RESEARCH ARTICLE

DOI: 10.4274/tjh.galenos.2025.2024.0424
Turk J Hematol 2025;42:92-99

miR-379-5p Inhibited the Proliferation of Acute Myeloid Leukemia Cells Through Negative Regulation of *YBX1*

miR-379-5p *YBX1* Negatif Düzenlemesi Aracılığı ile Akut Miyeloid Lösemi Hücrelerinde Proliferasyonu İnhibe Etti

Huichao Wu[1]*, Lin Zhao[2]*, Huanyu Guo[3], Yingjie Xie[4], Jianhua Hu[5], Xinxia Tan[6,7]

[1]*The First People's Hospital of Jiashan, Department of Emergency, Jiashan, P.R. China*
[2]*Dongzhimen Hospital, Beijing University of Chinese Medicine, Department of Hematology and Oncology, Beijing, P.R. China*
[3]*Changchun University of Chinese Medicine, Faculty of Clinical Medicine, Changchun, P.R. China*
[4]*General Hospital of Southern Theater Command of the Chinese PLA, Departments of Cadre Ward, Guangzhou, P.R. China*
[5]*People's Hospital of Quzhou, Department of Intensive Care Medicine, Quzhou, P.R. China*
[6]*Huangshi Central Hospital (Affiliated Hospital of Hubei Polytechnic University), Department of Clinical Laboratory, Huangshi, P.R. China*
[7]*Huangshi Tumor Molecular Diagnosis and Treatment Key Laboratory, Huangshi, P.R. China*

**These authors contributed equally to this study.*

Abstract

Objective: Acute myeloid leukemia (AML) highly lethal hematological malignancy that is difficult to treat. This study aimed to clarify the molecular mechanisms of miR-379-5p in AML progression.

Materials and Methods: Quantitative real-time polymerase chain reaction was utilized to evaluate miR-379-5p expression levels in AML patients and a control group. A receiver operating characteristic curve was created to assess the clinical predictive value of miR-379-5p in AML, while cell experiments used the CCK-8 assay, flow cytometry, and transwell chambers. Potential target genes of miR-379-5p were predicted by employing online bioinformatics tools, followed by validation using a dual luciferase reporter assay.

Results: miR-379-5p expression was significantly decreased in AML patients and had clinical predictive value for the disease. In AML cell lines, miR-379-5p was downregulated; conversely, the upregulation of miR-379-5p inhibited proliferation, migration, and invasion while promoting apoptosis. Notably, *YBX1* was a potential target gene of miR-379-5p and its upregulation reduced the effects of miR-379-5p on AML cell behavior.

Conclusion: miR-379-5p has potential as a biomarker for AML by regulating cell proliferation and apoptosis through the targeting of *YBX1*.

Keywords: Acute myeloid leukemia, miR-379-5p, *YBX1*, Cell proliferation, Apoptosis, Diagnostic significance

Öz

Amaç: Akut miyeloid lösemi (AML) tedavisi zor olan ve oldukça ölümcül bir hematolojik malignitedir. Bu çalışmada AML progresyonunda miR-379-5p nin moleküler mekanizmalarını netleştirmeyi hedefledik.

Gereç ve Yöntemler: AML hastaları ve kontrol grup örneklerinde kantitatif gerçek zamanlı polimeraz zincir reaksiyonu kullanılarak miR-379-5p ekspresyon düzeyleri değerlendirildi. AML'de klinik prediktif miR-379-5p değerini ortaya çıkarabilmek için alıcı taraflı karakteristik bir eğri oluşturuldu. Hücre deneyleri ise CCK-8, akım sitometri ve transwell migrasyon tetkikini kullandı. miR-379-5p'nin potansiyel hedefleri online biyoinformatik tahmin araçları ile öngörülmüştür, peşinden dual lusiferaz raportör yöntemi ile doğrulanmıştır.

Bulgular: AML hastalarında miR-379-5p ekspresyonu belirgin şekilde azalmıştır ve hastalık için klinik prediktif değeri olduğu görülmüştür. AML hücre dizelerinde miR-379-5p azalmıştır, oysa ki artmış düzeyleri proliferasyonu, migrasyonu ve invazyonu inhibe ederek apopitozu tetikler. Özellikle *YBX1* miR-379-5p geni potansiyel hedefidir ve artmış seviyeleri miR-379-5p nin AML hücre davranışındaki etkilerini azaltmaktadır.

Sonuç: miR-379-5p *YBX1*'i hedef alarak hücre proliferasyonu ve apopitozisin düzenlenmesi üzerinden AML için potansiyel bir biyobelirteç olabilir.

