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Original Article

Increased expression of miR-24 is associated with acute myeloid leukemia with t(8;21)

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Abstract: This study was designed to learn the expression status of miR-24 and its clinical relevance in patients with acute myeloid leukemia (AML). We detected the miR-24 expression levels using real-time quantitative PCR in 84 AML patients and investigated the clinical significance of miR-24 expression in AML. There was no difference in clinical parameters between cases with miR-24 high expression and with miR-24 low expression. The frequency of miR-24 high expression was higher in patients with t(8;21) than in others (82% (9/11) versus 44% (32/72), *P*=0.026). The levels of miR-24 expression had no correlation with the mutations of nine genes (FLT3-ITD, NPM1, C-KIT, IDH1/IDH2, DNMT3A, N/K-RAS and C/EBPA). Meanwhile, among the group who obtained CR, the cases with miR-24 high expression had no difference in overall survival (OS) and relapse-free survival (RFS) than those with miR-24 low expression (*P*=0.612 and 0.665, respectively). These findings implicated that miR-24 high regulation is a common event in AML with t(8;21), and it might serve as a novel and selective therapeutic target for the treatment of AML with t(8;21).

Keywords: miR-24, acute myeloid leukemia, microRNA

Introduction

Acute myeloid leukemia (AML) is a heterogeneous malignant disease, which is characterized by arrested differentiation and abnormal proliferation, leading to bleeding, fatal infection, or organ infiltration [1]. Recurring chromosomal aberrations and gene mutations contribute to the pathogenesis of AML [2]. Recently, many researches have indicated that miRNAs play important roles in myeloid leukemogenesis [3-5].

MicroRNAs (miRNAs) are known as small non-coding single-stranded RNAs of 20-22 nucleotides that regulate the expression of over 60% of all human genes and are involved in pivotal biological processes, including development, differentiation, proliferation, as well as apoptosis [6-10]. A large body of evidences implicate that dysregulation of miRNA expression may take part in oncogenesis of human malignant cancers, such as non-small cell lung cancer (NSCLC), gastrointestinal carcinoma, hepatocellular carcinoma, pancreatic cancer, breast cancer, cervical cancer and the like [11-17]. Particular microRNA signatures have been discovered in myeloid and lymphoid leukemia, and have relationships with the pathogenesis, diagnosis and prognosis of myeloid and lymphoid leukemia, such as miR-124-1, let-7a-3, miR-181, miR-29B [4, 18-23].

Many researches have shown miR-24 takes control of cell cycle distribution and apoptosis [24-26]. Overexpression of miR-24 has been found in oral carcinoma and non-small cell lung cancer (NSCLC) [11, 27]. MiR-24 was reported to enhance invasion and metastasis in cancer cell [28]. However, the role of miR-24 in AML should be explored more. Here we addressed the question whether miR-24 expression is related to AML.

Materials and methods

Patients and samples

This study included 84 patients who had a diagnosis of de novo AML at the Affiliated People'

Table 1. Clinical characteristics at diagnosis of AML patients divided according to miR-24 expression status

	miR-24 high expression		
	+	-	*P*
Sex (male/female)	21/21	27/15	0.270
Median age at diagnosis, years (range)	53 (10-86)	57 (15-87)	0.164
Median WBC at diagnosis, $\times 10^9$ L^{-1} (range)	8.4 (0.3-185.4)	11.7 (1.1-528.0)	0.697
Median hemoglobin at diagnosis, g/L (range)	75.0 (34.0-131.0)	77.0 (40.0-138.0)	0.333
Median platelets at diagnosis, $\times 10^9$ L^{-1} (range)	33.0 (3.0-140.0)	38.0 (4.0-264.0)	0.707
FAB			0.053
M1	2	4	
M2	24	14	
M3	6	11	
M4	4	11	
M5	5	2	
WHO			0.080
AML with t(8;21)	9	2	
AML with t(15;17)	6	11	
AML without maturation	2	4	
AML with maturation	15	12	
Acute myelomonocytic leukemia	5	11	
Acute monoblastic and monocytic leukemia	4	2	
Karyotype classification			0.919
Favorable	15	13	
Intermediate	23	23	
Poor	3	4	
No date	1	2	
Karyotyping			0.250
Normal	20	20	
t(8;21)	9	2	
t(15;17)	6	11	
Complicated	3	3	
Others	3	4	
No date	1	2	
Gene mutation			
NPM1 (+/-)	5/37	4/37	1.000
FLT3 ITD (+/-)	6/36	6/35	1.000
C-KIT (+/-)	1/41	0/41	1.000
IDH1/IDH2 (+/-)	3/35	1/38	0.358
DNMT3A (+/-)	3/35	3/36	1.000
NRAS/KRAS (+/-)	4/34	3/36	0.711
C/EBPA (+/-)	6/36	3/38	0.483
CR (+/-)	23/18	20/19	0.823
Median miR-24 expression (range)	0.33 (0.13-3.31)	0.01 (0.00-0.12)	< 0.001

