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Original Article

miR-506 in patients with chronic myeloid leukemia and its effect on apoptosis of K562 cells

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Abstract: Objective: To explore the expression of miR-506 in chronic myeloid leukemia (CML) and its influence on the biological function of CML cells. Methods: Altogether 84 CML patients from February 2012 to September 2014 were obtained as the observation group (OG), and 71 healthy people were taken as the control group (CG). miR-506 was tested using RT-qPCR, and the 5-year survival of patients with high and low expression of miR-506 was compared with the median value of miR-506 as the limit. ROC curve was applied to detect the value of miR-506 in diagnosing CML and predicting the 5-year survival of patients, and K562 cell line was transfected with miR-506 inhibitor and miR-506 mimic for observing its effects on the cell proliferation and apoptosis. Results: miR-506 in CML patients was evidently lower than that in healthy people, the AUC of diagnosis of miR-506 was 0.883, the total survival of patients with low miR-506 was evidently lower than those with high miR-506, and the AUC of predicted survival of patients was 0.778. The proliferation of cells transfected with miR-506 inhibitor was promoted, the apoptosis and the survival rate reduced. Conclusion: miR-506 is evidently reduced in CML, and may be applied as a diagnostic and predictive treatment for CML and 5-year related survival; it can also can hinder the viability of K562 cells and promote apoptosis.

Keywords: miR-506, CML, apoptosis

Introduction

Leukemia is a common hematological malignancy, which has an impact on many patients and their families all over the world. Chronic myeloid leukemia (CML) accounts for about 15% of leukemia all found in adults [1, 2]. CML occurs at all ages. In many developed countries, because of the low level of medical care and the hidden symptoms, the patients often have developed to the advanced stages of CML by the time they are diagnosed [3, 4]. The treatment for CML patients is mainly tyrosine kinase inhibitors such as imatinib, dasatinib, nilotinib and other drugs, or stem cell transplantation. The formulation of a treatment plan for CML patients tends to be personalized and needs to be patient-centered and customized according to the stages and characteristics of patients [5, 6]. The mortality rate of CML patients with advanced stages will increase evidently. In the study of Wu et al. [7], the survival rate of some patients who received tyrosine kinase inhibitor treatment and bone marrow transplantation treatment was followed up and analyzed, and it was found that the overall 10-year survival of patients was 65.7%. Therefore, when CML patients are diagnosed in time the survival of patients is improved.

miRNA can regulate gene expression through the 3'-UTR of mRNA, which will lead to the degradation of corresponding mRNA or prevent its translation [8]. Previous studies have shown that miRNA can affect growth, apoptosis and differentiation, and therefore participate in the progression of many diseases. miRNA may also be diagnostic markers or therapeutic targets of diseases [9, 10]. Leukemia is also found to be related to in some miRNAs. Kou et al. [11] mentioned that miR-181b of patients with chronic lymphocytic leukemia was evidently lower than

that of healthy people, and the expression level of miR-181b in high-risk and very high-risk patients was lower than that in low-risk patients. Huang et al. [12] mentioned that reduction of miR-96 could promote the proliferation of CML carcinoma cells by targeting BCR-ABL1, and promoting miR-96 could enhance the sensitivity of CML carcinoma cells to imatinib. miR-506 belongs to an X chromosome linked miRNA cluster, which is involved in the development of many carcinomas in many ways. For example, miR-506 in colon carcinoma patients was up-regulated, and the proliferation of cervical carcinoma cells *in vivo* and *in vitro* was inhibited by up-regulating miR-506 [13-15]. However, there are few studies on miR-506 in CML, so the relationship between miR-506 and CML is still unclear.

Therefore, we will explore the specific clinical value of miR-506 in CML patients by detecting its expression level and further exploring its influence on the biological function of CML cells.

Methods and materials

Patient data

A total of 84 CML patients from February 2012 to September 2014 were selected as the observation group (OG), with an average age of (46.5±7.3) years, including 51 males and 33 females. In addition, 71 healthy people were collected as the control group (CG), with an average age of (47.1±7.5) years, including 50 males and 21 females. This research conformed to the Medical Ethics Committee standards, and all patients have signed an informed consent.

