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Down-regulation of JARID1B expression inhibits cell proliferation, induces apoptosis and blocks cell cycle in human acute lymphoblastic leukemia cells

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Abstract. – OBJECTIVE: Acute lymphocytic leukemia (ALL) is a multi-factorial blood disease with unknown pathogenesis. Histone H3K4 methylation was significantly reduced in ALL patients, whereas jumonji AT-rich interactive domain 1B (JARID1B) was the specific demethylase of H3K4me. This study explores the expression level of JARID1B in ALL patients and down-regulated JARID1B expression in ALL cells to explore the function of JARID1B in ALL.

PATIENTS AND METHODS: JARID1B mRNA expression level in ALL patients was detected by Real-time PCR. The peripheral blood mononuclear cells from healthy volunteers were selected as control. JARID1B shRNA was transfected with MOLT-4 cells and BALL-1 cells. JARID1B protein expression and H3K4me2 and H3K4me3 levels were detected by Western blot assay. Cell proliferation was assessed by 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT) assay. Cell apoptosis and cell cycle were determined by flow cytometry. Bcl-2, Bax, Procaspase 3, and cyclin P21 expressions were evaluated by Western blot assay.

RESULTS: JARID1B mRNA expression in primary bone marrow cells from ALL patients was significantly higher than that of healthy volunteers ($p<0.05$). The levels of histone H3K4me3 and H3K4me2 were up-regulated after JARID1B shRNA transfection. JARID1B shRNA significantly inhibited the proliferation of MOLT-4 and BALL-1 cells, induced apoptosis, and blocked cell cycle in G0/G1 phase compared with the control group ($p<0.05$).

CONCLUSIONS: JARID1B is highly expressed in ALL. Down-regulating its expression inhibited leukemia cell proliferation, promoted apoptosis, and blocked cell cycle in G0/G1 phase through histone H3K4 methylation. JARID1B is an oncogene in ALL.

Key Words:
JARID1B, H3K4, Histone methylation, Acute lymphocytic leukemia.

Introduction

Acute lymphoblastic leukemia (ALL) is currently considered as B-line or/and T-line lymphoid progenitor cell abnormal proliferation and apoptosis caused by a variety of factors, leading to clonal cell proliferation. However, it is currently still unknown about the exact mechanism. Traditional genetics believed that histone only plays a role in maintaining the folding structure of DNA, whereas recent studies[1-3] found that the different modification state of histone terminal can change chromatin structure and development, which further affects active protein binding in the chromatin DNA to regulate DNA-related gene transcription.

Histone methylation is a type of histone modification, usually referring to the methylation formed on N-terminal arginine or lysine residues of H3 and H4 histone[4]. Histone methylation and demethylation were catalyzed by histone methyltransferase and histone demethylase, respectively. At present, dozens of histones demethylase have been found[5]. Jumonji AT-rich interactive domain 1B (JARID1B) (also known as KDM5B or PLU1) is a newly discovered histone demethylase that specifically reduces the degree of H3K4 methylation, thus inhibiting the transcription of the corresponding genes[6]. JARID1B shows high specificity in normal human tissues, mainly in spermatogonia of normal adult testes and cell meiosis[7,8]. In the previous study[9], we found that histone H3K4 methylation level was significantly reduced in patients with acute leukemia compared with non-leukemia patients and healthy controls. Since JARID1B was H3K4me-specific demethylase, whether its expression was also changed in ALL? This investigation explores the expression level of JARID1B in ALL patients and down-regulated JARID1B expression

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in ALL cells to explore the function of JARID1B in ALL. Therefore, the aim is to provide new targets for the treatment of ALL.

Patients and Methods

Sample Collection

A total of 30 cases of ALL patients were enrolled from September 2011 to December 2012 in Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou, China. The mononuclear cells were extracted from the bone marrow. There were 18 males and 12 females with a median age at 38.5 (15-73) years old. All patients were in line with Franch-American-Britain (FAB) and morphology-immunology-cytogenetics-molecular biology (MICM) international typing diagnostic criteria, including 24 cases in Common B, 1 case in Pre-B, 3 cases in Pro-B, and 2 cases in Mature B. Another 12 healthy volunteers were selected as the control group, including 7 males and 5 females with the median age of 27.5 (23-36) years old. This study was approved by the Medical Ethics Committee in Zhangzhou Affiliated Hospital of Fujian Medical University Zhangzhou, China.