Anahtar Sözcükler: Akut miyeloid lösemi, miR-379-5p, *YBX1*, Hücre proliferasyonu, Apopitozis, Tanısal önem

Address for Correspondence/Yazışma Adresi: Xinxia Tan, M.D., Huangshi Central Hospital (Affiliated Hospital of Hubei Polytechnic University), Department of Clinical Laboratory; Huangshi Tumor Molecular Diagnosis and Treatment Key Laboratory, Huangshi, P.R. China
E-mail: tanxinxia435tt@163.com **ORCID:** orcid.org/0009-0004-9109-1506

Address for Correspondence/Yazışma Adresi: Jianhua Hu, M.D., People's Hospital of Quzhou, Department of Intensive Care Medicine, Quzhou, P.R. China
E-mail: qzhujianhua@163.com **ORCID:** orcid.org/0009-0008-1278-6895

Received/Geliş tarihi: November 14, 2024
Accepted/Kabul tarihi: February 24, 2025

Introduction

Acute myeloid leukemia (AML) interferes with the differentiation of myeloid cells, resulting in unchecked proliferation of leukemia progenitor cells and compromised development of normal blood cells [1]. AML has a high mortality rate and accounts for about two-thirds of adult leukemia cases [2]. Hematopoietic stem cell transplantation and chemotherapy are the most important means for treating AML. However, for patients with relapsed or metastatic advanced AML, these methods are still associated with poor prognosis [3]. AML is a malignant proliferative disease and abnormal gene mutations and gene expression might be linked to the abnormal proliferation of AML-associated cancer cells [4]. Therefore, identifying AML-related biomarkers is essential for effective clinical diagnosis.

Studies have confirmed that microRNA (miRNA) significantly regulates cell proliferation, angiogenesis, and the bone marrow microenvironment, thereby promoting the progression of leukemia [5]. Notable examples include miR-203 [6] and miR-217 [7]. As a tumor suppressor, miR-379-5p plays a crucial role in various cancers, including breast cancer [8], hepatocellular carcinoma [9], and oral squamous cell carcinoma [10]. Research has shown that the expression levels of miR-379-5p are reduced in $CD34^+$ cells from patients with primary myelofibrosis, suggesting its potential involvement in the pathogenesis of chronic myeloid neoplasms [11]. However, the precise mechanisms underlying the role of miR-379-5p in AML remain poorly understood.

YBX1 is a multifunctional cancer-related protein. Research indicates that *YBX1* is elevated in bladder [12], pancreatic [13], and nasopharyngeal cancer [14]. Furthermore, *YBX1* is significantly upregulated in small extracellular vesicles released from the cells of most pediatric AML patients [15]. However, the mechanisms of miR-379-5p and *YBX1* in AML remain poorly understood.

We hypothesized that miR-379-5p was downregulated in AML and involved in the regulation of AML cells based on previous findings. In this study, we enrolled 70 healthy individuals and 75 patients with AML. miR-379-5p was detected and compared between the two groups. We also explored the molecular mechanisms of miR-379-5p in AML and its clinical diagnostic value, providing guidance for the diagnosis and treatment of AML.

Materials and Methods

Patients and Specimens

This study enrolled 75 AML patients from Changchun University of Chinese Medicine, while the control group included 70 healthy individuals. Among the AML patients, 46 were younger than 60 years old, whereas 29 were 60 years old or older. The mean age of the AML group was 51.73±9.30 years. The patient cohort comprised 43 men and 32 women. In the control group, the mean age was 49.56±9.89 years, with 52 participants under 60 years old and 18 participants aged 60 years or older. This group consisted of 39 men and 31 women. According to the French-American-British (FAB) classification criteria, the subtypes of AML were distributed as follows: 6 patients had M0 type, 43 had M1/M2 type, and 26 had M4/M5 type. From a cytogenetic perspective, patients were further categorized based on prognosis: 30 patients had a favorable prognosis, 35 had an intermediate prognosis, and 10 had a poor prognosis. In this study, the age threshold for distinguishing adult from pediatric patients was set at 18 years. All 75 AML patients were adults as determined by their ages. All enrolled AML patients were newly diagnosed and had not yet received treatment. Ethical approval was obtained from the Ethics Committee of the Changchun University of Chinese Medicine (approval number: 2018005, date: August 15, 2018). Written informed consent was obtained from all participants and all procedures were conducted in strict accordance with the Declaration of Helsinki. After confirming the participants' informed consent, peripheral blood samples were collected. The collected samples were left standing at room temperature for 2 h and then centrifuged for 10 min, and upper serum samples were collected. The serum samples were stored in a refrigerator at -20 °C for subsequent experiments.

