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miR-143-3p represses leukemia cell proliferation by inhibiting KAT6A expression

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The present study is designed to investigate the expressions of microRNA-143-3p (miR-143-3p) and Lysine acetyltransferase 6A (KAT6A) in acute myeloid leukemia (AML) samples and AML cell lines and to explore the possible effects and underlying mechanisms of miR-143-3p on the proliferation of AML cells. The expressions of miR-143-3p and KAT6A in AML samples and cell lines were detected by RT-qPCR assay. CCK-8 and flow cytometry were performed to evaluate the role of KAT6A in viability of AML cells. EdU assay was performed to determine the effects of KAT6A on proliferation of AML cells. Western blot analysis was utilized to assess the impacts of KAT6A on proliferation-related protein expressions of AML cells. ELISA assay was adopted to illustrate the influence of KAT6A on inflammatory responses of AML cells. In addition, the relationship between KAT6A and miR-143-3p was predicted by ENCORI and miRWalk, and confirmed by dual-luciferase reporter assay. Moreover, the effects of KAT6A on the proliferation of AML cells mediated with miR-143-3p were carried out by rescue experiment. The expression of KAT6A was significantly upregulated, while miR-134-4p was downregulated both in the AML tissues and in AML cell lines. In addition, the silence of KAT6A significantly inhibited the viability of AML cells. Besides, KAT6A silencing notably suppressed the proliferation of AML cells and reduced the protein expressions of Ki-67 and PCNA. Knockdown of KAT6A notably decreased the expression levels of IL-1β, TNF-α and IL-6, and increased the expression levels of TGF-β and IL-10. Moreover, overexpression of miR-143-3p repressed viability and proliferation of AML cells and overexpression of KAT6A partially reversed the inhibitory effects of miR-143-3p mimic on viability and proliferation of AML cells. miR-143-3p/KAT6A played an essential role in the viability and proliferation of AML cells. *Anti-Cancer Drugs* 33: e662–e669 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous clonal malignancy caused by accumulated genetic aberrations characterized by increased proliferation and blocked differentiation of leukemia cells [1]. AML accounts for about 34% of all leukemia cases [2]. Most AML patients will get remission after one or two courses of chemotherapy, but a considerable proportion of these patients will relapse [3]. According to statistics, about 24% of AML patients are between 75 and 84 years old, approximately 10% of patients are 85 years old or above [4]. Chemotherapy alleviates more than 80% of AML patients, but the survival rate of AML is still shallow due to the failure of remission induction and the recurrence after remission [5]. At present, the treatment of AML includes chemotherapy and hematopoietic stem cell transplantation. Although the treatment of some particular subtypes of AML has been improved, it is still no ideal treatment for the vast majority of AML patients [6,7]. Therefore, it is essential to develop a more effective treatment for AML. AML results from genetic and epigenetic changes accumulated in the multistep process of tumorigenesis, including activation of oncogenes and inactivation of tumor suppressor genes [8]. Many transcription factors play essential roles in invasive hematological tumors [9]. In the past decade, evidence shows that protein post-transcriptional modifications, including phosphorylation, acetylation and ubiquitination, display a key role in the initiation, progression and maturation of AML [10–12]. However, the pathogenesis of AML remained unclear.

KAT6A, a gene commonly found in the 8p11-p12, is first identified in 1996 as part of a chromosomal translocation t(8;16)(p11;p13) with CREB-binding protein in a subtype of AML [13]. Moreover, additional translocations involving KAT6A in AML have been discovered, including translocations with the HATs p300 and TIF2 [14]. Besides, KAT6A-TIF2 fusion is capable of immortalizing myeloid progenitor cells and inducing AML [15]. These findings indicate that KAT6A is an oncogene in AML.

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However, the detailed role and possible mechanisms of KAT6A in AML remained unknown. MicroRNAs (miRNAs) are composed of 18–25 noncoding and conserved single-stranded molecules, which regulate expressions of target genes by targeting mRNA degradation or inhibiting translation and participate in regulating various biological behaviors [16–18]. Previous studies have shown that during the progress of AML, miRNAs exhibit an essential role. For example, miR-22 is significantly downregulated in AML patients, and forced expression of miR-22 significantly suppresses AML cell viability and growth [19]. In addition, miR-34a is lower expressed in HL-60 and THP-1 cells, and forced expression of miR-34a significantly promotes apoptosis and inhibits autophagy in HL-60 and THP-1 cells [20]. MiR-143-3p, as a matured form of miR-143, located on chromosome 5q32, has been reported to be involved in the occurrence and development of many cancers, including colon cancer, lung cancer, liver cancer, etc. [21–23]. Furthermore, miR-143-3p mainly acted as a tumor suppressor gene. However, in the development of AML, whether miR-143-3p targeted KAT6A or the molecular mechanisms of this regulation had not been reported yet.