Main Reagents

TRIzol Reagent was purchased from Invitrogen (Carlsbad, CA, USA). Roswell Park Memorial Institute-1640 (RPMI-1640) cell culture medium was purchased from HyClone (South Logan, UT, USA). RNA reverse transcription kit and Real-time PCR kit were purchased from TaKaRa Corporation (Dalian, China). Annexin-V/PI staining kit and cell cycle kit were purchased from BD (BD Biosciences, San Jose, CA, USA). Dimethyl-Histone H3 (Lys4), Trimethyl-Histone H3 (Lys4), JARID1B antibody, Bcl-2, Bax, Procaspase3, P21, β-actin antibodies were purchased from Abcam Biotech. (Cambridge, MA, USA).

Cell Line

ALL cell lines MOLT-4 and BALL were purchased from the Chinese Academy of Sciences Institute of Biochemistry and Cell Biology Shanghai Cell Bank (Shanghai, China).

ALL Patients Bone Marrow and Healthy Volunteers Mononuclear Cell Extraction

A total of 5 ml bone marrow samples were collected from the ALL patients. A total of 15 ml peripheral blood samples were obtained from healthy volunteers and add with a double volume of lymphocyte separation solution (Sigma-Aldrich, St. Louis, MO, USA). Next, the samples were centrifuged at 2500×g and room temperature for 20 min. After centrifugation, the specimen was divided into four layers, including plasma layer, mononuclear cell layer, liquid separation layer, and red blood cell and platelet. The mononuclear cell layer was collected as centrifuged at 2000×g for 5 min. The cell precipitation was stored at -80°C to extract RNA and protein.

Real-time PCR

The RNA was extracted by TRIzol method and reverse transcribed into complementary DNA (cDNA) using RNA reverse transcription kit (Invitrogen, Carlsbad, CA, USA). The Real-time PCR was performed by SYBR Premix Ex TaqII dye method on ABI 7900HT Real-time PCR amplifier (ABI, Foster City, CA, USA). β-actin was selected as loading control. JARID1B primer sequence: forward, 5'-CTCTCTTAGAGGTGCTGTG-3', reverse, 5'-CAGTCTCCTTGCTTTCAG-3'; β-actin primer sequence: forward, 5'-TTCTACAATGAGCTGCGTG-3', reverse, 5'-CTCAAACATGATCTGGGTC-3'. The reaction was performed at 95°C for 30 s, followed by 40 cycles of 95°C for 5 s and 60°C for 34 s. mRNA expression level was calculated by $2^{-\Delta\Delta Ct}$ method.

JARID1B Interference Adenovirus Vector

Adenovirus-JARID1B-RNAi-GFP interference adenovirus (JARID1B shRNA) was purchased from Heyuan Biotechnology Company (Shanghai, China). The sequence was GGAGCTATTCAATTAACTA.

3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium Bromide (MTT) Assay

MOLT-4 and BALL-1 cells in logarithmic phase were seeded on 96-well plate at 2×10^4/well. The cells were divided into Control, JARID1B shRNA, and neg shRNA groups. The MOI was 80. The cells were cultured at 37°C and 5% CO_2 after transfection. The cells were harvested at 24, 48, 72, and 96 h, respectively. A total of 20 µl MTT (5 mg/ml) was added to each well and incubated for 4 h. After centrifuged at 800 ×g for 10 min, the plate was added with 150 µl DMSO and tested at 570 nm to obtain the absorbance (OD) value. The experiment was repeated for three times.