Cell Culture and Cell Transfection

Human bone marrow stromal cells of the HS-5 line and AML cells of lines K562, THP-1, KG-1, and HL-60 were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and maintained in RPMI-1640 medium (Gibco, Waltham, MA, USA) supplemented with 10% fetal bovine serum in a humidified incubator (SANYO, Osaka, Japan) at 37 °C with 5% CO_2.

Lipofectamine 3000 (Invitrogen, Waltham, MA, USA) was utilized for the transfection of synthetic sequences, including miR-379-5p-mimic (miR-mimic) (GenePharma, Shanghai, China) and its negative control (mimic-NC), pcDNA-3.1 empty vector (p-control), and YBX1 recombinant pcDNA-3.1 plasmid (p-YBX1). The concentration of both miR-379-5p-mimic and the miR-379-5p inhibitor was 50 nM.

Quantitative Real-Time Polymerase Chain Reaction

The total RNA of miR-379-5p and *YBX1* was respectively extracted. Subsequently, the obtained cDNA was amplified using reverse transcription reagents on the LightCycler 96 device (Roche, Basel, Switzerland). Real-time polymerase chain reaction (RT-qPCR) was used to detect the expression levels of miR-379-5p and *YBX1* using cDNA as the template. The RT-qPCR reaction protocol was as follows: initial denaturation at 95 °C for 3 min, followed by 40 cycles consisting of denaturation at

95 °C for 5 s, annealing at 55 °C for 10 s, and extension at 72 °C for 15 s. Gene expression levels were determined using the $2^{-\Delta\Delta Ct}$ method with *U6* and *GAPDH* serving as internal controls.

CCK-8 Assay

Approximately $2x10^3$ cells were carefully plated in a 96-well plate. Experimental groups were established based on the experimental objectives and measurements were taken at designated time points of 0, 24, 48, and 72 h. Subsequently, CCK-8 solution was added to each well, followed by an additional incubation period of 4 h. The absorbance at 450 nm was then measured using a spectrophotometer. Cell viability, as an indicator of cell proliferation, was evaluated according to the manufacturer's instructions provided with the CCK-8 kit (Hamby Biotechnology, Beijing, China). Each experiment was performed in triplicate for each cell group.

Measurement of Cell Apoptosis

The necessary samples were collected, washed repeatedly with phosphate-buffered saline, resuspended, and counted. Annexin V-FITC and propidium iodide reagents (Sigma-Aldrich, St. Louis, MO, USA) were added. Cell samples were incubated on ice for 15-20 min before being analyzed by flow cytometry. The apoptosis rate was calculated based on the intensity of the fluorescence signal.

Cell Migration and Invasion Experiments

Transwell chambers (BD Biosciences, San Jose, CA, USA) with 8-µm pores were coated with Matrigel (BD Biosciences) for invasion assays, while uncoated chambers were used for migration assays. In brief, $1x10^4$ cells were suspended in serum-free medium and seeded into the upper chamber. Following 24 h of incubation at 37 °C, non-migrated cells in the upper chamber were gently removed. Migrated or invaded cells were then fixed with methanol and stained with crystal violet. All assays were performed in triplicate.

Bioinformatics Analysis

miR-379-5p targets were predicted using the miRDB, miRTarBase, and TargetScan databases, and a Venn diagram was constructed to identify the overlapping targets.

Dual Luciferase Reporter Assay

The primers for the 3'-UTR of the *YBX1* gene were designed using Primer Premier 5.0 (PREMIER Biosoft, San Francisco, CA, USA) and subsequently amplified by PCR. The resulting PCR product was cloned into the pGLO plasmid (Promega, Madison, WI, USA) to generate the wild-type *YBX1* vector (WT-*YBX1*). Additionally, site-directed mutagenesis was performed on the 3'-UTR sequence of *YBX1* to construct the mutant vector (MUT-*YBX1*). These vectors were co-transfected with miR-379 mimics or appropriate controls using Lipofectamine 3000 (Invitrogen). Following 48 h of incubation, luciferase activity was measured using a luciferase reporter assay kit.

Statistical Analysis

Data analysis was conducted using SPSS (SPSS Inc., Chicago, IL, USA) and GraphPad Prism (GraphPad Inc., San Diego, CA, USA) software. For inter-group data comparisons, Student t-tests, chi-square tests, and one-way analysis of variance were employed. The diagnostic efficacy of miR-379-5p in AML was assessed via receiver operating characteristic (ROC) curve analysis. Each experimental condition was replicated three times to ensure reliability. Statistical significance was set at $p<0.05$.

