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Research Article

miRNA-126 as a Biomarker for Cancer Stem Cells: Role in Chemotherapy Resistance in Iraqi Patients with Acute Myeloid Leukemia

Noorhan Sabih Al-Maliki[1]*, Zahraa Kamel Zedan[1]

[1]*College of Biotechnology, Al-Nahrain University, Baghdad, Iraq*

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Abstract

Background: Acute myeloid leukemia (AML) is characterized as an aggressive blood cancer with rapid growth of immature leukemic cells. It appears that each subtype of AML displays a distinct miRNA profile. miRNAs play a role in regulating gene expression that is implicated in AML pathogenesis. ***Objective***: This study was designed to assess the level of miRNA-126 gene expression in relation to chemotherapy resistance in various AML groups with the hope of developing a novel marker for targeted therapy and the early diagnosis and prognosis of cancer stem cells in AML patients. ***Methods***: 120 AML cases were studied. Based on the chemotherapy stage, 40 patients were assigned to each group (newly diagnosed, under treatment, or relapsed). Baghdad Teaching Hospital, Iraq, provided the cases and samples from February 2022 to April 2023. This study also included 40 healthy controls. We used the qRT-PCR method to count the genes after setting them to the same level as a housekeeping gene (GAPDH). This method uses the ΔCt-value and fold change (2-ΔΔCt). ***Results***: In this study, there were significant elevated levels of miRNA-126 in AML patients compared to controls, with a higher fold change detected in the newly diagnosed group. ***Conclusions***: The miRNA-126 upregulation is suggested to be linked to AML development and relapse, with a contribution to leukemic stem cell proliferation and treatment failure. We hypothesized that miR-126 could be an effective target for eradicating the LSC in AML.

Keywords: Acute myeloid leukemia, Cancer biomarker, Chemotherapy resistance, Leukemic stem cells, miRNA-126.

miRNA-126 كمؤشر حيوي للخلايا الجذعية السرطانية: دوره في مقاومة العلاج الكيميائي لدى المرضى العراقيين المصابين بسرطان الدم النخاعي الحاد

الخلاصة

الخلفية: يتميز ابيضاض الدم النخاعي الحاد (AML) بأنه سرطان دم عالي الضراوة مع نمو سريع لخلايا اللوكيميا غير الناضجة. كل نوع فرعي من AMLيعبر عن miRNA مميزا له. miRNAs تلعب دورا مهما في تنظيم التعبير الجيني المسؤول عن التسبب في مرضAML. **الهدف**: صممت هذه الدراسة لتقييم مستوى التعبير الجيني لل miRNA-126 فيما يتعلق بمقاومة العلاج الكيميائي في مجاميع AML المختلفة على أمل تطوير طريقة مستحدثة للعلاج الموجه والتشخيص المبكر للخلايا الجذعية السرطانية لدى مرضىAML. **الطرق**: تمت دراسة 120 حالة لمرضى سرطان الدم النخاعي المزمن. بناءا على مرحلة العلاج الكيميائي، تم تسجيل 40 مريضًا لكل مجموعة (المشخصة حديثًا، تحت العلاج، والذين انتكسوا). قدم مستشفى بغداد التعليمي في العراق الحالات والعينات للفترة من شباط 2022 إلى نيسان 2023. وتضمنت هذه الدراسة أيضاً 40 من الاصحاء. استخدمنا طريقة qRT-PCR لحساب الجينات بعد ضبطها على نفس مستوى جين (GAPDH). تستخدم هذه الطريقة قيمة ΔCt وتغاير مستوى ال 2-ΔΔCt. **النتائج**: في هذه الدراسة، كانت هناك مستويات مرتفعة كبيرة من miRNA-126 في مرضى AML مقارنة بمجموعة السيطرة، مع اكتشاف تغير أعلى في الطيات في المجموعة التي تم تشخيصها حديثًا. **الاستنتاجات**: وجد ان تنظيم تعبير ال miRNA-126 مرتبط بتطور AML والانتكاس، مع المساهمة في تكاثر الخلايا الجذعية اللوكيمية وفشل العلاج. مع امكانية استخدام miRNA-126 كهدف فعال للقضاء على خلايا LSC في مرضAML .