In the present study, KAT6A was significantly upregulated, while miR-143-3p was significantly downregulated in AML samples and cell lines. In addition, KAT6A was predicted as a target of miR-143-3p by bioinformatics analysis and further verified by dual-luciferase reporter assay. Moreover, our data showed that miR-143-3p/KAT6A played a vital role in the viability and proliferation of AML cells.

Materials and methods

Collection of AML tissues

A total of 30 bone marrow samples were obtained from each case at the same time before any therapeutic intervention in the Funing People's Hospital according to a standard protocol. All patients signed written informed consent, and the Ethics Committee of Funing People's Hospital approved the protocol.

Cell lines and cell culture

The AML cell lines, including HL-60, KG1a, K562 and THP-1, and bone marrow stromal cell HS-5 were obtained from American Type Tissue Culture Collection (Manassas, Virginia, USA). Routinely cultured in RPMI-1640 medium (Invitrogen, Carlsbad, California, USA) supplemented with 10% fetal bovine serum (FBS, Invitrogen, Grand Island, New York, USA) and 1% penicillin-streptomycin (Sigma-Aldrich, St. Louis, Missouri, USA) in a humidified condition with 5% CO_2 at 37°C.

Cell transfection

MiR-143-3p mimic or NC mimic, shRNA for knocking down KAT6A (sh-KAT6A) and negative control (sh-NC) and pcDNA3.1-KAT6A overexpressing KAT6A and the control group were synthesized in GenePharma Company (Shanghai, China). Lipofectamine 2000 (Invitrogen) was performed for cells transfection on the basis of the specification. Relative expressions of miR-143-3p and KAT6A were determined by RT-qPCR assay 48 h later.

CCK-8 assay

Transfected HL-60 and K562 cells (1×10^4 cells per well) were maintained in 96-well plates for predetermined times (0, 24, 48 and 72 h). Afterward, cell viability was examined by CCK-8 kit (Beyotime, Shanghai, China) on the basis of the protocols. In addition, the optical density was detected at 490 nm by a microplate reader (Bio-Red, Carlsbad, California, USA) and analyzed by GraphPad Prism 5.0.

Flow cytometry assay

The cells (1×10^5 cells) were stained with 4.5 ml propidium iodide (5 mL) and 4.5 ml Annexin V-FITC (5 mL) (BD Pharmingen, San Diego, California, USA), trailed by fluorescence determination by a Flow cytometer (Beckman, Miami, Florida, USA). All investigations were estimated in triplicate.

EdU assay

Transfected HL-60 and K562 cells (5×10^4/well) were cultured in 24-well plates and incubated for 48 h. Then HL-60 and K562 cells were fixed with 4% paraformaldehyde, Triton X-100 was used to permeabilize the nuclear membrane, and HL-60 and K562 cells were blocked with goat serum for 1 h. Further, according to the manufacturer's instructions, HL-60 and K562 cells were stained with EdU (Beyotime, Shanghai, China). Finally, images were taken and analyzed using a microscope (Olympus, Tokyo, Japan).

RT-qPCR analysis

Total RNA was extracted from human AML samples, and cell lines using TRIzol reagent (Invitrogen), The PrimeScript reverse-transcription reagent kit (Thermo Fisher Scientific, Waltham, Massachusetts, USA) was applied for carrying out reverse-transcription reaction on RNA. SYBR Green qPCR Master Mixes (Thermo Fisher Scientific) plus Biosystems 7500 Sequence Detection System (Applied Biosystems, Foster City, California, USA) were applied for implement of RT-qPCR. β-actin and U6 were used for normalizations. RNA expression was assessed using $2^{-\Delta\Delta Ct}$ approach. The sequences of the primers used were miR-143-3p forward, 5′-GGGGTGAGATGAAGCACTG-3′, and reverse, 5′-CAGTGCGTGTCGTGCAGT-3′, KAT6A forward, 5′-GAGGCCAATGCCAAGATTAGAA C-3′, and reverse, 5′-GTTGATACTAGAGCCGCTGCCTC-3′, β-actin forward, 5′-GTCACCTTCACC GTTCCAGTTTT-3 and reverse, 5′-CTTAGTTGCGTTACACCCTTTCTT-3′. U6 forward, 5′-CTCGC TTCGGCAGCACA-3′, and reverse, 5′-AACGCTTCACGAATTTGCGT-3′. The procedure was as followed: 95°C for 30 seconds, 95°C for 5 s and 60°C for 30 s with 40 cycles.

