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Original Article

Expression of miR-625-3p in colon cancer and its correlation with prognosis

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Abstract: Objective: This study aimed to investigate the expression and prognostic significance of miR-625-3p in peripheral blood of patients with colon cancer. Methods: 64 patients with colon cancer were selected as the study group, and 64 healthy people as control group. The correlation between the expression of miR-625-3p and CEA, CA199 and the correlation among the different pathological characteristics of the study group were evaluated. The change of the expression of miR-625-3p before and after treatment in the study group was analyzed. Study group were followed up for 3 years. Results: The level of miR-625-3p in the study group before treatment was higher than that in the control group ($P < 0.001$), showing good diagnostic efficiency for diagnosing colon cancer and was positively correlated with the concentrations of CEA and CA199. The higher the level of miR-625-3p, the worse the prognosis. Conclusion: The expression of miR-625-3p in peripheral blood of patients with colon cancer is markedly increased, which is closely related to the development of colon cancer. It is of great significance for the diagnosis of colon cancer.

Keywords: miR-625-3p, colon cancer, CEA, CA199

Introduction

Colon cancer is most commonly observed malignant tumor. It has a very high incidence all over the world. Some data showed that the global incidence of colon cancer is as high as 6.1% [1]. Colon cancer occurs mostly at the junction of rectum and rectosigmoid colon. The prevalence of colon cancer in male patients is markedly higher than that in female patients [2]. In addition, the incidence of colon cancer has greater regional differences in the world. The incidence of colon cancer in North America, Australia and other regions is obviously higher than that in other countries [3]. In recent years, with the improvement of people's living standards and the change of dietary structure, the incidence of colon cancer has been increasing year by year [4]. According to the study of Arnold et al. [5], the global burden of colorectal cancer is expected to increase by 60% by 2030, with more than 2.2 million new cases and 1.1 million deaths. At present, the pathogenesis of colorectal cancer is not completely clear. Some studies have shown that the intestinal inflammation, parasites and genetic family history might cause the occurrence of colorectal cancer [6]. The early colorectal cancer has no obvious and special clinical symptoms, so the patients often miss the best treatment period due to the lack of medical and health care knowledge. Once diagnosed, the cancer has developed to the middle and late stages [7]. At this time, the common clinical treatment schemes, such as surgery, radiotherapy and chemotherapy, were often difficult to achieve an ideal efficacy, which was one of the main reasons for poor prognosis of patients with colon cancer [8]. Therefore, the researchers at home and abroad continue to explore new markers of colon cancer to effectively improve the screening rate and prognosis of colon cancer.

With the deepening of researches in recent years, more and more studies are directed to miRNAs [9-11]. The miRNA is a conservative non-coding RNA that can regulate gene expres-

Table 1. Primer sequence

	Upstream	Downstream
miR-625-3p	5'-GGGGAGGGGGAAAGTTCTA-3'	5'-GTGCGTGTCGTGGAGTCG-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'

sion at the post-transcription level. It has been proved that the miRNAs are closely related to the occurrence and development of various human cancers [12-15]. It has been reported that the over-expression of microRNAs could promote apoptosis of acute lymphoblastic leukemia cells [16]. However, the effect of miR-625-3p on colon cancer has not been verified. It was uncertain whether miR-625-3p had a related effect on the occurrence of colon cancer. To verify its mechanism, the expression of miR-625-3p in patients with colon cancer was explored, and the clinical significance of miR-625-3p in colon cancer was analyzed in this experiment. The aim is to provide a new direction of the diagnosis and treatment of colon cancer for clinical reference in the future.

Materials and methods

Patients

64 patients with colon cancer in our hospital from April 2014 to October 2015 were selected as the study group, including 48 males and 16 females. Their age ranged from 41 to 69 years, with the average age of 53.1 ± 10.8 years. Another 64 healthy people in the same period were selected as the control group, including 50 males and 14 females. Their age ranged from 40 to 70 years, with the average age of 54.2 ± 9.7 years. The experiment has been approved by the Ethics Committee of our hospital. All the above subjects have signed the informed consent.