Flow Cytometry

The cells were seeded in 6-well plate by Roswell Park Memorial Institute-1640 (RPMI-

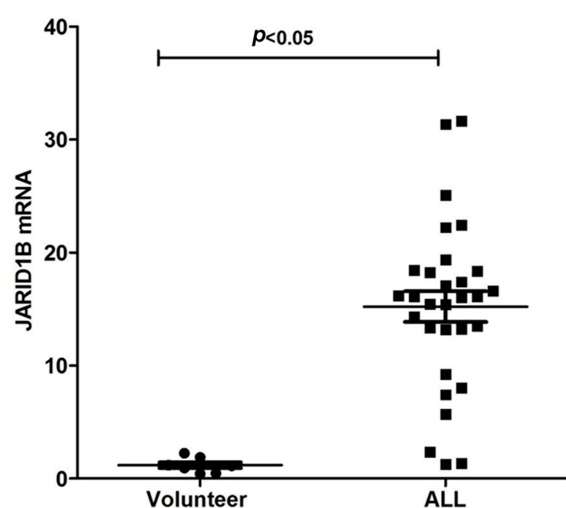

Figure 1. JARID1B mRNA expression in the primary bone marrow cells from ALL patients and healthy volunteers.

1640) medium containing 20% fetal bovine serum (FBS) at 2×10^6/well. The cells were divided into Control, JARID1B shRNA, and neg shRNA groups. The MOI was 80. The cells were cultured at 37°C and 5% CO_2 for 48 h after transfection. After centrifuged at 800×g at room temperature for 10 min, the cells were collected to stain Annexin-V/PI or propidium iodide (PI) (BD Biosciences, San Jose, CA, USA) and flow cytometry was performed (FACSCalibur, BD Company, San Jose, CA, USA).

Western Blot

The cell precipitation was washed with pre-cooling phosphate-buffered solution (PBS) twice and lysed by adding 100 μl lysate + 1 μl enzyme inhibitor (Sigma-Aldrich, St. Louis, MO, USA) for 30 min on ice. After centrifuged at 10000 × g at 10°C for 10 min, the protein was quantified by bicinchoninic acid (BCA) protein assay kit (Sigma-Aldrich, St. Louis, MO, USA). The protein was separated by 12% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) electrophoresis and transferred to membrane. After blocked at room temperature for 1 h, the membrane was incubated with primary antibody at 4°C overnight. After that, the membrane was washed with a Tris-buffered solution (TBS) and incubated with horseradish peroxidase (HRP) conjugated goat anti-mouse secondary antibody at 1:5000 (Santa Cruz Biotechnology, Santa Cruz, CA, USA). At last, the membrane was developed and analyzed by AlphaDigiDoc image analysis software (version 7.1; Alpha Innotec, Kasendorf, Germany).

Statistical Analysis

All data analyses were performed using SPSS19 software (IBM, Armonk, NY, USA). Homogeneity of variance test and normality test were routinely adopted. The data were presented as mean ± standard deviation. The Student's *t*-test was used to compare the differences between two groups. Tukey's post-hoc test was used to validate the ANOVA for comparing measurement data between groups. $p<0.05$ was depicted as statistical significance.

Results

JARID1B highly Expressed in the Primary Bone Marrow Cells from ALL Patients

To clarify the expression of JARID1B in ALL, we used Real-time PCR to detect the expression of JARID1B mRNA in primary bone marrow cells from 30 primary ALL patients and peripheral blood mononuclear cells from 6 healthy volunteers. JARID1B mRNA in ALL patients was significantly higher than that in the control group ($p<0.05$, Figure 1).

JARID1B shRNA Reduced JARID1B Expression and up-Regulated Histone H3K4 Methylation in MOLT-4 and BALL-1 Cells

JARID1B shRNA recombinant adenovirus was transfected into MOLT-4 cells for 48 h to test the expression of JARID1B mRNA by Real-time PCR. The results showed that the RQ value of JARID1B mRNA was 1.007 ± 0.008 in the JARID1B shRNA group, which was significantly lower than that of control group ($p<0.0001$). No statistical difference was observed between neg shRNA group and control group ($p>0.05$). The expression of JARID1B mRNA in BALL-1 cells was detected by Real-time PCR after transfection for 48 h. The results revealed that the RQ value of JARID1B mRNA in the JARID1B shRNA group was 0.084 ± 0.015, which was statistically lower than that of control ($p<0.05$). JARID1B protein level was decreased in JARID1B shRNA group, while histone H3K4me3 and H3K4me2 expressions were significantly increased compared with control group and neg shRNA group ($p<0.05$). The results demonstrated that JARID1B shRNA declined the expression of JARID1B gene and elevated the levels of H3K4me3 and H3K4me2 in MOLT-4 and BALL cells (Figure 2).

