RESEARCH ARTICLE
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MiR-379-5p Inhibited the Proliferation of Acute Myeloid Leukemia Cells Through Negative Regulation of YBX1

Wu H. et al.: Role of MiR-379-5p in AML

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Abstract
Objectives: Acute myeloid leukemia (AML) is a frequent and highly lethal hematological malignancy that is difficult to treat. The research aimed to clarify the molecular mechanisms of *MIR-379-5p* in AML progression.
Materials and methods: RT-qPCR was utilized to evaluate *MIR-379-5p* expression levels in AML patients and a control group. A ROC curve was created to assess the clinical predictive value of *MIR-379-5p* in AML, while cell experiments used CCK-8 assay, flow cytometry, and Transwell chambers. Predicted potential target genes of *MIR-379-5p* by employing online bioinformatics tools, followed by

validation using a dual luciferase reporter assay.
Results: *MIR-379-5p* was significantly decreased in AML patients and had clinical predictive value for the disease. In AML cell lines, *MIR-379-5p* was down-regulated; conversely, the up-regulation 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* had the potential as a biomarker for AML by regulating cell proliferation and apoptosis through targeting *YBX1*.

Keywords: AML; *MIR-379-5p*; *YBX1*; cell proliferation; apoptosis; diagnostic significance

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, accounting for about two-thirds of adult leukemia[2]. Hematopoietic stem cell transplantation and chemotherapy are the most important means to treat 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 leukemi[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 cells[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]. 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 bladde[12], pancreatic [13], and nasopharyngeal cancer[14]. Research has demonstrated that *YBX1* is significantly upregulated in small extracellular vesicles (sev) released from the cells of most pediatric AML patients [15]. However, the mechanisms of *MIR-379-5p* and *YBX1* in AML remain poorly understood.

This study hypothesizes that *MIR-379-5p* was downregulated in AML based on previous findings and was involved in the regulation of AML cells. The study enrolled 70 healthy subjects and 75 AML patients. *MIR-379-5p* was detected and compared between the two groups. Further studies explored the molecular mechanisms of *MIR-379-5p* in AML and its clinical diagnostic value, providing a reference for diagnosing and treating AML.

Materials and methods

Patients and specimens

This study enrolled 75 AML patients from Changchun University of Chinese Medicine, and 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 cohort comprised 43 males and 32 females. 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 males and 31 females. According to the French-American-British (FAB) classification criteria, the subtypes of AML were distributed as follows: 6 patients had M0 type, 43 had

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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 age. All enrolled AML patients were newly diagnosed and had not yet received treatment. Written informed consent was obtained from all participants, and peripheral blood samples were collected. All enrolled AML patients were newly diagnosed and untreated. All participants provided written informed consent. Peripheral blood samples of samples from subjects were collected. The collected samples were left standing at room temperature for 2 hours, centrifuged for 10 minutes, and the upper serum samples were collected. The serum samples were stored in a refrigerator at -20°C for subsequent experiments. Additionally, all procedures were conducted in strict accordance with the Helsinki Declaration.

Cell culture and cell transfection

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

Lipofectamine 3000 (Invitrogen, USA) was utilized for transfection of synthetic sequences, including *MIR-379-5p* -mimic (miR-mimic) (GenePharma, Shanghai), 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 the *MIR-379-5p* mimic and *MIR-379-5p* inhibitor was 50 nM.

Quantitative real-time PCR (RT-qPCR)

The total RNA of *MIR-379-5p* and *YBX1* was extracted respectively. Subsequently, the obtained cDNA was amplified using the reverse transcription reagents on the Light Cycler® 96 (Roche, Switzerland) instrument. 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: an initial denaturation at 95°C for 3 minutes, followed by 40 cycles consisting of denaturation at 95°C for 5 seconds, annealing at 55°C for 10 seconds, and extension at 72°C for 15 seconds. Gene expression levels were determined using the $2^{-\Delta\Delta Ct}$ method, with U6 and GAPDH serving as internal controls.