Results

miR-379-5p was Expressed at Lower Levels in Acute Myeloid Leukemia Cells

We investigated the correlation between miR-379-5p expression levels and various clinicopathological parameters in patients with AML. No significant differences were observed in age or sex distribution between the low-expression and high-expression groups of miR-379-5p ($p>0.05$). While there were some variations in white blood cell count and bone marrow blast percentage, these differences did not reach statistical significance ($p>0.05$). However, significant differences in miR-379-5p expression were noted for platelet counts, FAB subtypes, and cytogenetic characteristics ($p<0.05$) (Table 1). RT-qPCR results indicated that the miR-379-5p expression of AML patients was significantly lower than that observed in the control group (Figure 1A). Serum miR-379-5p had clinical diagnostic value for AML with diagnostic specificity of 85.71%, sensitivity of 86.67%, and ROC curve area of 0.929 (Figure 1B). Moreover, miR-379-5p expression was significantly lower in HL-60, KG-1, K562, and THP-1 cells compared to HS-5, with the lowest levels obtained in HL-60 and THP-1 (Figure 1C), leading to further experiments using those two cell lines.

miR-379-5p Regulated Cellular Behaviors

RT-qPCR results showed that miR-mimic transfection significantly increased miR-379-5p levels in the HL-60 and THP-1 cell lines compared to the control group (Figures 2A and 2B). CCK-8 results showed a significant decrease in proliferation capacity in the miR-379-5p overexpression group (Figures 2C and 2D). Transwell assay results indicated that the migration levels of HL-60 and THP-1 cells transfected with miR-mimic were significantly lower (Figures 2E and 2F) and cell invasion ability was significantly inhibited (Figures 2G and 2H). Cell apoptosis experiments revealed a significant increase in the apoptosis rate in the miR-mimic group (Figures 2I and 2J).

Table 1. Correlation of miR-379-5p levels with clinicopathological parameters of acute myeloid leukemia patients.

Characteristics	Number	Serum miR-379-5p		p
		Low expression (n=39)	High expression (n=36)	
Age, years				
<60	46	24 (52.17%)	22 (47.83%)	0.970
≥60	29	15 (51.72%)	14 (48.28%)	
Sex				
Male	43	21 (48.83%)	22 (51.16%)	0.525
Female	32	18 (56.26%)	14 (43.75%)	
WBC count (x10^9/L)				
<10	33	13 (39.39%)	20 (60.61%)	0.053
≥10	42	26 (61.9%)	16 (38.10%)	
Platelet count (x10^9/L)				
<50	39	16 (41.03%)	23 (58.97%)	0.048
≥50	36	23 (63.89%)	13 (36.11%)	
BM blasts (%)				
<50	44	19 (43.18%)	25 (56.82%)	0.069
≥50	31	20 (64.51%)	11 (35.48%)	
FAB subtype				
M0	6	1 (16.67%)	5 (83.33%)	0.013
M1/M2	43	19 (44.19%)	24 (55.81%)	
M4/M5	26	19 (73.08%)	7 (26.92%)	
Cytogenetics				
Favorable	30	9 (30.00%)	21 (70.00%)	0.005
Intermediate	35	22 (62.86%)	13 (37.14%)	
Poor	10	8 (80.00%)	2 (20.00%)	

WBC: White blood cells; BM: bone marrow; FAB: French-American-British classification.

