clinical signs, symptoms and commonly used tumor indicators monitoring, thus causing some patients to miss the early diagnosis and delay the treatment [19].

With the development of gene detection technology, studies have found that some related non-coding RNAs (miRNAs) have different effects of inhibition or promotion in the process of tumor occurrence, development, invasion and metastasis [20-22]. And studies have shown that abnormal expression of miRNAs in plasma of gastric cancer patients can be used as markers for early diagnosis of gastric cancer [23, 24]. Moreover, some studies have pointed out that miR-320a expression in gastric cancer patients is significantly reduced, and its effect is mainly to inhibit the progression of cancer by inhibiting vimentin and ubiquitinated protease

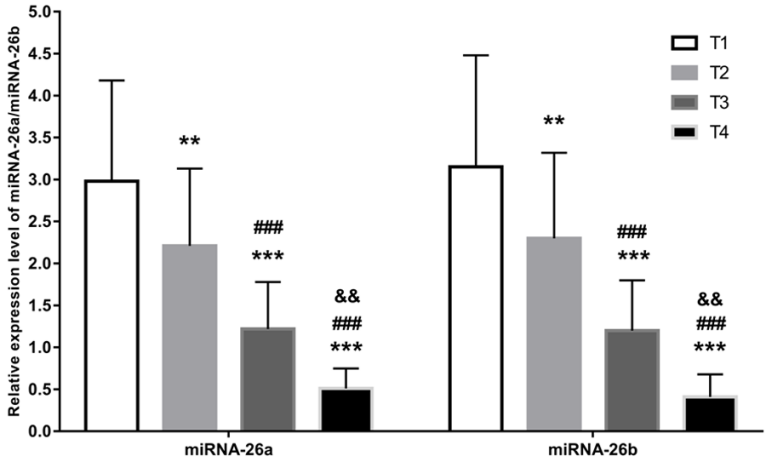

Figure 1. Comparison of relative expression of miR-26a/b in T staging. Compared with T1, ***P<0.001, **P<0.01; compared with T2, ###P<0.001; compared with T3, &&P<0.01.

Table 7. Comparison of relative expression of miR-26a/b in different tumor stages

Group	Relative expression of miR-26a	Relative expression of miR-26b
Early gastric cancer (n=28)	2.96±1.05	3.13±1.16
Advanced gastric cancer (n=60)	1.21±0.81	1.19±0.90
t	8.572	8.558
P	<0.001	<0.001

Table 8. Comparison of relative expression of miR-26a/b in different pathological types of advanced gastric cancer

Group	Relative expression of miR-26a	Relative expression of miR-26b
Protuberant type (n=17)	2.17±0.66	2.07±0.78
Localized ulcer type (n=16)	1.19±0.48	1.37±0.76
Infiltrating ulcer type (n=16)	0.72±0.31	0.65±0.35
Infiltrative type (n=11)	0.40±0.16	0.28±0.18
F	41.497	24.926
P	<0.001	<0.001
P1	<0.001	<0.001
P2	<0.001	<0.001
P3	<0.001	<0.001
P4	0.006	0.001
P5	<0.001	<0.001
P6	0.077	0.131

Note: P1, compared protuberant type and localized ulcer type; P2, compared protuberant type and infiltrating ulcer type; P3, compared protuberant type and infiltrative type; P4, compared localized ulcer type and infiltrating ulcer type; P5, compared localized ulcer type and infiltrative type; P6, compared infiltrating ulcer type and infiltrative type.

14 which promote the progression of gastric cancer [25]. However, RNA-H19, miR4435-2HG and lncRNA-LINC00857 have been found to promote the progress of gastric cancer and enhance the migration and invasion of cancer cells [26-28]. In our study, it was found that the expression of miR-26a and miR-26b in peripheral blood of patients diagnosed with gastric cancer was significantly lower than that of healthy people.