Inclusion and exclusion criteria

Inclusion criteria: The diagnosis referred to the diagnostic guidelines for CML issued by NCCN [16], the Ph chromosome test and BCP/ABL fusion gene test showed positive results, and the patient's clinical data were complete.

Exclusion criteria: Patients had received chemotherapy or immunotherapy before the study; patients were combined with other malignant tumors, combined with other immune system diseases; patients had liver and kidney dysfunction and mental disorders.

Follow-up of patients

All patients were followed up for 5 years, and their living conditions were investigated by telephone, outpatient medical record inquiry and follow-up. The patients were followed up every 3 months in the first two years and every 6 months in the next three years.

Outcome measures

Main outcome measures: miR-506 in two groups, the total survival of patients in 5 years, and the effects of K562 transfection with miR-506 inhibitor and miR-506 mimic on cell proliferation and apoptosis were observed.

Secondary outcome measures: The clinical data of patients were observed, the value of miR-506 in diagnosing CML and predicting patients' 5-year survival was observed by ROC curve, the patients were grouped into high and low expression groups according to the median value of miR-506 to observe patients' 5-year death rate and visualize K-M survival curve.

Cell culture and transfection

Human chronic myeloid leukemia cell line K562 (ATCC, CCL-243) was cultured in Roswell Park Memorial Institute (RPMI) 1640 medium, including 10% FBS (Sigma, USA), with 5% CO_2 at 37°C. miR-506 inhibitor, miR-506 mimic, and negative control (inhibitor-NC and mimic-NC) were transfected by Lipofectamine™ 2000 kit (Thermoscientii Company, USA, 11668019). miR-506 inhibitor, miR-506 mimetic and negative control (inhibitor NC and mimetic NC) were all synthesized by Ribobio (Guangzhou, China), and miR-506 inhibitor was: UCUACUCAGAGUGCCUUA; miR-506 mimic was: UAAGGCACUCUGAGAGAGGCCUUUU.

RT-qPCR method

In the morning after admission, 5 mL of venous blood was taken from all patients, and the blood serum was collected by centrifuge (3000×g, 4°C, 10 min) and placed at -80°C. Total RNA was obtained from the serum and K562 cells were collected using mirVana™ PARIS™ kit (Thermo Fisher Scientific, USA, AM1556), and the purity of total RNA was tested using ultraviolet spectrophotometer (UV-1800, Shimadzu, Japan). Reverse transcription

Table 1. Primer sequence

Gene	Forward primers	Reverse primers
miR-506	5'-TGCGGTAAGGCACCCTTCTGAGTAC-3'	5'-CCAGTGCAGGGTCCGAGGT-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'

Table 2. Baseline data

	CG (n=71)	OG (n=84)	t/X^2	P
Age (years)	47.1±7.5	46.5±7.3	0.504	0.614
Gender			1.597	0.206
Male	50 (70.42%)	51 (60.71)		
Female	21 (29.58)	33 (39.29)		
Residence			1.252	0.263
Urban	60 (84.51)	65 (77.38)		
Rural	11 (15.49)	19 (22.62)		
Smoking history	14 (19.72)	19 (22.62)	0.193	0.660
Drinking history	12 (16.90)	13 (15.48)	0.058	0.081
White blood cell count ($\times10^9$/L)	5.17±2.06	42.31±4.14	68.776	<0.001
Course of disease (months)		9.33±4.2		
Clinical phase				
Chronic phase		40 (47.62)		
Accelerated phase		26 (30.95)		
Blast crisis		18 (21.43)		

was performed using PrimeScript™ RT Master Mix. Reverse transcription system was as follows: 0.5 μl reverse transcriptase, 0.5 μl reverse transcriptase, 2.0 μl buffer, 2 μl RNA, finally DEPC water was added to make up to 15 μl. Reaction conditions were as follows: 37°C for 10 min, 95°C for 5 min. Then TaqMan™ MicroRNA Assay Kit (Thermo Fisher Scientific, USA, 4427975) was applied for amplification. The reaction conditions were as follows: 94°C for 30 s, 94°C for 5 s, 60°C for 30 s. U6 was applied as internal reference gene, and $2^{-\Delta\Delta Cq}$ was applied for data processing. The primer sequences are shown in **Table 1**.