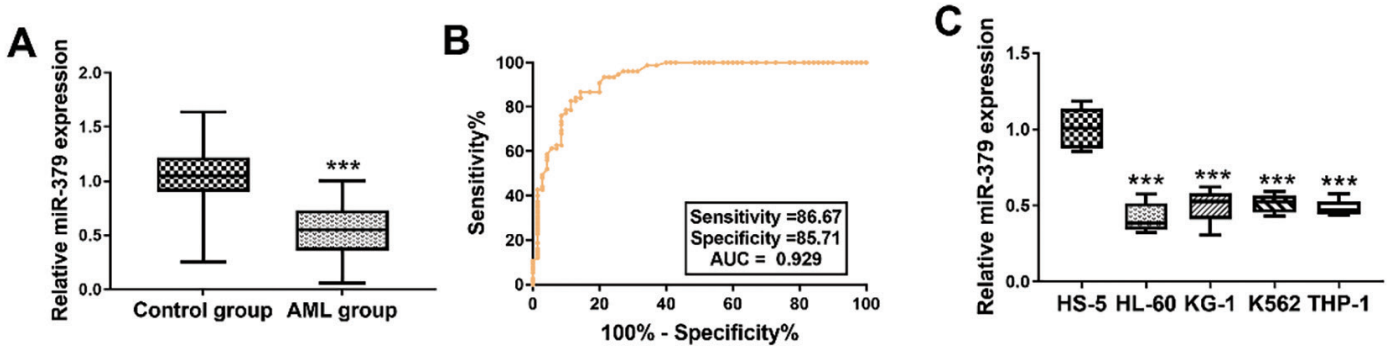

Figure 1. Expression level and diagnostic value of miR-379-5p. A) miR-379-5p was downregulated in acute myeloid leukemia. B) miR-379-5p possesses diagnostic value. C) miR-379-5p was downregulated in acute myeloid leukemia cell lines.

***: p<0.001; AML: acute myeloid leukemia; AUC: area under the curve.

The Targeting Relationship of miR-379-5p and *YBX1*

Venn diagram analysis identified 10 overlapping target genes: *EIF4G2*, *ELMOD2*, *NHLRC3*, *HSPA5*, *YBX1*, *EDN1*, *EDEM3*, *PCGF3*, *SLC20A1*, and *LIN28B* (Figure 3A). *YBX1* was identified as a target gene of miR-379-5p, with its targeting sequence predicted (Figure 3B). The luciferase reporter assay confirmed that in the WT-*YBX1* group, miR-mimic co-transfection significantly reduced luciferase activity, while no substantial alteration was witnessed in the MUT-*YBX1* group (Figure 3C).