MiR-26a-1, miR-26a-2, and miR-26b are three subtypes of miR-26 family, located on chromosomes 3, 12, and 2 respectively. The mature miRNAs of miR-26a-1 and miR-26a-2 have the same sequence, which is 2 nucleotides different from the mature miRNA of miR-26b [29]. Compared with other miRNAs whose functions and effects have been confirmed, the "role" of miR-26a/b in malignant tumors is still controversial. For example, in hepatocellular carcinoma, miR-26a/b inhibits tumor cell growth and angiogenesis by blocking HGF/c-Met signaling pathway [30]. And in breast cancer, it has also been proved that they play the "role" of tumor suppressor gene [31]. However, miR-26a/b has been found to promote the growth and metastasis of tumor cells and function as protooncogene in glioma, lung cancer and cholangiocarcinoma [32-34]. At present, there are few studies on the correlation between miR-26a/b and gastric cancer. Only one study has suggested that miR-26b inhibits the growth of gastric cancer cells through KPNA2/c-Jun pathway [35]. Therefore, this study focused on whether the correlation between serum miR-26a/b and gastric cancer can be used as an indicator for early diagnosis of gastric can-

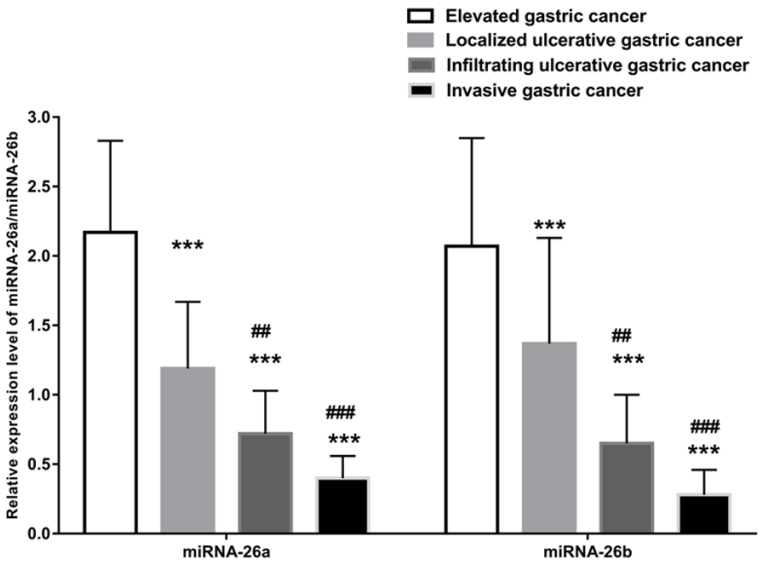

Figure 2. Comparison of relative expression of miR-26a/b in different pathological type of advanced gastric cancer. Compared with protuberant type, ***P<0.001; compared with localized ulcer type, ##P<0.01, ###P<0.001.

cer. In this study, it was found that the relative expression of miR-26a/b was not correlated with the gender and age of patients. The larger the tumor diameter was, the lower the miR-26a/b expression was. The miR-26a/b expression in peripheral blood of patients with gastric cancer metastasis was significantly decreased, and the decrease was more obvious in patients with distant metastasis. In the correlation of the relative expression of miR-26a/with in different tumor stages, it is found that the later the tumor stage was, the lower the relative expression of miR-26a/b was. The relative expression of miR-26a/b in patients of advanced gastric cancer was lower than that of early stage, and the deeper the tumor invasion degree was, the lower the relative expression of miR-26a/b was. The above pathological conditions show that when the invasion and proliferation of tumor cells got greater in gastric cancer patients, the relative expression of miR-26a/b in peripheral blood became lower, which may be related to the inhibitory effect of miR-26a/b on cancer cell proliferation in gastric cancer patients.

Inadequacy of this study: the sample size of this study was small, which can be further expanded for multi-center study.

To sum up, the expression of miR-26a/b is decreased in patients with gastric cancer, especially in advanced one, and the decrease of miR-26a/b expression is related to the malignant degree of tumor.

Disclosure of conflict of interest

None.

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