Western blot assay

Protein was isolated from AML cell lines by RIPA lysis buffer and quantified by BCA kit (Beyotime). Protein was

extracted by 12% SDS-PAGE and then shifted into PVDF membranes (Millipore, Bedford, Massachusetts, USA). Next, the membranes were interfered with 5% non-fat milk and treated with the primary antibodies overnight at 4°C. Membranes were washed and probed with HRP-conjugated secondary antibody (1:2000, ab6728) for 1 h at room temperature. At last, protein blots were observed by an enhanced chemiluminescence kit (ECL, Millipore) and quantified using ImageJ software (NIH, version 4.3). The primary antibodies were as below: anti-KAT6A (ab41718, 1:1000), anti-Ki-67 (ab15580, 1:1000), anti-PCNA (ab92552, 1:1000) and anti-β-actin (1:1000, ab8226). All antibodies were obtained from Abcam (Massachusetts, USA).

ELISA

Cytokine concentrations, such as human IL-1β, TNF-α, IL-6, TGF-β and IL-10, isolated inHL-60 and K562 cells were analyzed through ELISA in line with specific protocols.

Dual-luciferase reporter assay

The upstream miRNAs regulating KAT6A were predicted by ENCORI and miRwalk. KAT6A WT/ MUT was subcloned into pmirGLO dual-luciferase vector (Promega, Madison, Wisconsin, USA) to generate pmirGLO-KAT6A WT/ MUT, which was then co-transfected into cells with miR-143-3p mimic or NC mimic. After 48-h co-transfection, the relative luciferase activities were detected utilizing dual-luciferase reporter assay system (Promega). The Renilla luciferase activity was used for normalization.

Statistical analysis

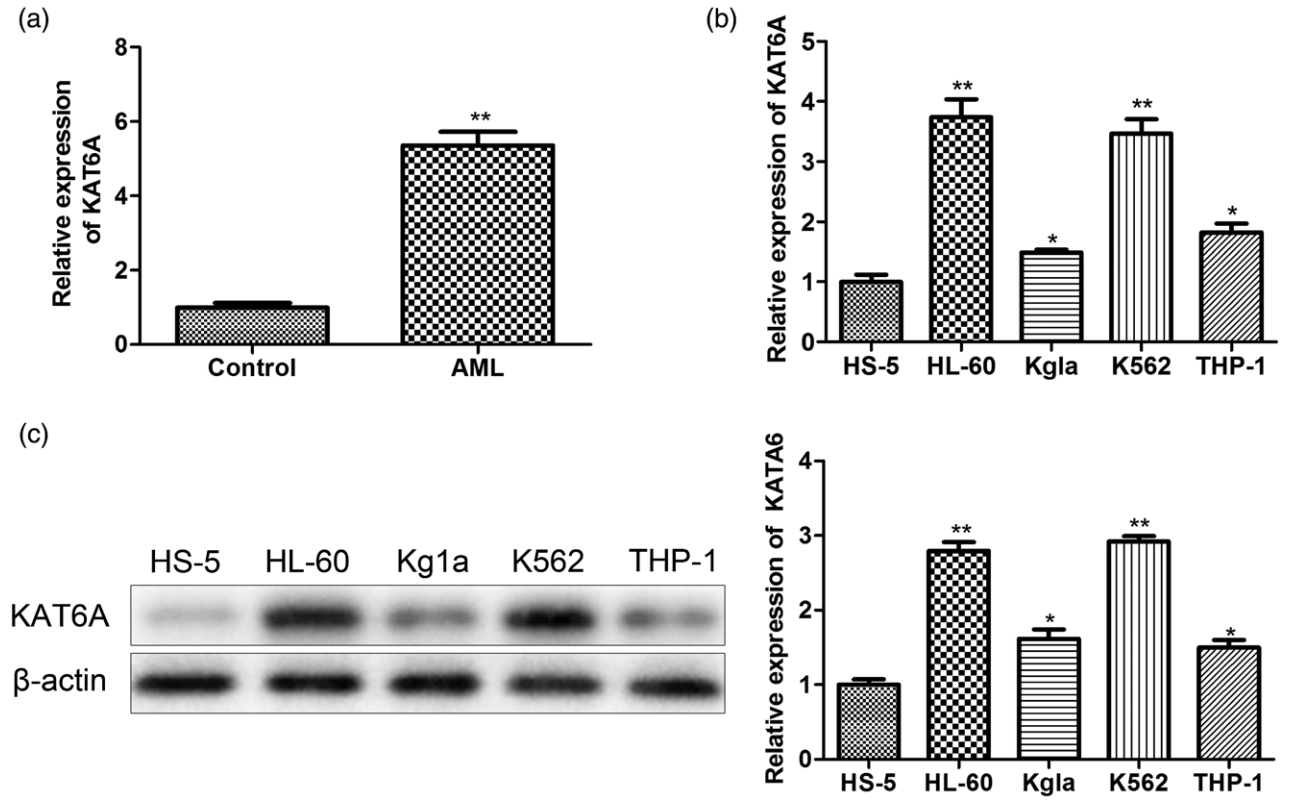
Statistical analysis was performed using Prism 5.0 (GraphPad, San Diego, California, USA). Quantitative data were presented as means ± SD. The perform comparisons were performed via Student's *t*-test or one-way ANOVA. $P < 0.05$ was considered statistically significant.