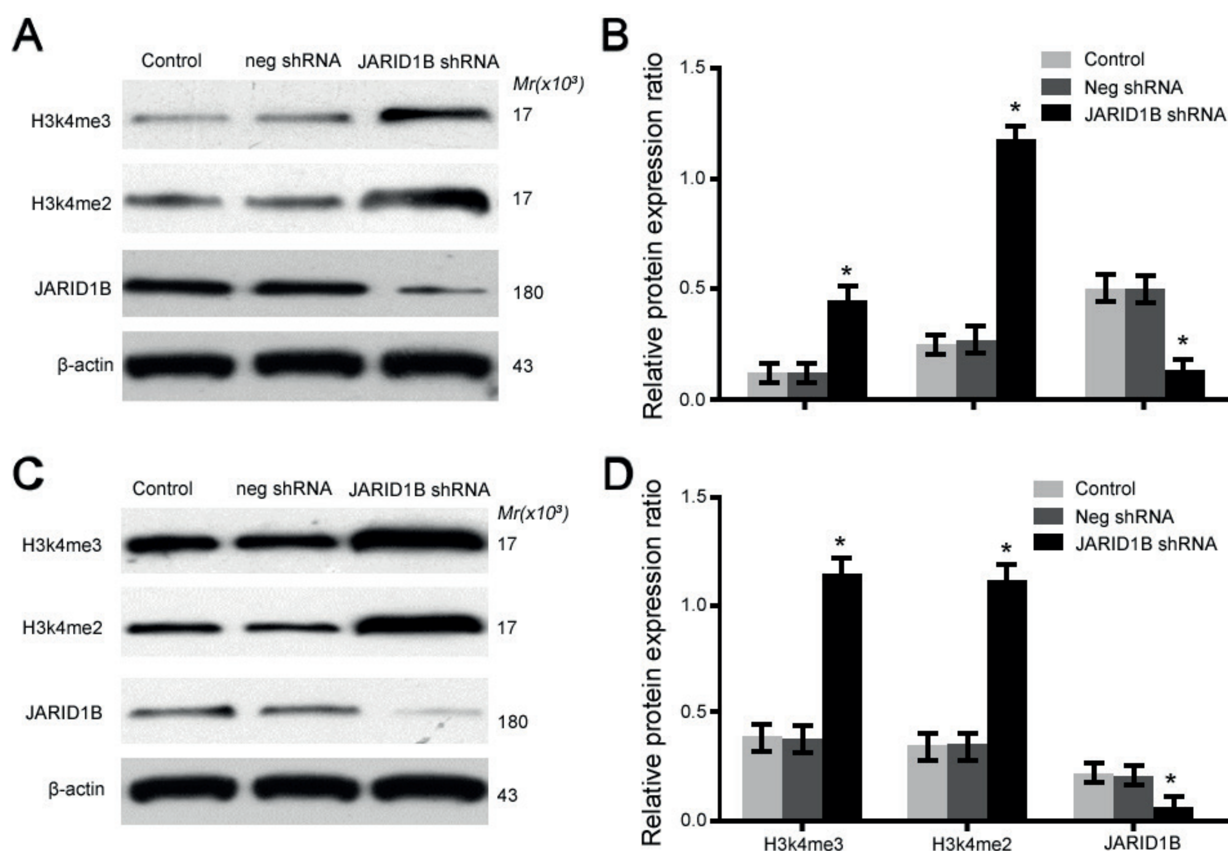

Figure 2. JARID1B shRNA reduced JARID1B expression and upregulated histone H3K4 methylation in MOLT-4 and BALL-1 cells. *$p<0.05$, compared with Control. A and B, MOLT-4 cell line; C and D, BALL-1 cell line.