CCK-8 assay

The approximately 2×10^3 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 (0, 24, 48, and 72 hours). Subsequently, CCK-8 solution was added to each well, followed by an additional incubation period of 4 hours. 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 Cell Counting Kit-8 (Hamby Biotechnology, China). Each experiment was performed in triplicate for each cell group.

Measurement of cell apoptosis

The requisite samples were collected, washed repeatedly with PBS, resuspended, and counted. A certain amount of Annexin V-FITC (Sigma-Aldrich, USA) and Propidium Iodide (Sigma-Aldrich, USA) reagents were added. Cell samples were incubated on ice for 15 to 20 minutes before being analyzed by flow cytometry. The apoptosis rate could be calculated based on the intensity of the fluorescence signal.

Cell migration and invasion experiments

Transwell chambers (BD Biosciences, USA) with 8 μm pores were coated with Matrigel (BD

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Biosciences, USA) for invasion assays, while uncoated chambers were used for migration assays. In brief, 1 × 10^4 cells were suspended in a serum-free medium and seeded into the upper chamber. Following a 24-hour 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 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 and subsequently amplified by PCR. The resulting PCR product was cloned into the pair GLO plasmid (Promega, 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, USA). Following a 48-hour incubation period, luciferase activity was measured using a luciferase reporter assay kit.

Statistical analysis

Data analysis was conducted using SPSS and GraphPad Prism software. For inter-group data comparisons, Student's 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 a lower level of AML 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 gender 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 (WBC) 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 in platelet counts, FAB subtypes, and cytogenetic characteristics ($P < 0.05$) (Table 1). RT-qPCR results indicated that *MIR-379-5p* expression of AML patients was significantly lower than in the control group (Figure 1A). Serum *MIR-379-5p* had a certain clinical diagnostic value for AML, with a diagnostic specificity of 85.71% sensitivity of 86.67%, and a 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 compared to HS-5, with the lowest levels in HL-60 and THP-1 (Figure 1C), leading to further experiments using these two cell lines.

MIR-379-5p regulated cellular behaviors.

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

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The targeting relationship of MIR-379-5p and YBX1

Venn diagram analysis revealed that 10 overlapping target genes were identified, namely *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 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* (Figure 3C).

YBX1 reversed the cellular behavior of MIR-379-5p

To further explore the working principle 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-379-5p* mimic and *YBX1* reversed this trend (Figure 4 A, 4B).

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

Discussion

AML is featured by aberrant proliferation of primitive myeloid cells in the bone marrow and blood, with its pathogenesis still unclea[16]. The incidence and mortality rates of AML are continuously rising[17]. Our study demonstrated that *MIR-379-5p* exhibited significant diagnostic value for AML.

MiRNAs have a propensity for loss and transfer, influencing the proliferation and migration of malignant tumor cells, etc.[18]. *MIR-379-5p* inhibits hepatocellular carcinoma invasion [19]; *MIR-379-5p* also plays a significant role in studies on endometrial cancer[20] and lung cancer[21]. Our study discovered that *MIR-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 activated 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 (MMPs), which play a critical role 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 on non-small cell lung cancer[25], glioma cells[26] cell proliferation, and promoting effects on 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 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

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patients were often associated with poor prognosis. *MIR-379-5p* exerts its effects by negatively regulating *YBX1*; thus, decreased *MIR-379-5p* expression weakened its suppressive effect on *YBX1*, thereby enhancing *YBX1*'s proliferative and other oncogenic effects. Moreover, *YBX1* can counteract the inhibitory effects of *MIR-379-5p* on AML cell proliferation, apoptosis, migration, and invasion. These findings were in alignment with prior research studies. Previous studies have shown that *MIR-379-5p* showed a decreased expression level in osteoarthritis and stimulated cell activity by negatively regulating *YBX1*[27]; *MIR-379-5p* and *YBX1* collaborated to regulate the biological activities of nasopharyngeal carcinoma cells[28]. In addition, research indicated that *YBX1* was upregulated in AML cells and enhances their proliferation [29], while the knockout of this gene inhibits cell proliferation[30]. In adult AML patients, a high expression of *YBX1* was often accompanied by an adverse prognosis [31]. These findings were in agreement with our research outcomes, demonstrating that *YBX1* counteracted the effects of *MIR-379-5p* on AMI cell proliferation, apoptosis, migration, and invasion.