Results

KAT6A is upregulated in AML tissues and cell lines

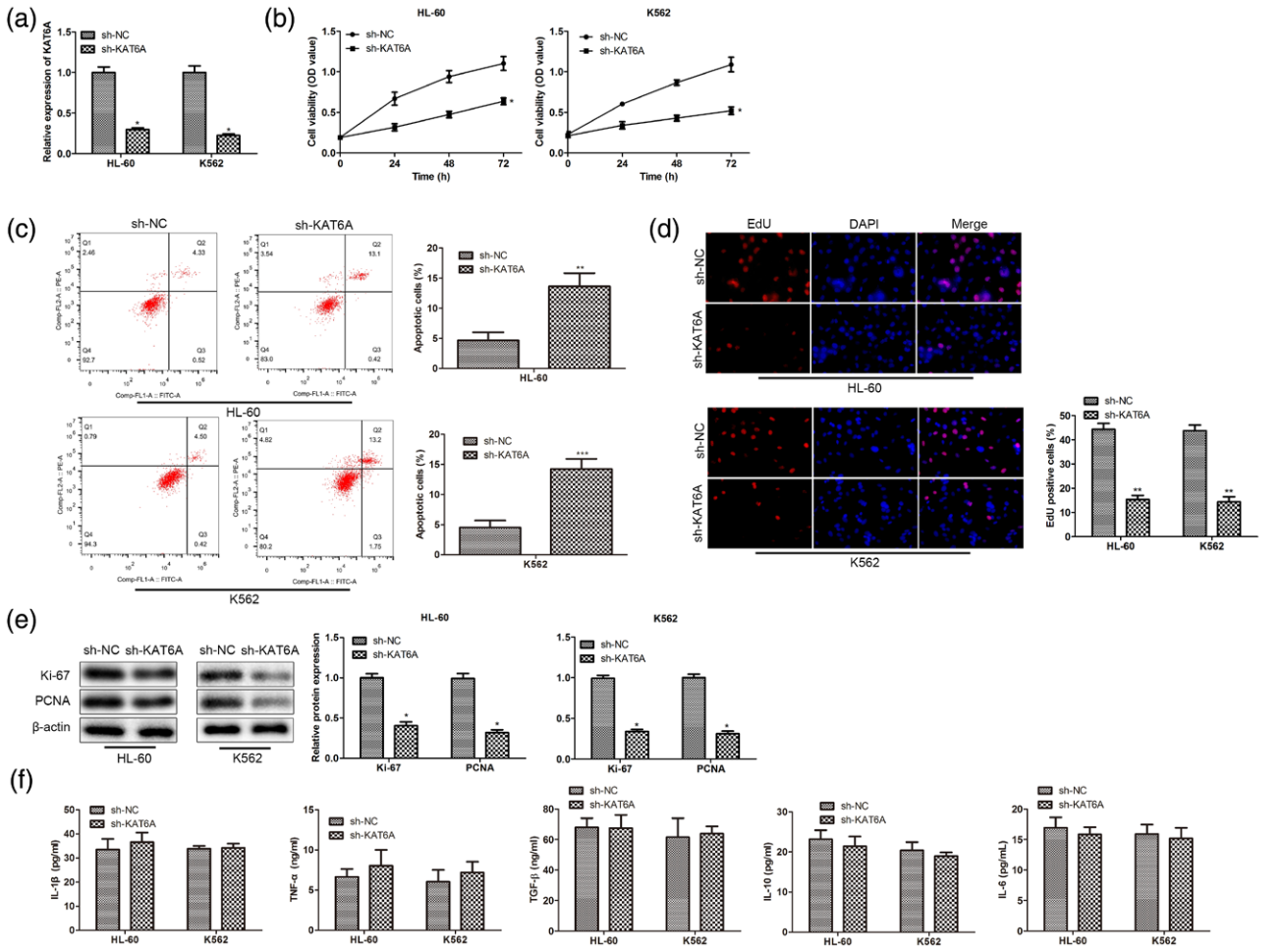
To investigate the role of KAT6A in AML, qRT-PCR was firstly adopted to evaluate the mRNA expression of KAT6A in AML tissues. The data in Fig. 1a showed that KAT6A was increased in AML tissues compared with the control group. Moreover, the mRNA and protein expressions of KAT6A in AML cell lines (HL-60, Kgla, K562 and THP-1) were determined by qRT-PCR and western blot assays. The data of Fig. 1b,c displayed that KAT6A was

Fig. 1



KAT6A is upregulated in AML tissues and cell lines. (a) The expression of KAT6A in AML tissues was detected by the qRT-PCR assay. $^{*}P < 0.01$ vs. control group. The mRNA and protein expressions of KAT6A in AML cell lines were detected by (b) qRT-PCR and (c) western blot assays. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. HS-5 cells. All data were presented as mean ± SD. $n = 3$.