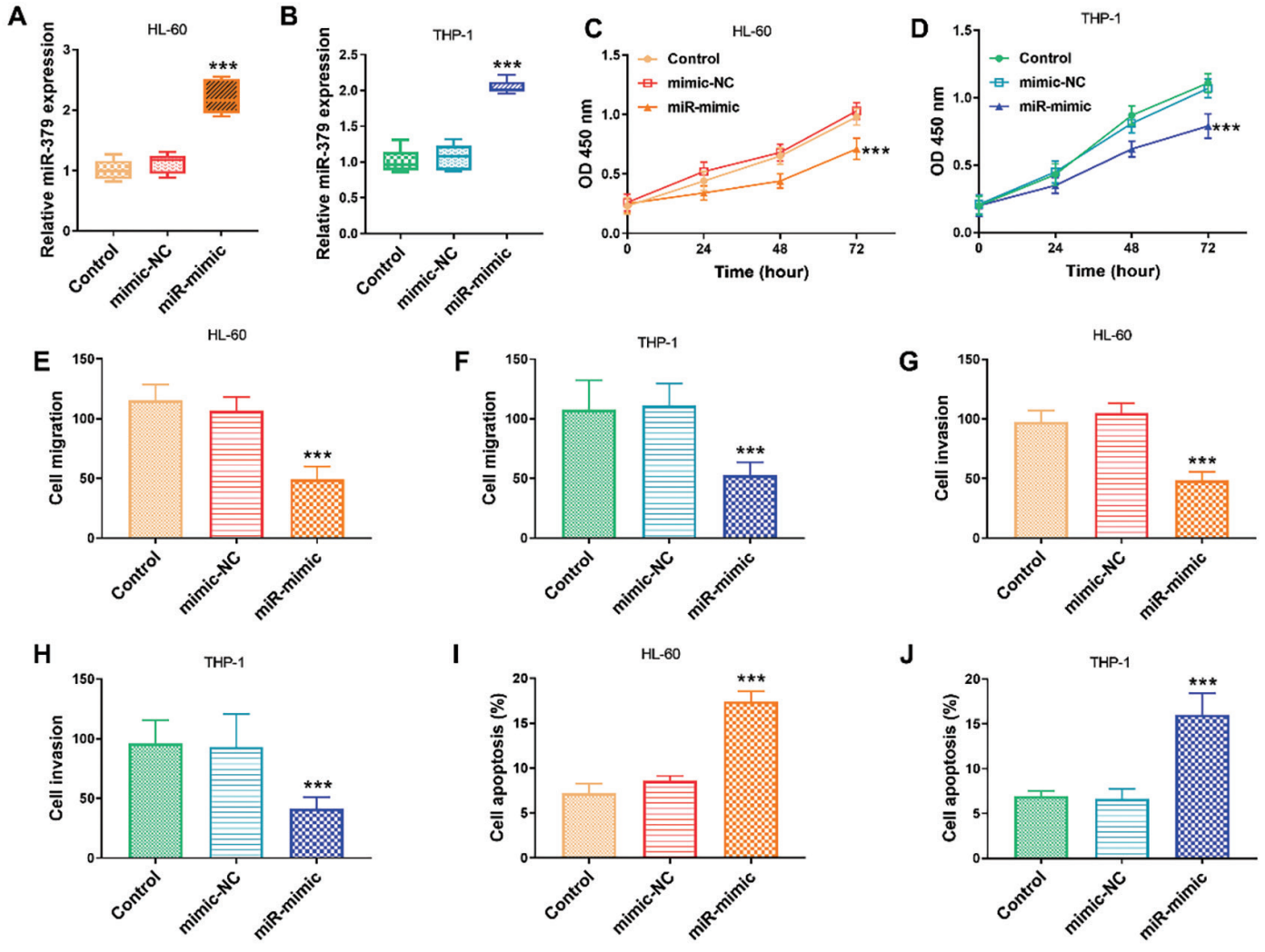

Figure 2. Role of miR-379-5p in HL-60 and THP-1 cells. A, B) After transfection with miR-379-5p mimics, the expression level of miR-379-5p was elevated. C, D) miR-379-5p suppressed proliferation. E, F) miR-379-5p suppressed migration. G, H) miR-379-5p inhibited invasion. I, J) miR-379-5p promoted apoptosis.

***: p<0.001.

YBX1 Reversed the Cellular Behavior of miR-379-5p

To further explore the working principles of the miR-379-5p/*YBX1* axis, a rescue experiment was performed. RT-qPCR results revealed that *YBX1* expression declined in the miR-mimic group. However, in the co-transfection group, the miRNA expression level of *YBX1* recovered to a certain extent. This indicated that miR-379 suppressed *YBX1* expression, while co-transfection of miR-mimic and *YBX1* reversed this trend (Figures 4A and 4B).

Cell proliferation assays showed decreased proliferation in the miR-mimic group, which was reversed in the miR-mimic + p-*YBX1* group (Figures 4C and 4D). Transwell assay results indicated that migration and invasion were reduced in the miR-mimic group, while *YBX1* upregulation mitigated these effects (Figures 4E-4H). Apoptosis assay results showed increased apoptotic capacity in the miR-mimic group, which was counteracted by *YBX1* upregulation (Figures 4I and 4J).

Discussion

AML is characterized by aberrant proliferation of primitive myeloid cells in the bone marrow and blood, but its pathogenesis is still unclear [16]. The incidence and mortality rates of AML are continuously rising [17]. Our study demonstrated that miR-379-5p has significant diagnostic value for AML.

miRNAs have a propensity for loss and transfer, influencing the proliferation and migration of malignant tumor cells [18]. miR-379-5p inhibits hepatocellular carcinoma invasion [19] and is also found to play significant roles in studies on endometrial cancer [20] and lung cancer [21]. Our study revealed that miR-

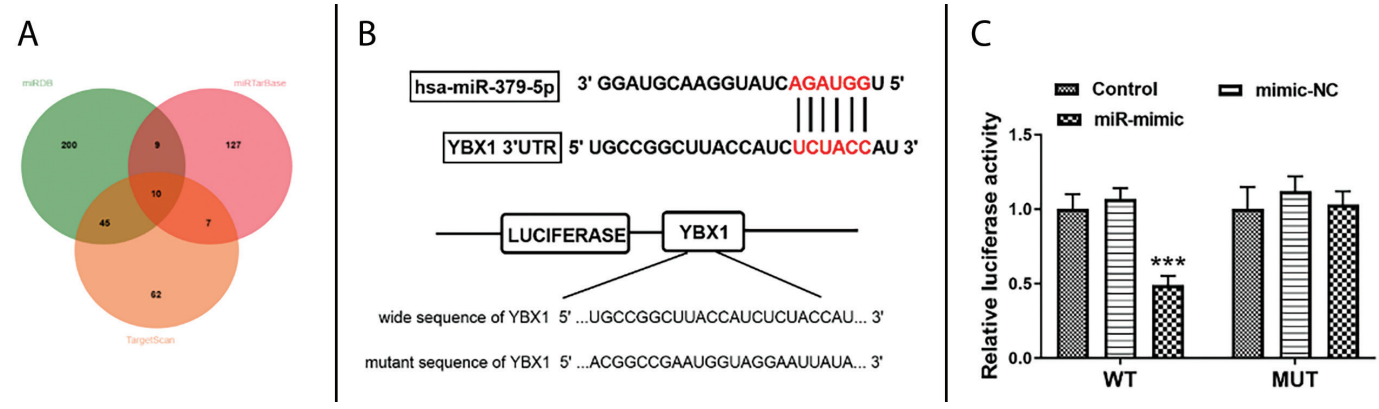

Figure 3. The targeting relationship of *YBX1* and miR-379-5p. A) The predicted results of target genes of miR-379-5p. B) Targeted binding sites. C) Validation of the targeted relationship.