Inclusion and exclusion criteria

Inclusion criteria: The patients conformed to the clinical manifestations of colon cancer and were diagnosed as colon cancer after biopsy in the pathology department of our hospital, ranging from 30 to 70 years old. The patients had complete case data and agreed to cooperate with the investigation work of our hospital. The patients did not receive any auxiliary treatment before admission. Exclusion criteria: patients with other tumors, cerebral-cardiovascular diseases, chronic diseases, psychiatric diseases and autoimmune diseases; patients with organ failure; patients with liver and kidney dysfunction; patients with allergic drug reactions; patients with physical disabilities and who are unable to take care of themselves; long term lying patients; and patients with intermediate transfer. The inclusion and exclusion criteria in the control group: The subjects had no disease, and all physical examinations were normal. The age of subjects was 30-70 years old. The subjects agreed to cooperate with the investigation work in our hospital.

Methods

All the patients in the study group received tumor resection and postoperative chemotherapy. The operation was performed by the senior digestive surgeon in our hospital. The postoperative intravenous chemotherapy was carried out. The 5-FU was the basic drug, and the tetrahydrofolate was used as a regulator to enhance the efficacy of 5-FU. The morning fasting peripheral venous blood of the study group and the control group was collected before and after treatment. The blood was centrifuged for 10 minutes (4000 rpm/min) after 30 minutes of rest at room temperature. The upper serum was packed with enzyme-free EP tubes, some of which were taken for experiment, and the rest were stored at -80°C.

RT-qPCR: The total RNA was extracted by EasyPure miRNA Kit (Beijing TransGen Biotech Co., Ltd., ER601-01). The purity, concentration and integrity of the total RNA were detected by ultraviolet spectrophotometer and agarose gel electrophoresis. The reverse transcription of total RNA extracted was carried out by the TransScript Green miRNA Two-Step qRT-PCR SuperMix (Beijing TransGen Biotech Co., Ltd., AQ202-01) in accordance with the kit instruction. The cDNA was collected for PCR amplification. The sequence of primers was shown in **Table 1**. The amplification system of qPCR was as follows: 1 μL of cDNA, 0.4 μL of upstream and downstream primers, 10 μL of 2 × TransTaq® Tip Green qPCR SuperMix, and 0.4 μL of Passive Reference Dye (50X). Finally, ddH_2O was added to make up to 20 μL. The amplification condition of qPCR was as follows: pre-denaturation at 94°C for 30 s, denaturation at 94°C for 5 s, and annealing at 60°C for 30 s with 40 cycles. Three wells were set in

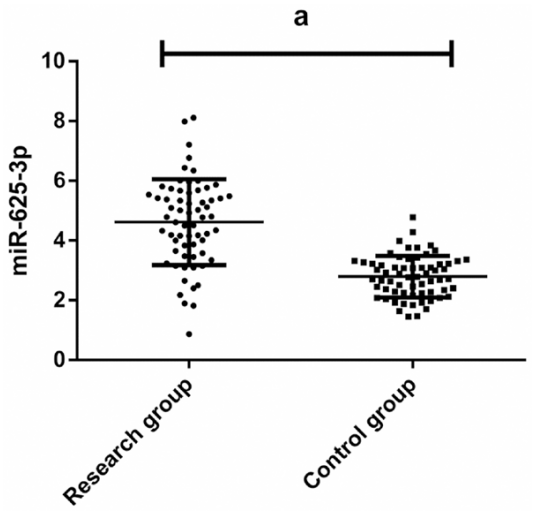

Figure 1. Comparison of peripheral blood miR-625-3p in the study group before treatment with the control group. [a]P < 0.001.

each sample and the experiment was carried out three times. In this study, U6 was utilized as internal reference, and the data were analyzed by 2-ΔΔct. The serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA199) were detected by electro-chemiluminescence. The kits were purchased from Shanghai Yaji Biotechnology Co., Ltd. CEA: CL01236; CA199: CL06872.