* ***Corresponding author***: Noorhan S. Al-Maliki, College of Biotechnology, Al-Nahrain University, Baghdad, Iraq; Email: noorhan.sabih@nahrainuniv.edu.iq

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INTRODUCTION

AML is a cancer of the myeloid line of blood cells that is caused by the unregulated proliferation and differentiation of the cells, which escapes the normal physiological checkpoints [1]. It is characterized by the rapid growth of immature leukemic cells, which are unable to carry out normal blood cell functions [2]. The resistance to chemotherapy drugs becomes the main problem in AML treatment, and research on the resistance mechanisms and novel strategies for treatment in AML is very active. AML patients remaining lack useful targets for effective targeting [3]. So, finding new biomarkers for disease diagnosis, prognosis, and use as therapeutic targets has become an area of concern recently. Several findings have indicated that miRNAs may serve as valuable diagnostic and prognostic biomarkers and are considered a continuously growing area of research [4]. So more research on miRNA imbalance in hematopoiesis may provide new strategies for improving patient outcomes [5]. Expression profiles of miRNA are also related to an individual's prognosis and responses to chemotherapy, especially when estimating AML therapy resistance [6]. MiRNAs create a network that regulates gene expression after transcription in leukemia [7-9]. Alterations in miRNA expression levels lead to changes in the expression of genes downstream, which in turn promote the development of AML [10]. MiR-126 is situated on human chromosome 9, specifically in the 7th intron of the EGFL7 gene. miR-126 regulates various hematopoietic proteins and pathways, many of which are linked to AML [11]. Another study found that miR-126 promotes LSC activity, maintenance, and treatment resistance in AML [12]. This study was assessed to detect gene expression of miR-126 in different groups of AML Iraqi patients and explore the significant impact of expression levels on chemotherapy resistance. Furthermore, there is a possibility of its utilization as a novel biomarker for treatment approaches or the early diagnosis and prognosis of leukemic stem cells.

METHODS

Study design and patient selection

Research was conducted from January 2022 until April 2023. 160 people participated in the study. One hundred and twenty Iraqi male and female AML patients from Baghdad Teaching Hospital, Baghdad, Iraq, were included in this study. Forty of them were newly diagnosed, forty were on treatment, and forty were relapsed. Their ages ranged from 15 to 75) years, and the clinical information was obtained from their hospital files and case-sheet records, with the other forty healthy people as controls. The research protocol was granted approval by the Ethics Committee of the Iraqi Ministry of Health and the College of Biotechnology, Al-Nahrain University (12189 in 23/3/2022). Prior to their inclusion in the study, all patients provided written informed consent.

Primers used in this study

The primers utilized in this work were constructed using the online platform https://www.ncbi.nlm.nih.gov/tools/primer-blast/primertool. The forward primer sequence for Homo sapiens miRNA-126 is 5'-GTACGGGGCCGAGCACT-3', and the reverse primer sequence is 5'-CGAGGAAGAAGACGGAAGAAT-3'. The glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was employed as the endogenous control. The forward primer sequence was 5'-TGATGACATCAAGAAGGTGGTGAAG-3', while the reverse primer sequence was 5'-TCCTTGGAGGCCATGTGGGCCAT-3'. The primers were designed and utilized in accordance with the specifications provided by the manufacturer (Macrogen, South Korea).

Expression of miRNA-126

The RNA was extracted and purified according to the manufacturer's instructions from blood samples using Relia-Prep® RNA Miniprep, Promega, USA. The QuantiFluor® RNA System was used to estimate the RNA concentration and purity in the samples. The LunaScript Reverse Transcriptase (Biolabs, England) kit was employed to convert total RNA into cDNA utilizing the reverse transcriptase (RT) mix reagent. The experiment was conducted utilizing a SaCycler-48 thermal cycler manufactured by Sacace, Italy. The reaction mixture for quantitative PCR (qPCR) was made using KAPA-SYBR® Fast qPCR master mix, which is manufactured in the United States. The GAPDH housekeeping gene served as the endogenous control. The melting-curve analysis was used to observe the separation patterns of double-stranded DNA as the denaturing temperature increased during cycles.

Statistical analysis

Data analyses were carried out using the statistical package SPSS version 23 and GraphPad Prism version 9. Values of $p<0.05$ were accepted as statistically significant unless otherwise stated. Relative gene expression was analyzed using the CT value and the 2-CT method of the target gene, depending on an individual endogenous control. The fold change was calculated by the equations ΔCT = CT of the target gene minus CT of the U gene, ΔΔCT = ΔCT of each sample minus the average control ΔC, and the fold change = $2^{-\Delta\Delta Ct}$, respectively. It was noted that a

control value of 1 was established. Samples with values below 1 were downregulated, while those with values above 1 were upregulated.

RESULTS

Table 1 shows the age range of samples was between 15 and 75 years old, and the overall mean age of AML patients was 43.2 years. The patients were distributed according to their gender into 74 males (61.67%) and 46 females (38.33%). Smoking was also recorded in this study in 57 (47.5%) smoker patients and 63 (52.5%) non-smoker patients.