Cell proliferation detection

Twenty-four hours after transfection, the cells were collected, adjusted to $4*10^6$ cells/well, and inoculated in a 96-well plate. After 24 h, 48 h, 72 h and 96 h of culture, 10 μL CCK-8 solution (Beyotime Biotechnology, Shanghai, China, C0037) and 90 μL culture medium (DMEM) were put into each well, and then the OD value at 490 nm was tested using microplate reader.

Determination of apoptosis

Transfected cells were treated with 0.25% trypsin (Thermo Scientifi, USA, 90059), rinsed twice with PBS, added with 100 μL binding buffer to prepare $1*10^6$ cells/mL suspension, and then added with AnnexinV-FITC and PI (Shanghai Yisheng Biotechnology Co., Ltd., 40302ES20) in turn, and placed in dark at room temperature. FC-500MCL flow cytometer (BD, USA, FACS Canto II) was applied for detection, and the experiment was repeated 3 times to get the average value.

Statistical method

SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was applied for data analysis, and the figures in this research were illustrated using Graph Pad Prism7 (Graph Pad Software, Inc., San Diego CA, USA). The counting data were analyzed with Chi-square test and were represented by X^2. The measurement data were in accordance with a normal distribution and analyzed using independent sample t-test. ROC was applied to evaluate the diagnostic and predictive value of miR-506 for CML patients and their 5-year survival. K-M survival was applied to analyze the 5-year survival. Log rank test was applied for testing. $P<0.05$ indicated a statistically significant differences.

Result

Baseline data

By comparing the baseline data of the two groups, we found that there was no statistical difference in age, gender, residence, smoking and drinking history between the OG and the CG, as shown in **Table 2**.

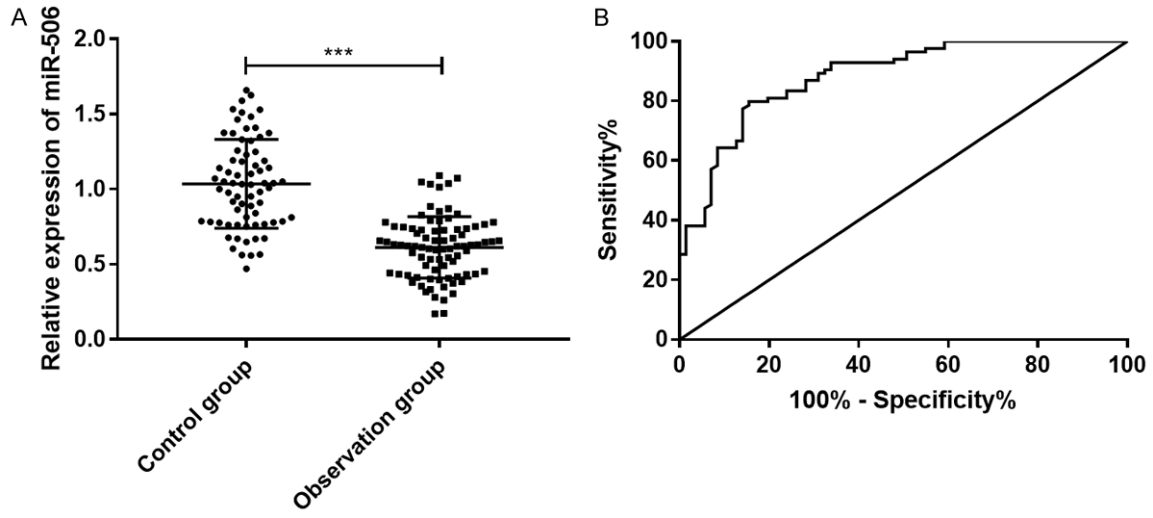

Figure 1. Diagnostic value of miR-506 in CML. A. The level of miR-506 in CG was evidently higher than that in OG (t=10.481, P<0.001). *** indicates P<0.001. B. AUC of miR-506 was 0.883. When cut off was less than 0.758, the best specificity and sensitivity were 84.51% and 79.76%, and Youden index was 64.27%.