In summary, our study 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 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 were relatively easy to obtain through non-invasive or minimally invasive methods, they impose a significantly lesser 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 the serum. Our findings may provide novel insights into AML treatment. However, our study possessed certain limitations, such as the absence of tissue samples. However, further investigation was warranted to explore *MIR-379-5p* as a potential biomarker.

Conflicts of Interest

The authors have declared no conflict of interest.

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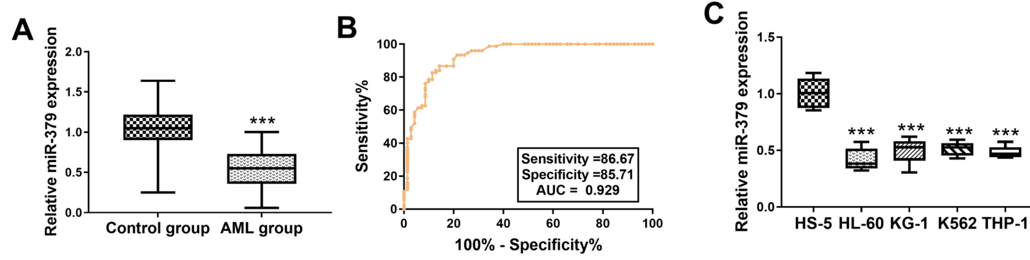

Figure 1. The expression level and diagnostic value of *MIR-379-5p*. A. *MIR-379-5p* was downregulated in the AML. B. *MIR-379-5p* possesses diagnostic value. C. *MIR-379-5p* was downregulated in AML cell lines. ***$P < 0.001$