***: p<0.001.

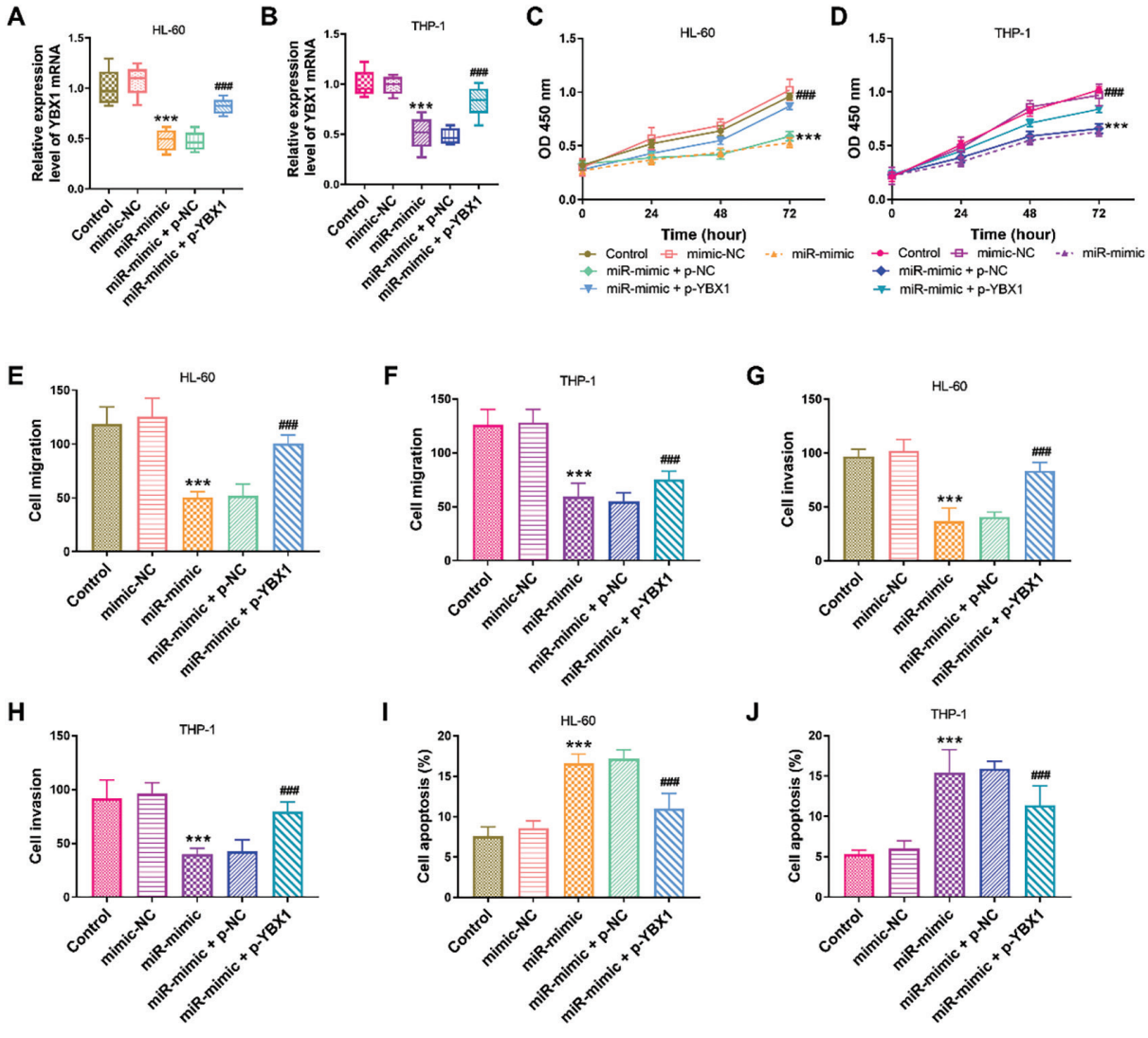

Figure 4. Regulation of HL-60 and THP-1 cells by the miR-379-5p/*YBX1* axis. A, B) Regulation of *YBX1* expression. C, D) Effect of miR-379-5p/*YBX1* on proliferation ability. E, F) Influence of miR-379-5p/*YBX1* on migration. G, H) Influence of miR-379-5p/*YBX1* on invasion. I, J) Impact of miR-379-5p/*YBX1* on apoptosis.