Outcome measures: The serum miR-625-3p expression in the study group and the control group before treatment; the diagnostic value of miR-625-3p for colon cancer; the correlation between miR-625-3p expression and CEA, CA199 before treatment in the study group; the correlation between different pathological characteristics of the study group and the miR-625-3p expression before treatment; the changes of miR-625-3p expression before and after treatment in the study group.

Statistical methods: SPSS24.0 statistical software (Beijing Strong Vinda Information Technology Co., Ltd.) was applied to calculate all the experimental results. Graphpad 8 software (Shenzhen Softhead Technology Co., Ltd.) was applied to draw all the graphics, and the results were checked twice. The enumeration data, such as gender and smoking, were expressed in the form of rate, and the chi-square test was utilized for comparison between groups. The measurement data, such as the expression of miR-625-3p, were expressed in the form of mean ± standard deviation, and t-test was applied for comparison between groups. The one-way analysis of variance (ANOVA) was used for comparison between two groups. The ROC curve was applied to measure the diagnosis value. Pearson correlation analysis was carried out for the correlation analysis. The patients in the study group were followed up for 3 years. The follow-up was conducted in the form of hospital review. According to the median expression of miR-625-3p before treatment, the patients were divided into the high miR-625-3p group (expression of miR-625-3p ≥ median) and low miR-625-3p group (expression of miR-625-3p < median). The 3-year survival rate was calculated by the Kaplan-Meier method, and the survival rate was compared by Log-rank test. P < 0.05 indicated that the difference was statistically significant.

Results

Comparison of general data

There were no remarkable differences in age, BMI, gender, smoking, drinking habits and residence between the two groups (P > 0.050), suggesting that there was comparability between the two groups. There were obvious differences in CEA, miR-625-3p, CA199, dietary habits and history of intestinal inflammation between the two groups (P < 0.001) (**Figure 1** and **Table 2**).

Diagnostic value of miR-625-3p for colon cancer

The ROC curve analysis of serum miR-625-3p expression in the study group and the control group before treatment suggested that when cut-off value was 3.80, the sensitivity and specificity of serum miR-625-3p in the diagnosis of colon cancer were 73.44% and 93.75%. The area under the curve (AUC) was 0.872, 95% CI: 0.806~0.938, and the Std. Error was 0.034, P < 0.001 (**Figure 2**).

Correlation between miR-625-3p expression and CEA, CA199

Pearson correlation analysis indicated that the expression of serum miR-625-3p was positively correlated with the concentrations of CEA (r = 0.682, 95% CI: 0.524~0.795 R square 0.465, P

Table 2. General data comparison [n (%)]

	Study group (n = 64)	Control group (n = 64)	t or x^2	*P*
Age	53.1 ± 10.8	54.2 ± 9.7	0.546	0.606
BMI (KG/cm^2)	24.23 ± 4.86	24.16 ± 5.02	0.080	0.936
CEA (ng/mL)	27.56 ± 0.72	2.68 ± 0.24	262.314	< 0.001
CA199 (U/mL)	45.13 ± 8.62	9.82 ± 3.05	30.893	< 0.001
Gender			0.174	0.676
Male	48 (75.00)	50 (78.13)		
Female	16 (25.00)	14 (21.88)		
Smoking			0.582	0.446
Yes	46 (71.88)	42 (65.63)		
No	18 (28.13)	22 (34.38)		
Drinking			1.550	0.213
Yes	39 (60.94)	32 (50.00)		
No	25 (39.06)	32 (50.00)		
Residence			0.434	0.659
Urban area	58 (90.63)	60 (93.75)		
Rural area	6 (9.38)	4 (6.25)		
Dietary habit			27.072	< 0.001
Vegetarian diet	4 (6.25)	30 (46.88)		
Meat diet	60 (93.75)	34 (53.13)		
Marital status			0.948	0.330
Married	56 (87.50)	52 (81.25)		
Unmarried	8 (12.50)	12 (18.75)		
History of intestinal inflammation			60.271	< 0.001
Yes	60 (93.75)	17 (26.56)		
No	4 (6.25)	47 (73.44)		