Hospital of Jiangsu University. The diagnosis and classification of AML patients were based on French-America-British (FAB) and World Health Organization (WHO) criteria [23, 29]. Treatment protocol was described as reported previously [21]. Written informed consent was obtained from all patients. The study was approved by the Institutional Review Board of

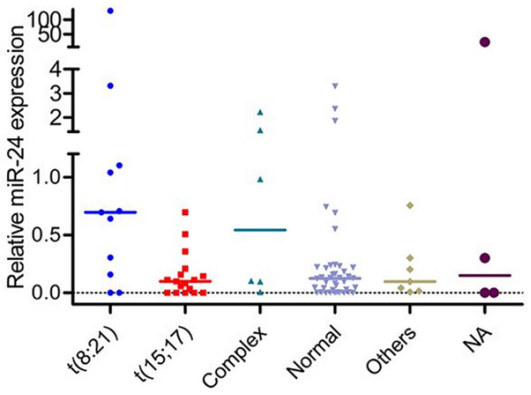

Figure 1. Relative miR-24 expression in AML with different kayotypes. NA: not available. The level of miR-24 was higher in AML with t(8;21) than in t(15;17) (P=0.0127), in normal (P=0.0214), in others (P=0.1237), and in complex (P=0.8802).

the Affiliated People' Hospital of Jiangsu University. The main clinical and laboratory features of the patient cohort were collected in **Table 1**. 16 healthy donors were collected as controls.

RNA extraction and reverse transcription

Using the mirVana miRNA isolation kit (Ambion, Austin, TX, USA), we extracted the total RNA. According to the manufacturer's protocol using miScript Reverse Transcription Kit (Qiagen, Duesseldorf, Germany), total RNA was reverse transcribed to cDNA.

Real-time quantitative PCR

Real-time quantitative PCR (RQ-PCR) was carried out according to the Manufacturer's instructions using miScript SYBR green PCR kit (Qiagen, catalog no. 218073) with the manufacturer-provided miScript Universal primer and miRNA-specific forward primer: TGGCTCAGTTCAGCAGGAACA (miR-24).

RQ-PCR was performed on a 7300 Thermo cycler (Applied Biosystems, Foster City, CA, USA), using 50 ng of cDNA in a 20 μl reaction volume with 1× QuantiTect SYBR Green PCR Master Mix, 1× miScript Universal Primer, and 1.0 μM of the specific forward primer. PCR program conditions were 95°C for 15 min, followed by 40 cycles at 94°C for 15 s, 55°C for 30 s and 72°C for 34 s. At the end of the PCR cycles, melting program (95°C for 15 s, 60°C for 60 s, 95°C for 15 s, and 60°C for 15 s) was performed to validate the specificity of the expected PCR product. PCR amplicons were also confirmed by direct DNA sequencing in three randomly selected patients. The relative expression level of miR-24 was calculated by the comparative $2^{-\triangle\triangle Ct}$ method using U6 small nuclear RNA level for normalization.

Gene mutation detection

NPM1 and C-KIT mutations were detected by high-resolution melting analysis (HRMA) as reported previously [3]. Briefly, genomic DNA samples were amplified using gene-specific primers. Mutation scanning was performed for PCR products using HRMA with the LightScannerTM platform (Idaho Technology Inc., Salt Lake City, Utah). All positive samples were directly DNA sequenced to confirm the results of HRMA. FLT3 internal tandem duplication (ITD) and C/EBPA mutations were detected using direct DNA sequencing [30, 31].