Fig. 2



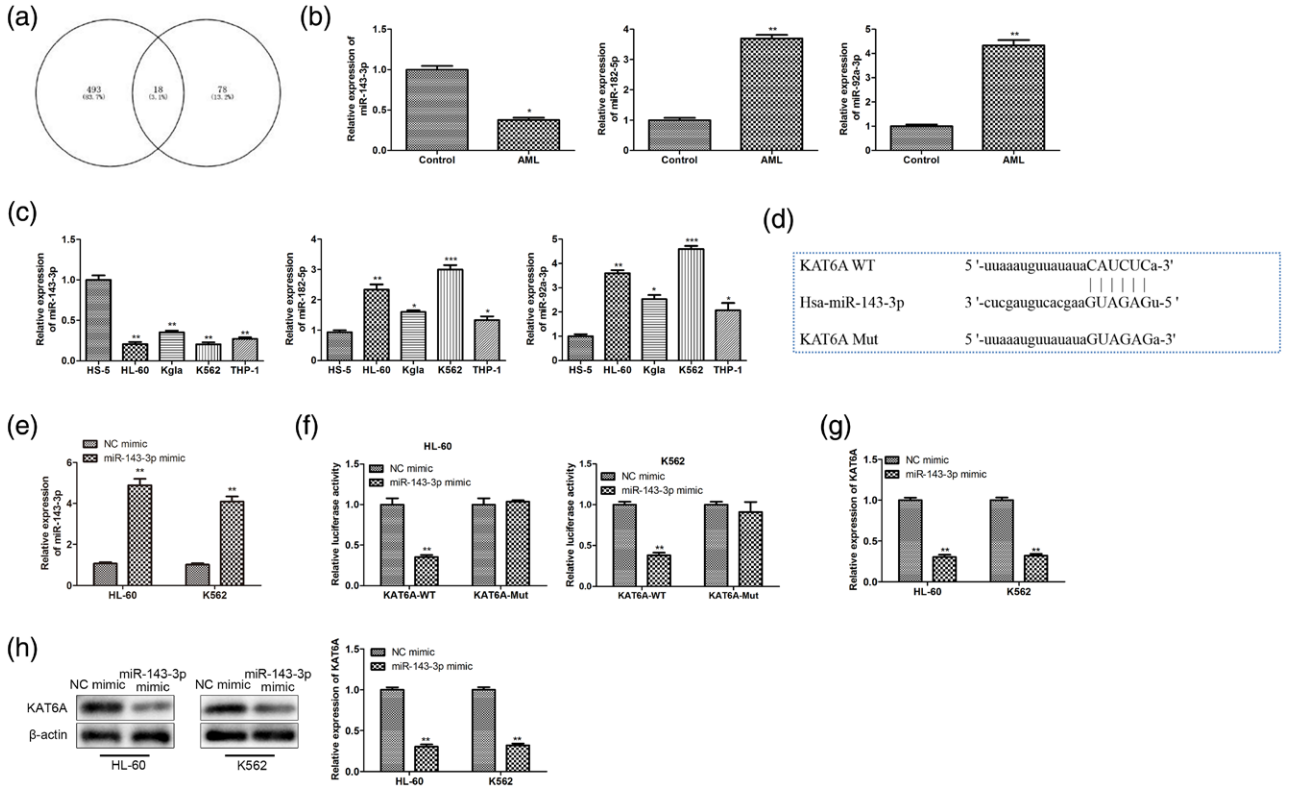
Downregulation of KAT6A inhibits viability and proliferation of AML cells. (a) qRT-PCR assays were performed to evaluate the KAT6A expression in HL-60 and K562 cells after transfection with sh-KAT6A. The viability of HL-60 and K562 cells transfected with sh-KAT6A was assessed by (b) CCK-8 and (c) flow cytometry assays at indicated times. (d) The proliferation of HL-60 and K562 cells transfected with sh-KAT6A was evaluated by EdU assay. (e) The protein expressions of PCNA and Ki-67 in HL-60 and K562 cells transfected with sh-KAT6A were evaluated by western blot assay. (f) The expression levels of inflammatory factors in HL-60 and K562 cells transfected with sh-KAT6A were evaluated by ELISA assays. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. pc-NC group. All data were presented as mean ± SD. $n = 3$.

also highly expressed in AML cells, especially in HL-60 and K562 cells, relative to that in HS-5 cells. These data suggested that KAT6A might act as an oncogene in AML.