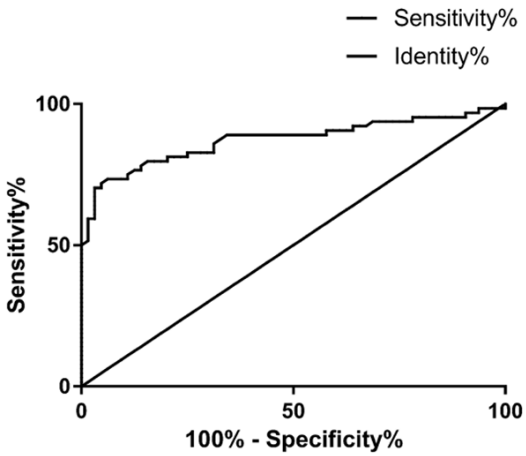

Figure 2. Diagnostic value of miR-625-3p for colon cancer. The ROC curve analysis showed that when cut-off value was 3.80, the sensitivity and specificity of serum miR-625-3p in the diagnosis of colon cancer were 73.44% and 93.75%.

< 0.001) and CA199 (r = 0.753, 95% CI: 0.622~0.843, R square: 0.567, P < 0.001) in the study group before treatment (P < 0.001) (**Figure 3**).

Relationship between miR-625-3p and clinical pathology of colon cancer

There was no obvious difference in the expression level of mir-625-3p among different age, BMI, gender, smoking, drinking, residence, dietary habits, marital status, history of intestinal inflammation, tumor type and tissue type (P > 0.05). In the different TNM staging, pathological staging, lymphatic metastasis and differentiation, there were differences in the expression of miR-625-3p (P < 0.050) (**Table 3**).

Expression of miR-625-3p in the study group before and after treatment

The expression of serum miR-625-3p in the study group after treatment was 3.12 ± 0.46, which was lower than that in the study group before treatment (4.82 ± 1.34, P < 0.001) (**Figure 4**).

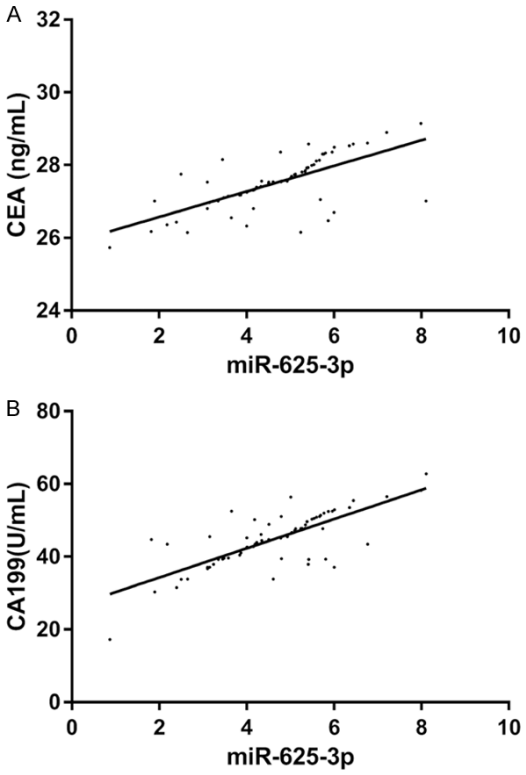

Figure 3. Correlation analysis of miR-625-3p with CEA and CA199 in the study group before treatment. The serum miR-625-3p was positively correlated with CEA ($r = 0.682$, $P < 0.001$) and CA199 ($r = 0.753$, $P < 0.001$) before treatment.

Prognosis of patients

63 out of 64 patients were successfully followed up in the study group, with a success rate of 98.44%. According to the median expression of miR-625-3p before treatment, the patients were divided into the high miR-625-3p group (36 cases) and low miR-625-3p group (27 cases). The 3-year prognostic follow-up results showed that the 3-year survival rate was 72.22% (26/36) in the high miR-625-3p group and 92.59% (25/27) in the low miR-625-3p group. The 3-year survival rate in the low miR-625-3p group was higher than that in the high miR-625-3p group ($P = 0.042$) (**Figure 5**).