***: p<0.001.

379-5p suppressed the proliferation, migration, and invasion of AML cell lines and promoted apoptosis. Collectively, these findings provided robust evidence that miR-379-5p functions as a potent tumor suppressor in AML cells. Specifically, miR-379-5p might inhibit cell proliferation by targeting key genes involved in cell cycle progression [22]. In the context of apoptosis signaling pathways, miR-379-5p probably activates the expression of both intrinsic and extrinsic apoptosis-related genes [23], thereby promoting apoptosis in AML cells. For cell migration and invasion, miRNA may exert an inhibitory effect, likely by modulating the expression of cytoskeletal proteins or the function of intercellular adhesion molecules [23]. miR-379-5p may downregulate the expression of matrix metalloproteinases, which play critical roles in cell migration and invasion [24], thereby reducing the degradation of the extracellular matrix and impeding the ability of AML cells to migrate and invade surrounding tissues. In addition, research has determined that miR-379-5p also exhibited inhibitory effects against the cell proliferation of non-small-cell lung cancer [25] and glioma cells [26], promoting cancer cell apoptosis. These findings collectively suggested that miR-379-5p may act as a tumor suppressor of AML cells.

YBX1 was recognized as the target gene of miR-379-5p. Our study has revealed that miR-379-5p exhibited significantly reduced expression in AML patients, which was frequently correlated with unfavorable prognosis. Specifically, elevated *YBX1* expression in AML cells promotes cell proliferation, whereas the knockout of *YBX1* inhibits this process. High *YBX1* levels in adult AML patients were often associated with poor prognosis. miR-379-5p exerts its effects by negatively regulating *YBX1*; thus, decreased miR-379-5p expression has a weaker suppressive effect on *YBX1*, thereby enhancing the proliferative and other oncogenic effects of *YBX1*. Moreover, *YBX1* can counteract the inhibitory effects of miR-379-5p on AML cell proliferation, apoptosis, migration, and invasion. These findings are in alignment with the results of prior research studies. Previous studies have shown that miR-379-5p expression was decreased in osteoarthritis and it stimulated cell activity by negatively regulating *YBX1* [27]; furthermore, miR-379-5p and *YBX1* were shown to collaborate to regulate the biological activities of nasopharyngeal carcinoma cells [28]. In addition, research indicated that *YBX1* was upregulated in AML cells and enhanced their proliferation [29], while the knockout of this gene inhibited cell proliferation [30]. In adult AML patients, high expression of *YBX1* was often accompanied by an adverse prognosis [31]. These findings are in agreement with our research outcomes, demonstrating that *YBX1* counteracted the effects of miR-379-5p on AML cell proliferation, apoptosis, migration, and invasion.

Conclusion

This study has demonstrated that miR-379-5p inhibited the proliferation of AML cells by downregulating *YBX1*. The relative expression level of miR-379-5p was significantly reduced in both AML patients and AML cell lines, suggesting its potential as a clinical biomarker. Elevated levels of miR-379-5p were associated with inhibited cell proliferation, enhanced apoptosis, and suppressed cell migration and invasion. *YBX1*, identified as a target gene of miR-379-5p, promotes cell proliferation, migration, and invasion, thereby inhibiting apoptosis and exerting an opposing effect on miR-379-5p. We chose to isolate miR-379-5p from serum. Because serum samples are relatively easy to obtain through non-invasive or minimally invasive methods, they impose a significantly smaller burden on patients with AML compared to tissue sampling. Furthermore, the ability to collect multiple serum samples at different treatment stages is an important consideration in sample selection. Additionally, miRNA in serum can reflect the overall physiological and pathological state of the body. For systemic diseases such as AML, detecting miR-379-5p expression in serum may provide a more comprehensive reflection of the disease's impact on the entire body and its potential role in disease progression, rather than being confined to changes in specific local tissues. This approach can complement tissue-based studies to better elucidate disease mechanisms. Therefore, we chose to isolate miR-379-5p from serum. Our findings may provide novel insights into AML treatment. However, our study possessed certain limitations, such as the absence of tissue samples. Further investigation is warranted to explore miR-379-5p as a potential biomarker.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Changchun University of Chinese Medicine (approval number: 2018005, date: August 15, 2018).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.W., Y.X., X.T.; Concept: L.Z., H.G., Y.X., J.H.; Design: H.W., H.G., Y.X.; Data Collection or Processing: H.W., J.H., X.T.; Analysis or Interpretation: L.Z., J.H., X.T.; Literature Search: H.G., X.T.; Writing: H.W., L.Z., H.G., Y.X., J.H., X.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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