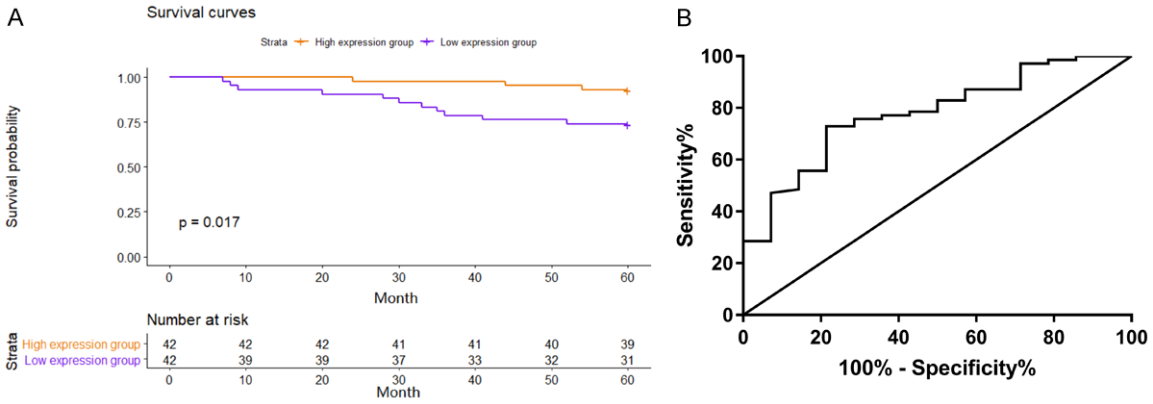

Figure 2. Five-year survival of patients. A. In the high expression group, 3 patients died and 39 survived in 5 years, with a survival rate of 92.86%. In the low expression group, 11 patients died and 31 patients survived in 5 years, with a survival rate of 26.19%. The overall survival of patients in the low expression group was evidently lower than that in high expression group. B. miR-506 was applied to predict the survival of AML patients with ROC curve, the AUC was 0.778, when cut off was less than 0.596, the best specificity and sensitivity were 78.57% and 72.86%, and Youden index was 64.27%.

Diagnostic value of miR-506 in CML

By comparing miR-506 between the OG and the CG, we found that miR-506 in the OG was evidently lower than that in the CG. The diagnostic value of miR-506 in CML was analyzed by ROC curve, and it was revealed that the AUC of miR-506 was 0.883, as shown in **Figure 1**.

Five-year survival

By counting the 5-year survival in the OG, it was found that 70 patients survived, 14 died, with the 5-year total survival being 83.33%. The patients in the OG were grouped into high and low miR-506 groups. Comparing the 5-year total survival between the OG and the CG, the 5-year total survival of low miR-506 group was lower than those in the high miR-506 group. The AUC of ROC curve for predicting the survival was 0.778, as shown in **Figure 2**.

Expression of miR-506 in different disease stages

The expression level of miR-506 in patients with a chronic phase was significantly higher than that in the accelerated and blastic phase,

Table 3. miR-506 expression in different disease phases

Phases	Number of cases	miR-506	F value	*P* value
Chronic phase	40	0.75±0.17	32.693	<0.001
Accelerated phase	26	0.54±0.13		
Blastic phase	18	0.42±0.15		

and that in the accelerated phase was significantly higher than that in the blastic phase, as shown in **Table 3**.

Biological effects of K562 cells

By observing the transfected K562 cells, we found that the proliferation of miR-506 inhibitor cells was promoted and the apoptosis was reduced, while the proliferation of miR-506 mimic cells were evidently reduced and the apoptosis was promoted, but there was no obvious difference between inhibitor-NC and mimic-NC in the proliferation and apoptosis rate, as shown in **Figure 3**.