Discussion

Colon cancer is commonly diagnosed [17]. Recently, the role of microRNAs in various cancer diseases was confirmed [18-20]. microRNAs have become a major research hotspot in clinic. miR-625-3p has been proved to be closely related to human cholesterol [21]. However, the role of mir-625-3p in colon cancer has not been clear yet.

The results revealed that the relative expression of miR-625-3p in peripheral blood of patients with colon cancer was higher than that of normal subjects, suggesting that miR-625-3p may be involved in the occurrence and development of colon cancer. Kirschner et al. [22] reported there was a high expression of miR-625-3p in malignant pleural mesothelioma, which can support the results of this experiment. Currently, the studies on miR-625 worldwide predominantly focus on tumors. Li et al. [23] suggested that miR-625 can regulate cell invasion and epithelial mesenchymal transition (EMT) in laryngeal carcinoma, while Fang et al. [24] proved that miR-625 is a tumor suppressor to inhibit the development and progression of malignant melanoma. In this study, there was a high expression of miR-625-3p in peripheral blood of patients with colon cancer, which may be related to the mechanism of miR-625. The miR-625 can regulate the proliferation and migration of cancer cells by the targeted induction of the expression of high mobility group proteins [25]. The miR-625-3p can accelerate the proliferation and invasion of cancer cells by binding to the DNA transport in cancer cells. Some studies have shown that the proportion of cells in G_2/M phase was decreased dramatically after transfection with the miR-625-3p inhibitor [26]. The regulation of miR-625-3p for cells was also demonstrated. After further analysis, it was found that miR-625-3p has a good diagnostic efficacy in the diagnosis of colon cancer, and has an obvious correlation with the classical tumor markers (CEA and CA199), suggesting that the detection of miR-625-3p in peripheral blood can be applied to determine the occurrence of colon cancer in the future. CEA and CA199 are currently recognized as the tumor markers [27].

The ROC curve analysis revealed that the AUC of miR-625-3p in the diagnosis of colon cancer was 0.872, with a specificity of 93.75%. However, due to the limited number of cases included in this study, this needs further confirm.

By comparing the expression of miR-625-3p in different clinical and pathological stages, it was found that there were obvious differences in the expression of miR-625-3p in different TNM staging, pathological staging, lymphatic metas-

Table 3. Relationship between miR-625-3p and clinical and pathological data of colon cancer

	n	miR-625-3p	t or F	P
Age			0.244	0.808
≤ 53	16	4.54 ± 1.47		
> 53	48	4.63 ± 1.21		
BMI (KG/cm^2)			0.106	0.916
≤ 24	12	4.68 ± 1.52		
> 24	52	4.73 ± 1.46		
Gender			0.007	0.994
Male	48	4.60 ± 1.06		
Female	16	4.73 ± 1.30		
Smoking			0.255	0.800
Yes	46	4.92 ± 1.34		
No	18	4.83 ± 1.07		
Drinking			0.246	0.807
Yes	39	4.73 ± 1.52		
No	25	4.82 ± 1.27		
Residence			0.122	0.903
Urban area	58	4.68 ± 1.52		
Rural area	6	4.76 ± 1.60		
Dietary habit			0.141	0.888
Vegetarian diet	4	4.83 ± 1.82		
Meat diet	60	4.94 ± 1.49		
Marital status			0.168	0.867
Married	56	4.62 ± 1.24		
Unmarried	8	4.70 ± 1.38		
History of intestinal inflammation			1.210	0.231
Yes	60	5.24 ± 1.36		
No	4	4.38 ± 1.67		
TNM staging			2.816	0.007
I-II	12	3.69 ± 1.73		
III-IV	52	4.94 ± 1.30		
Pathological staging			2.237	0.029
I-II	7	3.47 ± 1.27		
III-IV	57	4.73 ± 1.42		
Tumor type			0.033	0.967
Massive type	36	4.72 ± 1.24		
Ulcerative type	19	4.80 ± 1.16		
Infiltrative type	7	4.69 ± 1.35		
Tissue type			0.022	0.978
Adenocarcinoma	30	4.84 ± 1.48		
Mucoid carcinoma	24	4.76 ± 1.20		
Undifferentiated carcinoma	10	4.80 ± 1.52		
Lymphatic metastasis			2.931	0.005
Yes	12	5.12 ± 1.42		
No	52	4.05 ± 1.07		
Lymphatic differentiation			2.513	0.015
Middle and high	18	4.23 ± 1.12		
Low	46	5.09 ± 1.27		