JARID1B shRNA inhibited MOLT-4 and BALL-1 cell proliferation

MTT assay was applied to test MOLT-4 cell proliferation. At 48 h after JARID1B shRNA transfection, the OD value was 0.487 ± 0.046 in the JARID1B shRNA group, which was markedly lower than 0.965 ± 0.043 in the control and 0.887 ± 0.076 in the neg shRNA group ($p<0.05$) (Figure 3A). MTT assay was selected to test BALL-1 cell proliferation. At 48 h after JARID1B shRNA transfection, the OD value was 0.513 ± 0.039 in the JARID1B shRNA group, which was apparently lower than 1.096 ± 0.044 in the control and 1.021 ± 0.043 in the neg shRNA group ($p<0.05$) (Figure 3B).

JARID1B shRNA induced MOLT-4 and BALL-1 cell apoptosis

Flow cytometry was used to detect MOLT-4 cell apoptosis after JARID1B shRNA transfection. The cell apoptosis rate in the JARID1B shRNA group (28.62 ± 2.23%) was significantly higher than that in the control (2.08 ± 0.82%) and neg shRNA group (3.58 ± 0.93%) ($p<0.05$) (Figure 4A).

Flow cytometry was performed to determine BALL-1 cell apoptosis after JARID1B shRNA transfection. The cell apoptosis rate in the JARID1B shRNA group (22.52 ± 3.42%) was higher than that in the control (2.72 ± 0.52%) and neg shRNA group (3.27 ± 0.74%) ($p<0.05$) (Figure 4B).

JARID1B shRNA Arrested MOLT-4 and BALL-1 Cell Cycle in G0/G1 Phase

Flow cytometry was used to detect MOLT-4 cell cycle after JARID1B shRNA transfection. The cell rate in the G0/G1 phase of JARID1B shRNA group (67.54 ± 3.43%) was significantly higher than that in the control (53.54 ± 3.27%) and neg shRNA group (67.54 ± 3.43%) ($p<0.05$).

Flow cytometry was selected to assess BALL-1 cell cycle after JARID1B shRNA transfection. The cell rate in the G0/G1 phase of JARID1B shRNA group (56.82 ± 2.57%) was significantly higher than that in the control (44.28 ± 3.52%) and neg shRNA group (46.24 ± 3.47%) ($p<0.05$) (Figure 5).

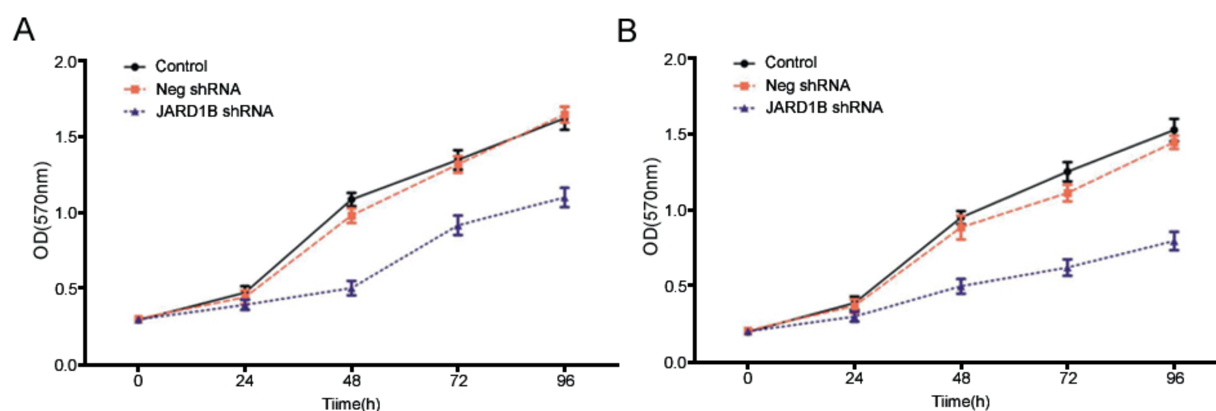

Figure 3. JARID1B shRNA inhibited MOLT-4 and BALL-1 cell proliferation. A, MOLT-4 cell line; B, BALL-1 cell line.