Statistical analyses

All statistical analyses were implemented using spss17.0. Chi-square analysis or Fisher exact test was executed to compare the distinction of categorical variables. The comparison of miRNA expression status between patients and controls was executed using Mann-Whitney test. Survival was analyzed according to the Kaplan-Meier method. All values showed two-sided with a P-value < 0.05 considering statistically significant.

Results

MiR-24 expression in AML

In our 84 samples, miR-24 expression levels represented a continuum ranging from 0.000011 to 130.192 (median 0.123342). To evaluate the impact of miR-24 expression levels on clinical outcome without seeking an optimal cut-point, patients were divided into low and high expressers according to the median expression level of miR-24.

Association of miR-24 expression with clinical and laboratory characteristics in AML

There was no significant difference in sex, age, WBC, hemoglobin and platelets between patients with and without miR-24 high expression (**Table 1**). MiR-24 high expression could be observed in each AML subtype analyzed (**Table**

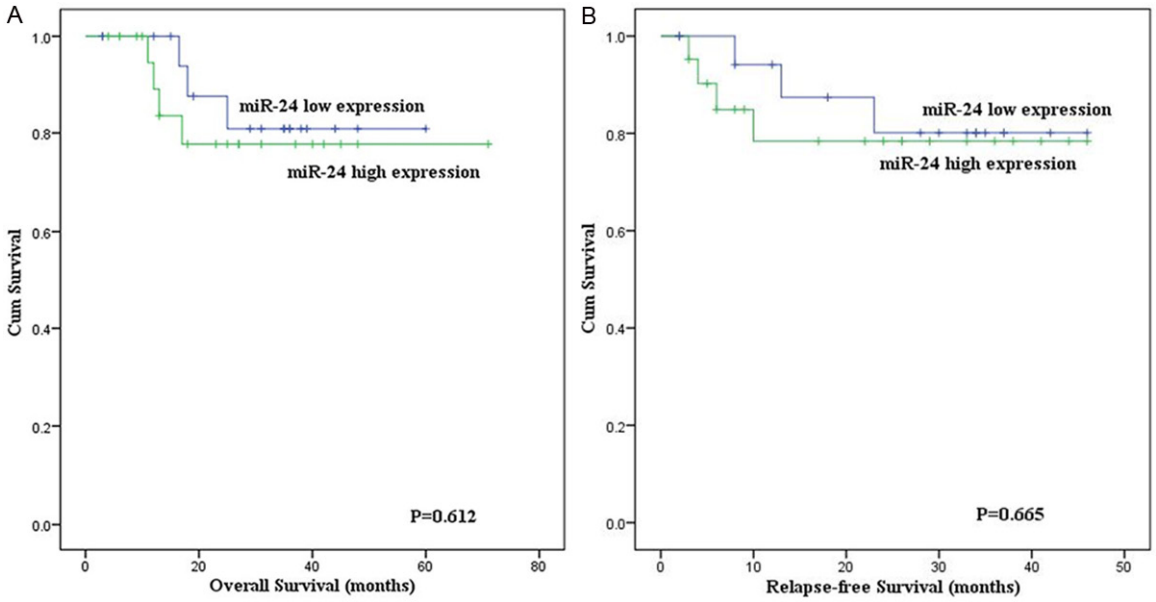

Figure 2. Overall and relapse-free survival of AML patients obtained complete remission. A. Overall survival; B. Relapse-free survival.

1). The level of miR-24 was higher in AML with t(8;21) than in t(15;17) (*P*=0.0127), in normal (*P*=0.0214), in others (*P*=0.1237), and in complex (*P*=0.8802) (**Figure 1**). Meanwhile, the frequency of miR-24 high expression was higher in patients with t(8;21) than in others (82% (9/11) versus 44% (32/72), *P*=0.026). There was no significant difference in the mutations of nine genes between low expressers and high expressers (**Table 1**).