tasis and differentiation, suggesting that miR-625-3p was closely related to the progress of tumors. The previous studies have shown that miR-625-3p could promote the expression of Bcl-2 [28]. As an antiapoptotic protein, Bcl-2 exerted a role in regulating cell apoptosis and proliferation in human body [29]. It was speculated that miR-625-3p could increase the expression of Bcl-2 in patients with colon cancer, thus greatly increasing the survival cycle of tumor cells. With the increase of tumor cells, the development of patients' condition became more and more serious, which led to the higher expression of miR-625-3p in patients with more severe clinical pathology. After treatment, the expression of miR-625-3p in patients with colon cancer was decreased, which also proved that miR-625-3p has a certain predictive value for the treatment process of colon cancer. In the future, by real-time monitoring of the expression of miR-625-3p in patients' peripheral blood, the rehabilitation of patients can be effectively judged to perform timely treatment and intervention measures. At the same time, miR-625-3p is expected to become a target for future treatment of colon cancer, which is of great significance for colon cancer. However, the expression of miR-625-3p in patients before and after the completion of the whole treatment cycle was only compared in this study, and the undesirable changes of miR-625-3p in the course of treatment weren't excluded, which also needs further detailed experiments to verify. The prognosis and survival of patients were observed after grouped according to the expression of miR-625-3p. It was also indicated that the prognosis of patients with low expression of miR-625-3p was better, which further confirmed the effect of miR-625-3p on colon cancer.

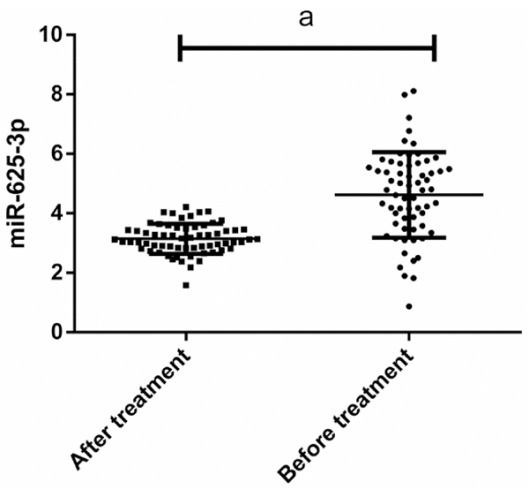

Figure 4. Comparison of peripheral blood miR-625-3p before and after treatment in the study group. [a]represents that compared with the level of miR-625-3p in peripheral blood before treatment, P < 0.001.

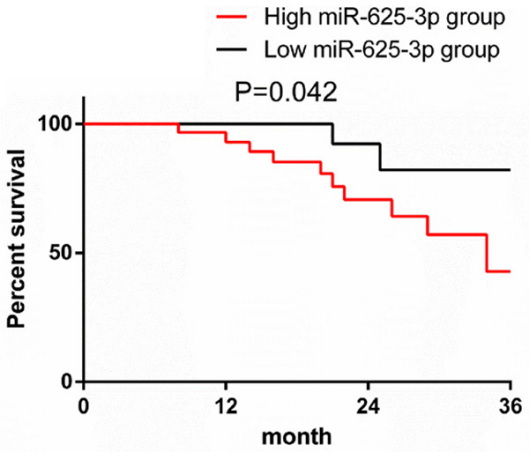

Figure 5. Prognostic 3-year survival curve of study group. The 3-year survival rate in the low miR-625-3p group was higher than that in the high miR-625-3p group (P = 0.042).

In conclusion, there was an obviously high expression of miR-625-3p in the peripheral blood of patients with colon cancer, which is closely related to the development of colon cancer.

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Disclosure of conflict of interest

None.

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