The Impact of JARID1B shRNA on Bcl-2, Bax, Procaspase3, and P21 Expressions

Bax and P21 expressions significantly increased, whereas Bcl-2 and Procaspase3 levels significantly down-regulated in MOLT-4 and BALL cells after JARID1B shRNA transfection compared with control ($p<0.05$) (Figure 6).

Discussion

The abnormality of histone methylation is closely related to the occurrence and development of tumor cells[10,11]. Histone methylation is catalyzed by histone methylase and demethylase synergistically, which is a dynamic modification process. There are many histone methyltransferases expressed abnormally in the tumor. EZH2 protein is the specific histone methylase of H3K27me3, which is found to be over-expressed in prostate cancer, bladder cancer, breast cancer, and many other tumors[12-14]. Histone methylase NSD2 can activate multiple myeloma-associated oncogenes by increasing H3K36me2 levels, leading to multiple myeloma[15]. H3K9me3 and its specific histone methylase Suv39h1 are found to be elevated in gastric cancer tissues and correlated with clinical stage[16].

JARID1B is a histone demethylase enzyme found in 2007 that specifically removes the methylation levels of H3K4me, H3K4me2, and H3K4me3. Since histone H3K4 methylation is a marker of gene transcriptional activation, JARID1B can inhibit the transcription of H3K4 by removing H3K4 methylation[17]. JARID1B shows high tissue specificity in normal human tissues, as its low expression in ovaries, lymph nodes, and other tissues, while high level in spermatogonia[7]. JARID1B inhibits the expression of multiple tumor suppressor genes, such as BRCA1, by mediating H3K4 demethylation, thus regulating

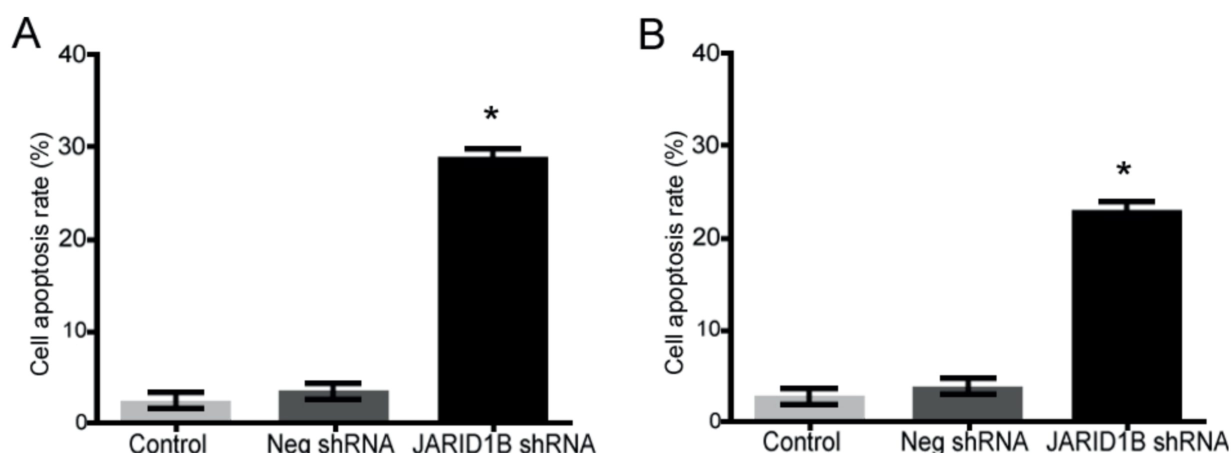

Figure 4. JARID1B shRNA induced MOLT-4 and BALL-1 cell apoptosis. A, MOLT-4 cell line; B, BALL-1 cell line. *$p<0.05$, compared with Control.