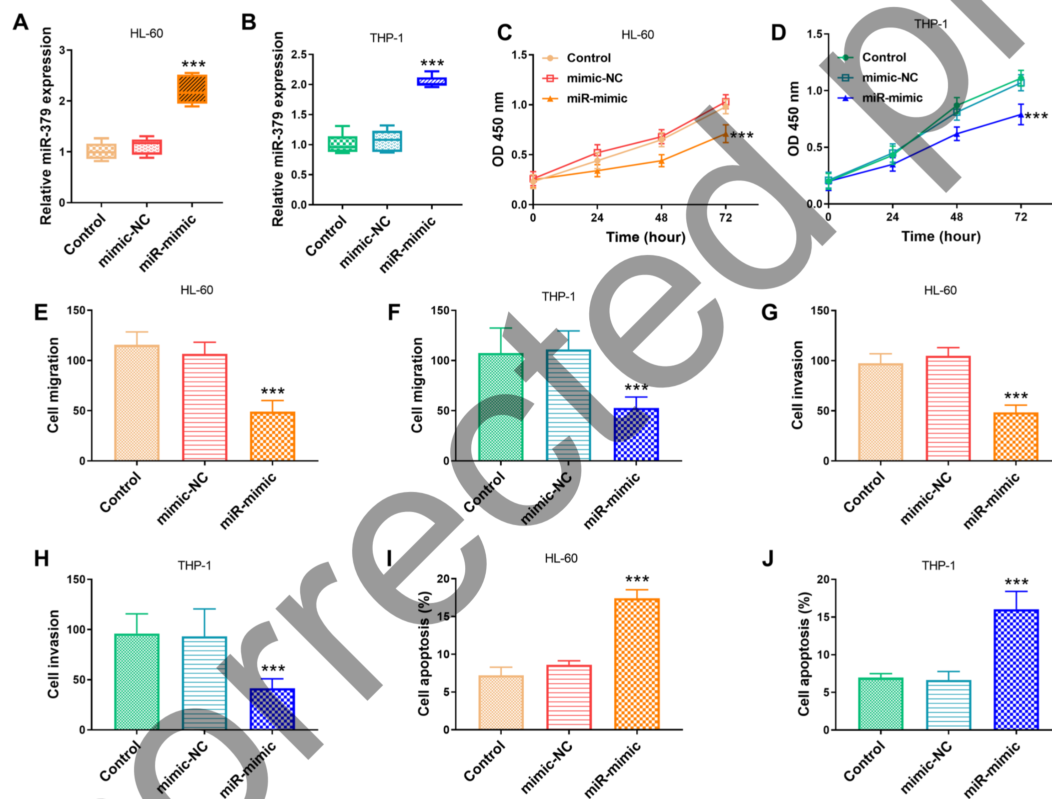

Figure 2. The role of *MIR-379-5p* in HL-60 and THP-1 cells. A-B. After transfection with *MIR-379-5p* mimics, the expression level of *MIR-379-5p* was elevated. C-D. *MIR-379-5p* suppressed the proliferation. E-F. *MIR-379-5p* suppressed the migration. G-H. *MIR-379-5p* inhibited the invasion. I-J. *MIR-379-5p* promoted the apoptosis. ***$P < 0.001$.

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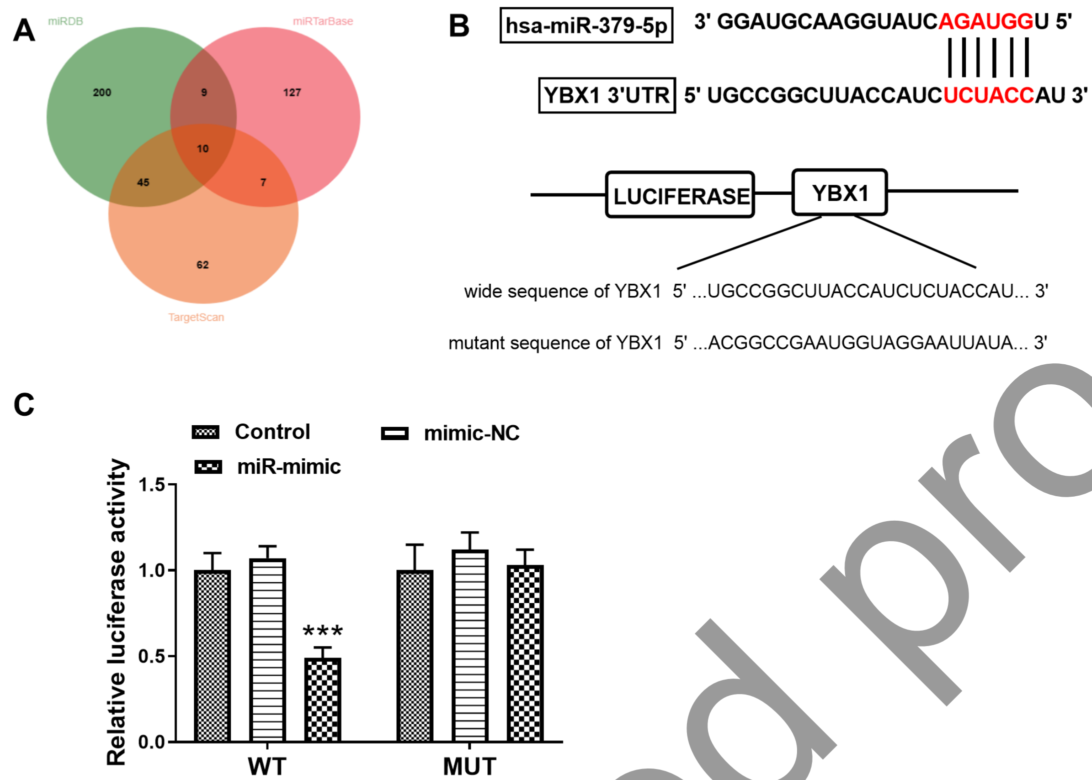

Figure 3. The targeting relationship of *YBX1* and *MIR-379-5p*. A. The predicted results of target genes of *MIR-379-5p*. B. The targeted binding sites. C. Validation of the targeted relationship. ***$P < 0.001$