Downregulation of KAT6A inhibits viability and proliferation of AML cells

To explore the functional role of KAT6A in AML, HL-60 and K562 cells were transfected with sh-KAT6A, and transfection efficiency was evaluated by qRT-PCR assay. The data in Fig. 2a illustrated that the expression of KAT6A was significantly suppressed in HL-60 and K562 cells after transfection with sh-KAT6A. Functionally, CCK-8 and flow cytometry assays were carried out to assess the effects of KAT6A on the viability of HL-60 and K562 cells. The data of Fig. 2b,c revealed that downregulation of KAT6A notably inhibited the viability of HL-60 and K562 cells in a time-dependent manner compared with sh-NC group. In addition, EdU assay was used to determine the role of KAT6A in the proliferation of HL-60 and K562 cells. The data of Fig. 2d showed that the EdU-positive cells in HL-60 and K562 cells transfected with sh-KAT6A were significantly reduced compared to sh-NC group. Moreover, western blot analysis was performed to evaluate the effects of KAT6A on the expressions of proliferation-related proteins, including PCNA and Ki67. The data of Fig. 2e illustrated that decreased KAT6A notably reduced the protein levels of PCNA and Ki67 in HL-60 and K562 cells compared to sh-NC group. Furthermore, ELISA assay was adopted to assess the effects of KAT6A on the expression levels of inflammatory factors, including IL-1β, TNF-α, IL-6, TGF-β and IL-10. The data of Fig. 2f displayed that

Fig. 3



KAT6A is direct target of miR-143-3p in AML cells. (a) The potential upstream miRNAs of KAT6A was predicted with ENCORI and miRWalk. The expressions of miR-143-3p, miR-182-5p and miR-92a-3p in (b) AML tissues and (c) cell lines were detected by qRT-PCR assay. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. control group or HS-5 cells. (d) Putative binding sites between miR-143-3p and KAT6A. (e) qRT-PCR assay was performed to evaluate the miR-143-3p expression in HL-60 and K562 cells transfected with miR-143-3p mimic. (f) Dual-luciferase reporter analysis was employed to validate the interactions between miR-143-3p and KAT6A. The mRNA and protein expressions of KAT6A in HL-60 and K562 cells transfected with miR-143-3p mimic were detected by (g) qRT-PCR and (h) western blot assays. $^{**}P < 0.01$ vs. NC mimic group. All data were presented as mean ± SD. $n = 3$.

knockdown of KAT6A inhibited the expression levels of IL-1β, TNF-α and IL-6, and promoted the expression levels of TGF-β and IL-10. These data suggested that downregulation of KAT6A inhibited the viability and proliferation of AML cells.

KAT6A is the direct target of miR-143-3p in AML cells

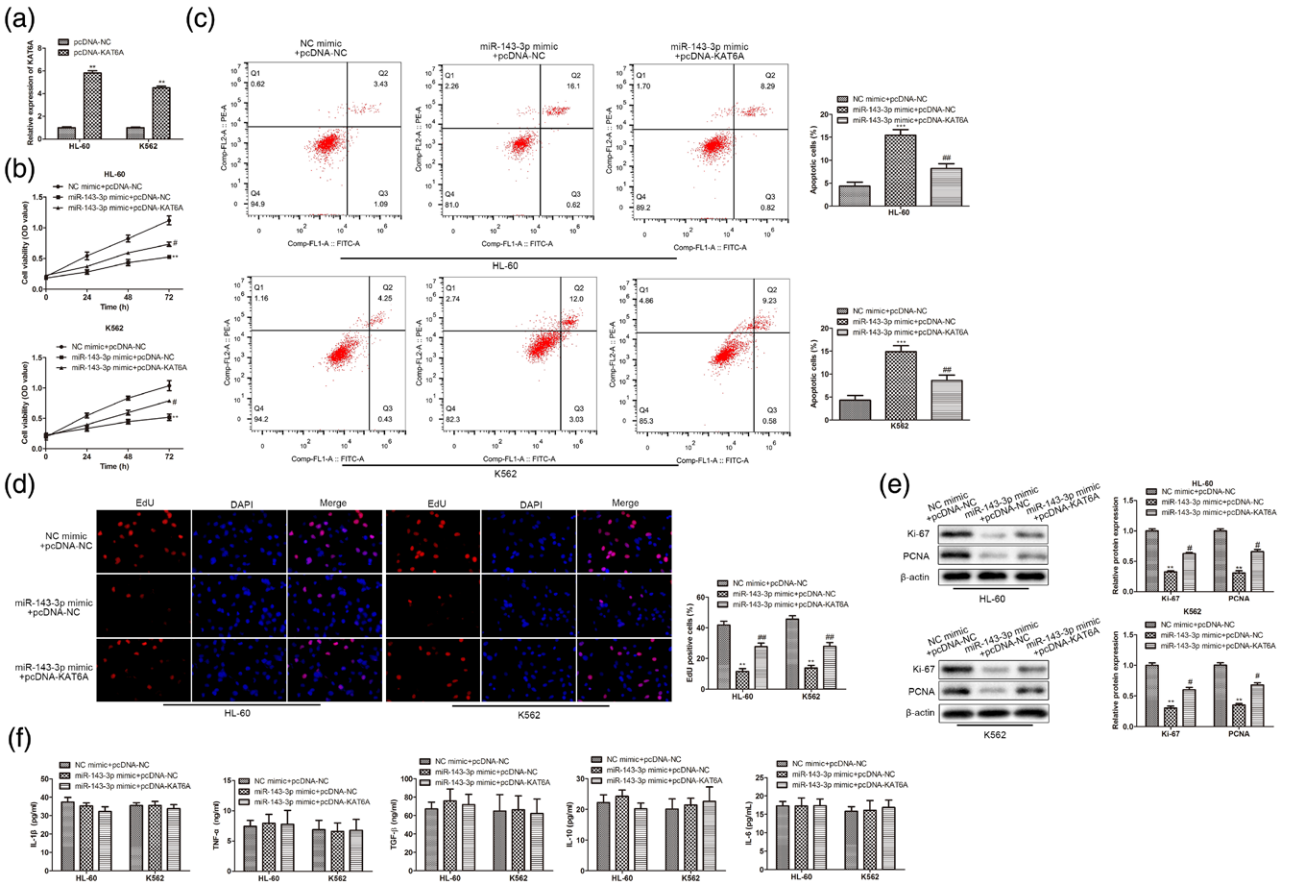
ENCORI and miRWalk were jointly performed in order to explore the possible upstream miRNAs regulating KAT6A in AML. The data of Fig. 3a showed that a total of 18 miRNAs were screened out. Then qRT-PCR was performed to evaluate the expression levels of selected miRNAs in AML tissues and cell lines. As shown in Fig. 3b,c showed miR-143-3p was obviously downregulated in AML tissues. Thus, miR-143-3p was chosen for further study (Fig. 3d).