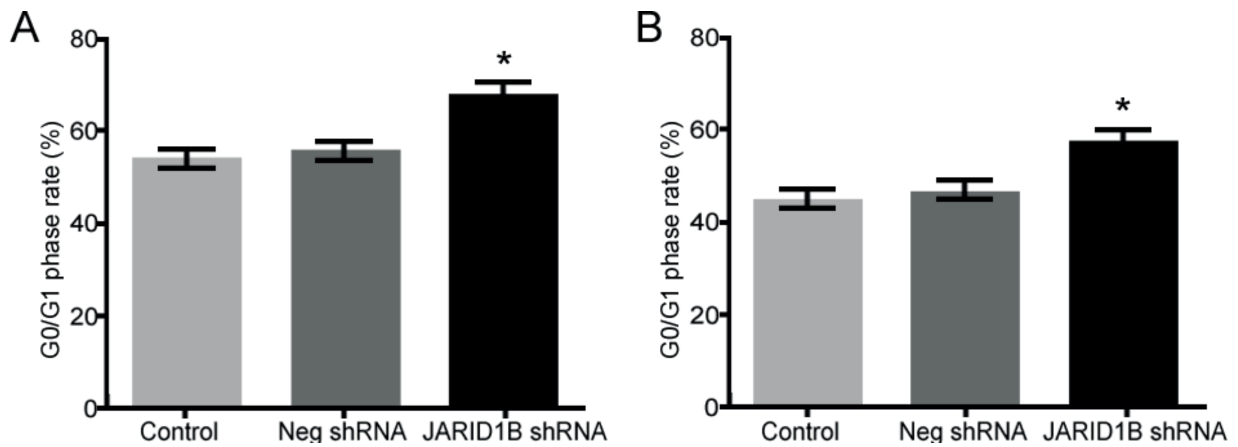

Figure 5. JARID1B shRNA arrested MOLT-4 and BALL-1 cell cycle in G0/G1 phase. ***A,*** MOLT-4 cell line; ***B,*** BALL-1 cell line. $^*p<0.05$, compared with Control.

Figure 6. The impact of JARID1B shRNA on Bcl-2, Bax, Procaspase3, and P21 expressions. ***A,*** MOLT-4 cell line; ***B,*** BALL-1 cell line. $^*p<0.05$, compared with Control.

cell cycle, cell differentiation, malignant transformation, and tumor formation. JARID1B also suppresses the transcription of related genes to be involved in the occurrence of tumor by recruiting the histone deacetylase to reduce acetylation of local histone[18]. It was found that JARID1B is highly expressed in prostate cancer tissue and related to prostate cancer metastasis and prognosis. Therefore, it is thought that the expression level of JARID1B gene can be used as a prognostic indicator of prostate cancer patients[6]. These studies suggest that JARID1B gene may be an effective target for tumor gene therapy. However, JARID1B exhibits different expression level in different tumor tissues. It plays an oncogene role in most tumor tissues[19,20], but inhibits tumorigenesis of malignant melanoma via the absence of expression[21]. Our previous work[22] also found that H3K4me3 methylation was low in mantle cell lymphoma and JARID1B was highly expressed as its specific demethylase. In this work, we also observed that JARID1 gene mRNA is highly expressed in the primary cells of bone marrow from ALL, suggesting it may be related to the pathogenesis of ALL.

In this investigation, the RQ value of JARID1B mRNA was 1.007 ± 0.008 in the JARID1B shRNA group of MOLT-4 cells, which was significantly lower than that of control group. The RQ value of JARID1B mRNA in the JARID1B shRNA group of BALL-1 cells was 0.084 ± 0.015, which was statistically lower than that of control. JARID1B protein level was decreased in JARID1B shRNA group, while histone H3K4me3 and H3K4me2 expressions were significantly increased compared with control group and neg shRNA group. JARID1B shRNA further restrained cell proliferation, enhanced cell apoptosis, and arrested cell cycle in G0/G1 phase. It was in accordance with our previous results in HL-60 and Jeko cells[23]. Lin et al[24] adopted drugs to inhibit JARID1B activity, thus to suppress oral cancer invasiveness and enhance radiotherapy sensitivity. In breast cancer MCF-7 cells, Mitra et al[25] silenced JARID1B gene to methylate H3K4, leading to cell cycle-related gene suppression, arrests cell cycle in G0/G1 phase, blocks cell proliferation, and inhibits colony formation, which was thought to be achieved by up-regulating BRCA1. In many stimulus-induced apoptosis, caspase-3 is the main effector protein, while procaspase-3 is the precursor form that cut the structural protein and regulation protein in the nucleus and cytoplasm[26,27]. The study also found that JARID1B shRNA can down-regulate Bcl-2 levels and increase Bax expression to change the Bcl-2/Bax ratio. It elevated procaspase 3 expression to induce cell apoptosis. P21 protein can inhibit the activity of CDK2, CDK4, and CDK6, so as to arrest cells in G0/G1 phase. Our results demonstrated that JARID1B shRNA can upregulate P21 protein to block cells in G0/G1 phase.