Discussion

Hematopoietic stem cells in CML patients will appear disordered, which is mainly related to differentiation and proliferation errors applied by BCR-ABL [17]. Tyrosine kinase inhibitor is the first-line treatment drug for CML and it has good therapeutic effects. However, 20-30% of CML patients will have drug resistance in the chronic phase, and many patients will relapse, which will affect the outcome of treatment [18, 19]. Many miRs are involved in the proliferation, differentiation and apoptosis of hematopoietic stem cells, so they are abnormally expressed in various hematological malignancies and may become potential therapeutic targets [20].

In this study, it was found that miR-506 in CML was evidently reduced, and we speculated that miR-506 might be regulated as a tumor suppressor gene in CML. Then we tested the diagnostic value of miR-506 in CML, and found that its AUC was 0.883, and its specificity and sensitivity were 84.51% and 79.76%. This also suggested that miR-506 had good diagnostic value in CML. In the research of Krawczyk et al. [21], the ROC curve of miR-506 in the diagnosis of colorectal carcinoma was visualized, and the area under the curve was 0.747, indicating that miR-506 not only has good diagnostic value in colorectal carcinoma, but also has good diagnostic value in CML, and it is more suitable for diagnosis in CML. After that, we followed up these patients and counted the 5-year survival. The 5-year total survival was 83.33%. The prognosis of AML patients has always been observed to predict the treatment outcome, so we can implement a more suitable and effective treatment plan [22]. In order to verify whether miR-506 is related to the prognosis of patients, we compared the survival of high and low miR-506 level patients and found that the 5-year total survival of low miR-506 group were evidently lower than those with high miR-506 group. The ROC curve of miR-506 in predicting the survival of CML patients was visualized by using miR-506 in surviving patients and dead patients, and the AUC of the curve was 0.778, indicating that miR-506 has a good predictive value for 5-year survival of CML patients.

Then, in order to verify the role of miR-506 as a tumor suppressor gene in CML, we conducted cell experiments *in vitro*. The effect on K562 cells was observed by transfecting an miR-506 inhibitory sequence and miR promoting sequence into CML cells. The viability of K562 cells transfected with the miR-506 inhibitory sequence was evidently improved, but the apoptosis rate was inhibited by flow cytometry. The cell viability of K562 cells transfected with the miR-506 promoter sequence was evidently reduced, and the apoptosis rate was evidently enhanced, which also verified the conjecture that miR-506 is a tumor suppressor gene in CML, and miR-506 may become a gene therapy target for CML. Zhu et al. [23] tested the biological function of miR-506 on lymphoma cells, and found that miR-506 is also a tumor inhibitor of lymphoma cells, and it hinders the proliferation and metastasis of carcinoma cells by inhibiting B7H3 expression.

However, there are some shortcomings in this study. First of all, this study did not include the patient's treatment plan. It is not clear whether different treatment plans will have an impact on miR-506 and the prognosis of patients. Therefore, we hope that future studies can include these treatment plans. Secondly, there are some signaling pathways that affect the