To assess the relationship between miR-143-3p and KAT6A in AML cells, HL-60 and K562 cells were transfected with miR-143-3p mimic, and transfection efficiency was evaluated qRT-PCR assay. The data of Fig. 3e showed that the expression of miR-143-3p was significantly promoted in HL-60 and K562 cells after being transfected with miR-143-3p mimic compared with NC mimic. Then, dual-luciferase reporter assay was adopted, and the exogenous expression of miR-143-3p distinctly weakened the luciferase activity of 3′-UTR of KAT6A. In contrast, the inhibitory effect was blocked by a mutation on the putative binding sites existing on the 3′-UTR of KAT6A (Fig. 3f). Furthermore, qRT-PCR and western blot assays were used to evaluate the mRNA and protein expression of KAT6A in HL-60 and K562 cells transfected with miR-143-3p mimic. As displayed in Fig. 3g,h, the mRNA and protein expression levels of KAT6A were significantly decreased in miR-143-3p mimic- transfected HL-60 and K562 cells. These data suggested that KAT6A was a direct target gene of miR-143-3p in AML.

KAT6A mediates the effects of miR-143-3p on viability and proliferation of AML cells

On the basis of the above results, the effects of miR-143-3p on the viability and proliferation of AML cells mediated with KAT6A were further studied. Firstly,

Fig. 4



KAT6A mediates the effects of miR-143-3p on the viability and proliferation of AML cells. (a) qRT-PCR assay was performed to evaluate the KAT6A expression in HL-60 and K562 cells transfected with pcDNA-KAT6A. $^{**}P < 0.01$ vs. pcDNA-NC group. The viability of HL-60 and K562 cells after transfection was assessed by (b) CCK-8 and (c) Flow cytometry assays at indicated times. (d) The proliferation of HL-60 and K562 cells after transfection was evaluated by EdU assay. (e) The protein expressions of PCNA and Ki-67 in HL-60 and K562 cells after transfection was evaluated by western blot assay. (f) The expression levels of inflammatory factors of HL-60 and K562 cells after transfection. $^{**}P < 0.01$ vs. NC mimic + pcDNA-NC group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ vs. miR-143-3p mimic + pcDNA-NC group. All data were presented as mean ± SD. $n = 3$.

HL-60 and K562 cells were transfected with pcDNA-KAT6A, and the data of Fig. 4a showed that the expression of KAT6A was notably upregulated in AML cells transfected with pcDNA-KAT6A compared with pcDNA-NC group. Functionally, the result of CCK-8 and flow cytometry assays illustrated that miR-143-3p mimic significantly inhibited the viability of HL-60 and K562 cells in a time-dependent manner. At the same time, overexpression of KAT6A partially reversed the inhibitory effects of miR-143-3p mimic on the viability of HL-60 and K562 cells (Fig. 4b,c). Besides, the result of EdU assay showed that miR-143-3p mimic suppressed the proliferation of HL-60 and K562 cells. At the same time, upregulation of KAT6A partially restored the inhibitory effects of miR-143-3p mimic on the proliferation of HL-60 and K562 cells (Fig. 4d). In addition, miR-143-3p mimic remarkably decreased the protein expressions of PCNA and Ki67 in HL-60 and K562 cells, while upregulation of KAT6A partly rescued the effects (Fig. 4e). Moreover, miR-143-3p mimic decreased the expression levels of IL-1β, TNF-α and IL-6, and increased the expression levels of TGF-β and IL-10, while upregulation of KAT6A partially restored the effects displayed in Fig. 4f. These data suggested that KAT6A was a critical mediator linking the function of miR-143-3p to AML.