Impact of miR-24 expression on outcome of AML patients

To investigate the prognostic impact of miR-24 high expression in AML, survival analysis was performed in 80 cases with follow-up data. There was no definite difference in the rates of CR between patients with and without miR-24 high expression (56% versus 51%, *P*=0.823). The patients with and without miR-24 high expression were similar in the overall survival (OS) (*P*=0.929). Among the group who obtained CR, although the OS of AML patients with miR-24 high expression (median 20.5 months, 95% confidence interval 17-32 months) was shorter than those with miR-24 low expression (median 30 months, 95% confidence interval 22-38 months), the difference was not statistically significant (*P*=0.612) (**Figure 2A**). In addition, the cases with miR-24 high expression had no difference in relapse-free survival (RFS) than those with miR-24 low expression (*P*=0.665) (**Figure 2B**). The size of cases with t(8;21) was small and most cases were still alive, so the OS and RFS could not be analyzed. In cases with cytogenetically normal AML, there was no significant difference in the OS and RFS between patients with and without miR-24 high expression (*P*=0.532 and 0.772, respectively).

Discussion

High endogenous expression levels of miR-24 were more abundant in myeloid cells compared with lymphoid cells [32]. Overexpression of miR-24 has been found in oral carcinoma, non-small cell lung cancer (NSCLC) and breast cancer [11, 27, 33]. The function of miRNAs was highly tissue-dependent, which means that in different types of tissues one specific miRNA might get involved in different functions [26]. In our study, we didn't see obvious difference between AML patients and controls. Meanwhile, we didn't find miR-24 expression had any influences on outcome of AML patients. Though the OS of AML patients with miR-24 high expression (median 20.5 months, 95% confidence interval 17-32 months) was shorter than those with miR-24 low expression (median 30 months, 95% confidence interval 22-38 months), the difference was not statistically significant (*P*=0.612) due to the small size of samples. Furthermore, more cases should be analyzed

to further confirm its clinical significance in AML.

In our previous studies, we found some microRNAs had close relationships with AML involving t(8;21) as well [3, 21]. However, lacking of definite mechanisms, regarding microRNA and AML with t(8;21), it seemed that there were no clinically meaningful findings. Recently, few studies have reported the expression status of miR-24 in AML. Zaidi et al. have reported that miR-24 may act as a novel and selective therapeutic target for the treatment of AML. The t(8;21)-encoded AML1-ETO hold the miR-24-23-27 locus and control miR-24 transcription. Disruption of Runx1/AML1 subnuclear localization, by a chromosomal translocation t(8;21), is connected to the etiology of acute myeloid leukemia. Modified Runx1 subnuclear targeting by leukemia-related translocation t(8;21) transcriptionally deregulates the miR-24. By activating a miR-24/MKP-7/MAP kinase network, modified Runx1 subnuclear targeting may enhance proliferation and block granulocytic differentiation [34]. In the present study, we investigated the expression status of miR-24 in patients with AML. Interestingly, high expression of miR-24 showed more frequently in AML patients with translocation t(8;21) than in others (82% (9/11) versus 44% (32/72), P=0.026). Zaidi et al. provided exact evidences for us to prove that miR-24 played an important role in AML involving t(8;21) translocation. It was a coincidence that the experiment we conducted corroborated association between miR-24 and AML with t(8;21) in clinic. Nowadays, a growing body of evidences showed microRNAs really had close relationships with this chromosomal translocation [5, 35-37]. According to those researches, they focused on the AML1/ETO, which is a fusion protein having functions of inhibiting differentiation and apoptosis, and triggering signals for cell proliferation [38, 39]. Next, we should take attentions to this fusion protein then we study the networks between microRNA and AML with t(8;21) translocation. Taken together with existing evidence from microRNA and AML with t(8;21) studies, the current results support a relationship between microRNA and AML with t(8;21) translocation, which merits further study.

In summary, we suggest that high expression of miR-24 in AML patients might imply miR-24 can serve as a valuable source for biomarker discovery and validation in AML patients with t(8;21), meanwhile, miR-24 might serve as a novel and selective therapeutic target for the treatment of AML patients with t(8;21).

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Disclosure of conflict of interest

None.

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