Table 1: Distribution of AML patients according to age, gender, and smoking habits

Parameter	*n*(%)	*p*-value
Age groups (year)		
10-20	9(7.5)	0.0001
20-30	26(21.66)	
30-40	13(10.83)	
40-50	38(31.67)	
50-60	19(15.83)	
60-70	13(10.83)	
> 70	2(1.67)	
Total	120(100)	
Gender		
Male	74(61.67	0.0044
Female	46(38.33)	
Total	120(100)	
Smoking habits		
Smokers	57(47.5)	0.527
Non-smokers	63(52.5)	
Total	120(100)	

The results indicated that a significant majority of clinical cases, as per the FAB classification, belonged to the M3 group (Table 2).

Table 2: Distribution of AML patients according to FAB

Subtype	*n*(%)	*p*-value
M0	4(3.33)	
M1	11(9.17)	
M2	29(24.17)	
M3	57(47.5)	
M4	1(0.83)	0.0001
M5	18(15)	
M6	0(0)	
M7	0(0)	
Total	120(100)	

The summary plot of the RT qPCR is assumed in Figure 1.

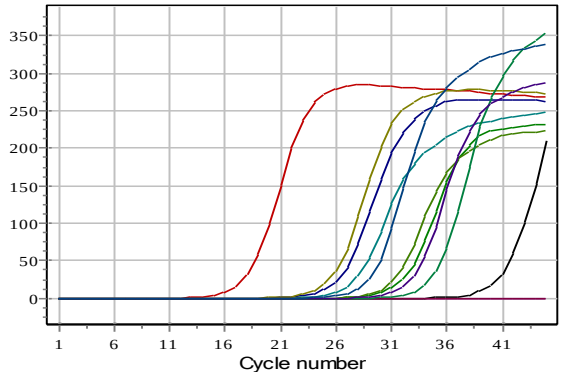

Figure 1: The RT-qPCR summary plot of miR-126.

Table 3 shows the results. The ROC analysis showed that miRNA-126 had a 75% sensitivity and a 100% specificity in newly diagnosed patients. The confidence interval was between 0.43 and 1.07, the AUC was 0.75±0.16, the cutoff value was 8.88, and the p-value was 0.130.

Table 3: Comparison between miRNA-126 gene expression/fold change in different groups

Groups		GAPDH CT	MIR-126 CT	ΔCT	ΔΔCT	$2^{-\Delta\Delta CT}$	Fold change
Controls		18.83±1.9A	33.12±1.2A	12.74±1.2A	-0.26±0.01A	1±0A	1
AML	Newly Diagnosed	19.19±2.7A	27.96±2.8A	8.44±2.2A	-4.56±1.4A	24.43±2.3B	24.43
Cases	Treated	19.84±1.8A	29.02±1.4A	11.2±1.2A	-1.8±0.02A	4.51±0.7B	4.51
	Relapse	20.28±2.3A	31.02±2.2A	12.16±2.4A	-0.84±0.01A	2.95±0.12B	2.95
	Total	19.77±1.9A	29.33±1.2A	10.6±1.2A	-2.4±0.01A	10.63±0B	10.63

Values were expressed as mean±SD.

In the treated group, the reported sensitivity was 35%, the specificity was 87%, the confidence interval was -0.08-0.68, the AUC was 0.3±0.2, the cutoff value was 8.57, and the *p*-value was 0.310. Meanwhile, in the relapsed patients, sensitivity was 20%, specificity was 70%, the confidence interval was -0.19–0.59, the AUC was 0.2±0.2, the cutoff value was 8.98, and the p-value was 0.130 (Figure 2 and Table 4). The expression of MIR-126 was quantified using quantitative RT-PCR. The gene expression was normalized using the housekeeping gene GAPDH and quantified using the 2−ΔΔCt technique.

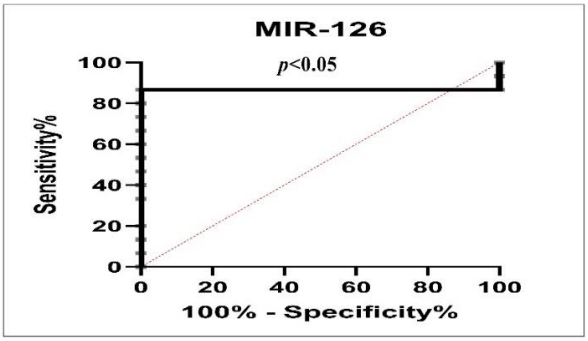

Figure 2: ROC curve analysis (Wilson/ Brown method) of MIR-126 in AML patients.