Discussion

KAT6A, also known as MOZ or MYST3, is located on chromosome 8p11, and contains 18 exons, encoding 2004 amino acids [24]. KAT6A protein, lysine acetyltransferase, belongs to the human MYST protein family [25]. Functionally, KAT6A acetylates cyclin-dependent kinase inhibitor p27kipl (p27), enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2), Akt serine/threonine kinase 1 (AKT1) and other tumor-related genes, and plays a direct role in transcriptional regulation [26,27]. Because of the acetylation and the role in transcriptional regulation, KAT6A is closely related to the occurrence and

development of tumors. For example, KAT6A is essential for the formation and maintenance of normal hematopoietic stem cells and is the target of recurrent chromosomal translocations, which result in AML [28–31]. In addition, heterozygous loss of KAT6A inhibits lymphoma progression [32]. KAT6A is known to suppress cellular senescence through the regulation of suppressors of the CDKN2A locus [33]. Thus, the opportunity to deliver therapeutic benefits, particularly in cancer and in a range of other disorders, will be realized through a systematic study on the detailed role and underlying mechanisms of KAT6A. As expected, our data showed that KAT6A was significantly upregulated in AML tissues, indicating that KAT6A might act as an oncogene in AML. Thus, we needed to further explore the molecular mechanisms of KAT6A in the development of AML. Downregulation of KAT6A remarkably inhibited the viability and proliferation of AML cells. Therefore, we tried to find the main factors that regulated KAT6A, becoming one of the new molecular biological markers for the diagnosis and treatment of AML.

Bioinformatics software was used to screen the upstream molecules of KAT6A, and miR-143-3p was selected, further confirmed by dual-luciferase reporter assay. MiRNAs are relatively conserved, noncoding and small molecular RNAs in organisms [34]. MiRNAs specifically bind to 3′-UTR of mRNA to inhibit the degradation or translation of target genes, thus achieving the goal of regulating the expression of target genes [35,36]. During AML, miRNAs exhibit significant effects on AML, acting as oncogenes or tumor suppressors. For example, downregulation of miR-9 retards the aggressive behaviors of AML cells by repressing CXCR4 [37]. Besides, miR-182-5p expression levels are higher in AML tissues. Suppression of miR-182-5p in AML cells decreases cell proliferation and promotes cell apoptosis by targeting BCL2 or BCL2L12 [38]. Therefore, miRNAs play an essential role in the biological physiology and pathology of AML, including cell proliferation, apoptosis and so on. More and more research show that miR-143-3p is abnormally expressed in various cancers. For instance, miR-143-3p expression is substantially lower in osteosarcoma (OS) tissues and cell lines and is lower in patients with poor prognoses. In addition, miR-143-3p inhibits OS cell proliferation and metastasis, while promoting apoptosis via targeting FOSL2 [39]. Besides, miR-143-3p is lowly expressed in breast cancer tissues and cells. Overexpression of miR-143-3p inhibits proliferation and induces apoptosis of breast cancer cells through negatively regulating MYBL2 [40]. Additionally, miR-143-3p is significantly decreased in ovarian cancer tissues and cell lines. Upregulation of miR-143-3p significantly reduces proliferation, migration, and invasion of ovarian cancer cells via targeting TAK1 [41]. Despite this, the role of miR-143-3p in AML remained unknown. Similarly, in our study, miR-143-3p was obviously downregulated in AML tissues and cell lines. Moreover, upregulation of miR-143-3p significantly inhibited the viability and proliferation of AML cells. Furthermore, the rescue experiment displayed that upregulation of KAT6A partially reversed the inhibitory effects of miR-143-3p mimic on viability and proliferation of AML cells.

To conclude, KAT6A was obviously upregulated, while miR-143-3p was notably downregulated in AML tissues and cell lines. In addition, downregulation of KAT6A significantly inhibited viability and proliferation of AML cells, which was negatively regulated by miR-143-3p. Taken together, miR-143-3p/KAT6A emerged as an effective target for treating AML patients, which provided a research basis for gene-targeted therapy of AML in the future.

Acknowledgements

The experimental protocol was established according to the ethical guidelines of the Helsinki Declaration and was approved by the Ethics Committee of Funing People's Hospital.

The authors consent for publication in the Journal.

All data generated or analyzed during this study are included in this published article.

Conflicts of interest

There are no conflicts of interest.

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