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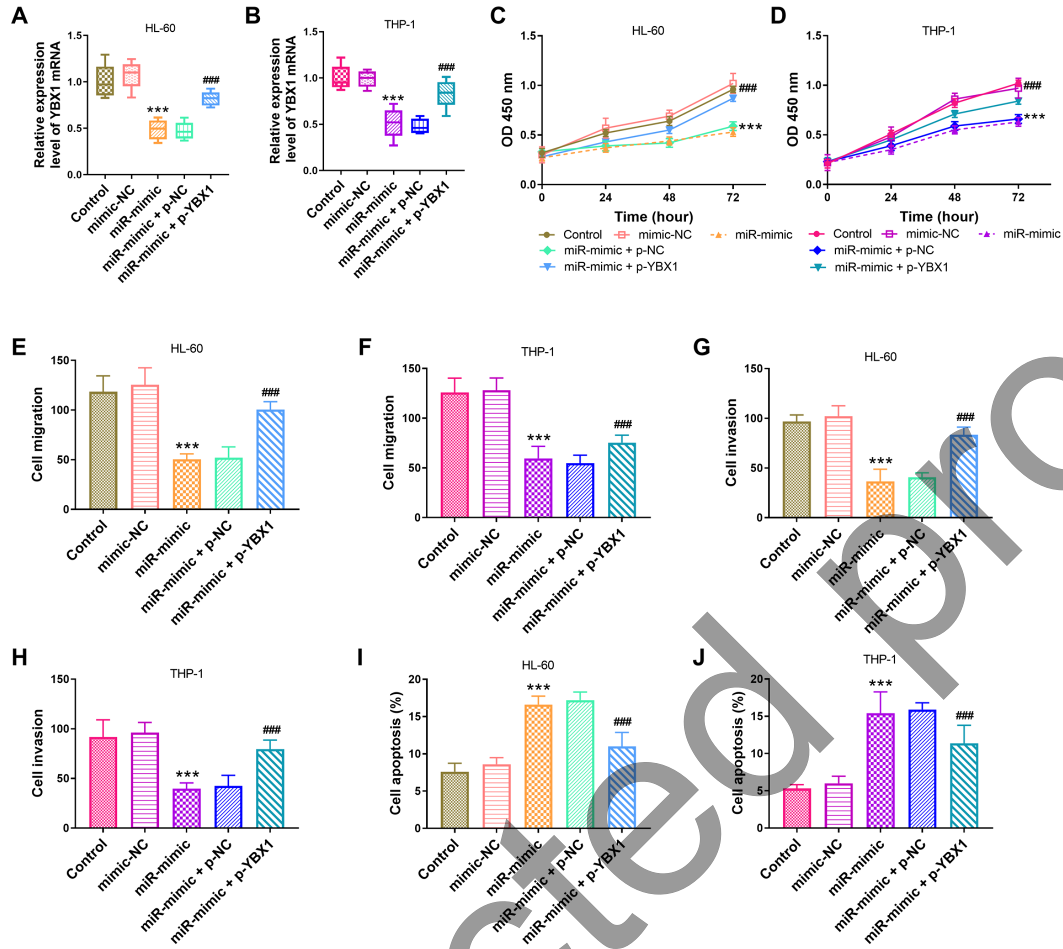

Figure 4. The regulation of HL-60 and THP-1 cells by the *MIR-379-5p/YBX1* axis. A-B. The regulation of *YBX1* level. C-D. The effect of *MIR-379-5p/YBX1* on the proliferation ability. E-F. The influence of *MIR-379-5p/YBX1* on migration. G-H. The influence of *MIR-379-5p/YBX1* on the invasion. I-J. The impact of *MIR-379-5p/YBX1* on the apoptosis. ***$P < 0.001$.

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Table 1 Correlation of miR-379-5p levels with clinicopathological parameters of AML patients

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

Note: WBC, white blood cells; BM, bone marrow; FAB, French-American-British classification; AML, acute myeloid leukemia.

uncorrected proof