Table 4: ROC curve analysis (Wilson/Brown method) of MIR-126 in AML patients group

Group	Sensitivity (%)	Specificity (%)	95% CI	AUC	Cut off	*p*
Newly diagnosed group	75	100	0.43-1.07	0.75±0.16	8.88	0.130
Treated group	35	87	-0.08-0.68	0.3±0.2	8.57	0.310
Relapsed group	20	70	-0.19-0.59	0.2±0.2	8.98	0.130

DISCUSSION

miR-126 was involved in a wide range of biological functions [13]. Hematopoietic stem cells (HSCs) have an increased expression of miR-126, which is essential for their quiescence and cell cycle progression [14]. miR-126 controls HSC cycling and self-renewal [15]. Leukemogenesis, malignant transformation, and the prognosis of AML are all impacted by an aberrant miR-126 transcription. Another potential treatment approach is the activation or inhibition of aberrant miRNAs to enhance the effectiveness of treatments. A considerable array of genes within individuals with AML are susceptible to targeting and repression by microRNAs [16]. In this study, we have recognized abnormalities in the level of miR-126 and fold changes in AML patients. The analysis of the data showed a higher significant elevation in the newly diagnosed AML patient group compared to the control and other subgroups. These findings were consistent with the results of Almohsen *et al*., which showed that AML patients have higher miR-126 and miR-423 levels than controls [17]. In 2022, Zhang *et al*. showed that AML with inv(16) expresses elevated miR-126 levels [18]. Another study by Amal (2021) reported that miR-126 was overexpressed in AML and found that the fold change of miR-126 was significantly higher in newly diagnosed patients than control [10]. Also, Lechman *et al*. [14] documented an increased miR-126 expression in AML patients with a 40-fold increase in populations that contain LSC. Also, other results were comparable to ours, which show miR-126 is highly expressed in patients with AML compared to controls [20]. Several mechanisms, including LSCs, are associated with chemoresistance, which is a big issue in the pathophysiology of AML [21,22]. LSCs enhance the progression and recurrence of AML and are resistant to standard treatment. This issue highlights the fact that miR-126, which promotes cell proliferation and anti-apoptotic activity, targets the PI3K/AKT/MTOR signaling pathway. As a result, it preserves LSC quiescence and increases chemotherapy resistance, which is associated with poor survival and a greater risk of relapse in patients with AML [14]. Another study by Ding *et al*. showed that a high miR-126 level suppresses apoptosis by downregulating TRAF7, which blocks the c-FLIP pathway [23]. Additionally, Smith *et al*. showed that miRNA126 may be involved in leukemogenesis through negative regulation of PLK2, which controls cell cycle progression and checkpoints caused by DNA damage [24]. The CBFB-MYH11 (CM) fusion protein upregulates miR-126, which is situated in the Egfl7 gene [18]. Not only does CM raise miR-126 levels via dysregulation of the Egfl7/miR-126 promoter, but it additionally improves miR-126 synthesis by phosphorylating SPRED1, which interferes with RAN-XPO5-induced pre-miRNA processing [25]. Several pathways critical for cancer progression or AML maintenance have their expression changed by the miR-126 deletion. There was no apparent change in the immune phenotype or frequency of normal HSPC subgroups after miR-126 deletion [18]. According to other research, inhibiting miR-126 led to LSC depletion while maintaining HSC expansion [26]. The possibility of therapeutically targeting miR-126 and selectively targeting LSCs is highlighted by this varied self-renewal outcome. Blocking miR-126 enhanced response to anti-proliferative medications or conventional chemotherapy in cytogenetically normal [14] and t(8,21) AML [27]. Current AML treatments attack quickly proliferating blast populations but fail to eliminate the functionally different LSC population, which is thought to cause resistance to treatment and relapse [11]. Because AML is a heterogeneous disease, optimizing targeted therapy for each case is challenging. However, discovering downstream miRNA targets of the AML fusion gene may lead to new treatments. ROC analysis of miRNA-126 showed higher sensitivity and specificity to the newly diagnosed AML patients group, suggesting the importance of miRNA-126 as an indicator to evaluate the AML patient prognosis, which can improve therapy. A recent study by Zhang *et al*. (2022) agreed with our results, which stated that in AML, serum miR-126 and miR-13 show high sensitivity, specificity, accuracy, and AUC, suggesting they are closely associated with patient prognosis [28].

Conclusion

Newly diagnosed AML patients had a substantially higher level of miRNA-126 expression than the control group. High amounts of miR-126 were linked to a gene expression profile of LSC and a worse outcome in AML patients who were treated with standard chemotherapy. Based on what has been said so far, blocking miR-126 may be a new way to treat AML because it can be used to target LSCs specifically and help HSCs recover. Combining miRNA therapy with standard chemotherapy could potentially eliminate LSCs.

Conflict of interests

No conflict of interests was declared by the authors.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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