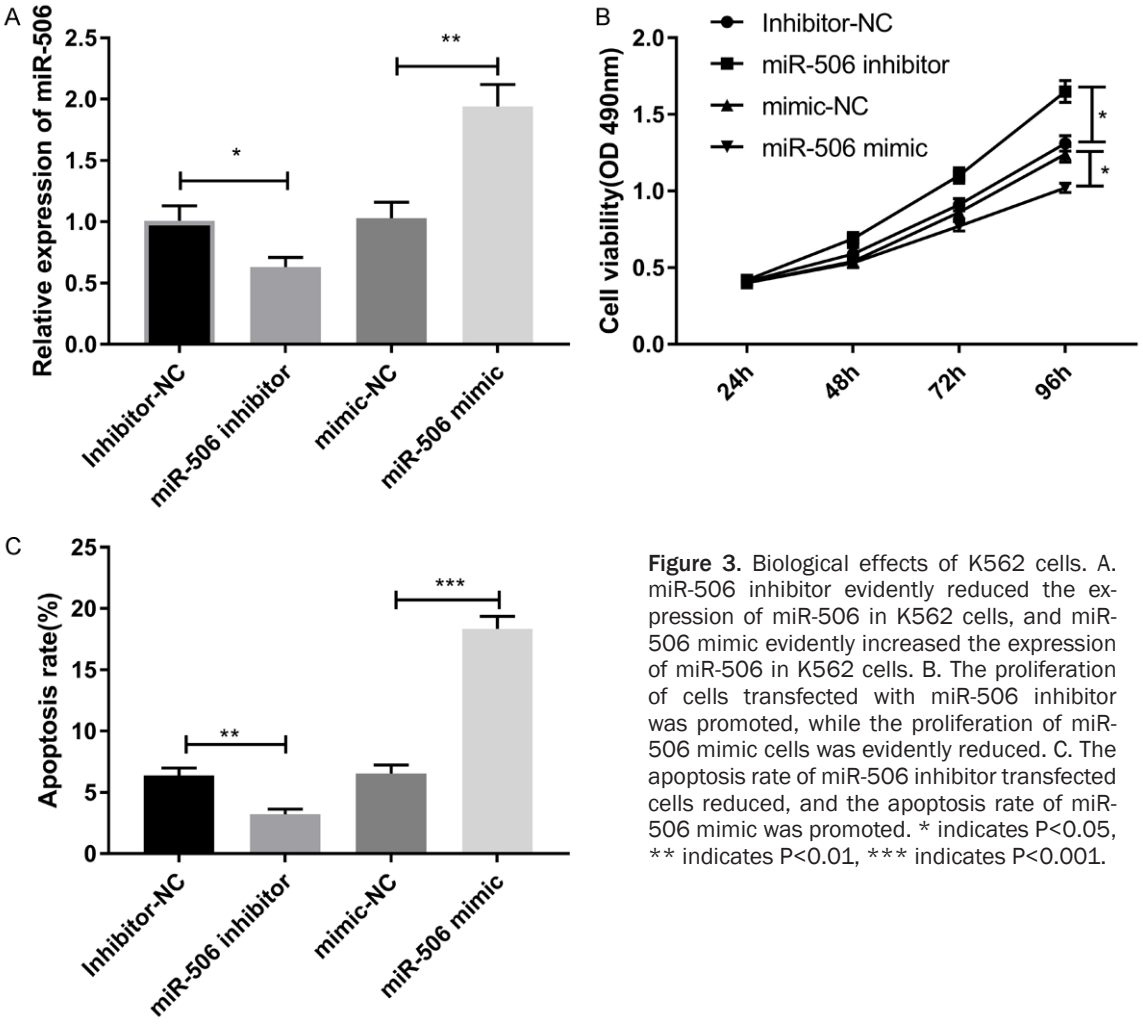

Figure 3. Biological effects of K562 cells. A. miR-506 inhibitor evidently reduced the expression of miR-506 in K562 cells, and miR-506 mimic evidently increased the expression of miR-506 in K562 cells. B. The proliferation of cells transfected with miR-506 inhibitor was promoted, while the proliferation of miR-506 mimic cells was evidently reduced. C. The apoptosis rate of miR-506 inhibitor transfected cells reduced, and the apoptosis rate of miR-506 mimic was promoted. * indicates $P<0.05$, ** indicates $P<0.01$, *** indicates $P<0.001$.

biological function of CML, such as PI3K/AKT/mTOR pathway and ERK/STAT3 pathway [24, 25], and the signal pathways affected by miR-506 need to be further explored. Finally, we have not carried out tumor-forming experiments in nude mice, and the specific therapeutic effect of miR-506 needs to be further studied in animal experiments.

To sum up, miR-506 is evidently reduced in CML, and may be applied as a diagnostic and predictive target for CML and the 5-year survival; miR-506 can hinder the vitality of K562 cells and promote apoptosis.

Disclosure of conflict of interest

None.

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