Conclusions

We showed JARID1B is highly expressed in ALL. Down-regulating its expression inhibited leukemia cell proliferation, promoted apoptosis, and blocked cell cycle in G0/G1 phase through histone H3K4 methylation. JARID1B is an oncogene in ALL.

Acknowledgments
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Conflict of Interest
The Authors declare that they have no conflict of interest.

References

1) Li B, Feng ZH, Sun H, Zhao ZH, Yang SB, Yang P. The blood genome-wide DNA methylation analysis reveals novel epigenetic changes in human heart failure. Eur Rev Med Pharmacol Sci 2017; 21: 1828-1836.
2) Strahl BD, Allis CD. The language of covalent histone modifications. Nature 2000; 403: 41-45.
3) Hake SB, Xiao A, Allis CD. Linking the epigenetic 'language' of covalent histone modifications to cancer, Br J Cancer 2004; 90: 761-769.
4) Lachner M, O'Sullivan RJ, Jenuwein T. An epigenetic road map for histone lysine methylation. J Cell Sci 2003; 116: 2117-2124.
5) Peters AH, Kubicek S, Mechtler K, O'Sullivan RJ, Derijck AA, Perez-Burgos L, Kohlmaier A, Opravil S, Tachibana M, Shinkai Y, Martens JH, Jenuwein T. Partitioning and plasticity of repressive histone methylation states in mammalian chromatin. Mol Cell 2003; 12: 1577-1589.
6) Xiang Y, Zhu Z, Han G, Ye X, Xu B, Peng Z, Ma Y, Yu Y, Lin H, Chen AP, Chen CD. JARID1B is a histone H3 lysine 4 demethylase up-regulated in prostate cancer. Proc Natl Acad Sci U S A 2007; 104: 19226-19231.
7) Barrett A, Madsen B, Copler J, Lu PJ, Cooper L, Scibetta AG, Burchell J, Taylor-Papadimitriou J. PLU-1

nuclear protein, which is upregulated in breast cancer, shows restricted expression in normal human adult tissues: a new cancer/testis antigen? Int J Cancer 2002; 101: 581-588.

8) Ahn A, Chatterjee A, Eccles MR. The slow cycling phenotype: a growing problem for treatment resistance in melanoma. Mol Cancer Ther 2017; 16: 1002-1009.

9) Zou Y, Ma X, Huang Y, Hong L, Chiao JW. Effect of phenylhexyl isothiocyanate on aberrant histone H3 methylation in primary human acute leukemia. J Hematol Oncol 2012; 5: 36.

10) Greer EL, Shi Y. Histone methylation: a dynamic mark in health, disease and inheritance. Nat Rev Genet 2012; 13: 343-357.

11) Latagliata R, Carmosino I, Breccia M, Minni A, Testi A, Iorio N, Lo-Coco F, Avvisati G, Petti MC, Mandelli F, Cimino G. Late relapses in acute promyelocytic leukaemia. Acta Haematol 2007; 117: 106-108.

12) Kleer CG, Cao Q, Varambally S, Shen R, Ota I, Tomlins SA, Ghosh D, Sewalt RG, Hayes DF, Sabel MS, Livant D, Weiss SJ, Rubin MA, Chinnaiyan. EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. Proc Natl Acad Sci U S A 2003; 100: 11606-11611.

13) Collett K, Eide GE, Arnes J, Stefansson IM, Eide J, Braaten A, Aas T, Otte AP, Akslen LA. Expression of enhancer of zeste homologue 2 is significantly associated with increased tumor cell proliferation and is a marker of aggressive breast cancer. Clin Cancer Res 2006; 12: 1168-1174.

14) Luan QX, Zhang BG, Li XJ, Guo MY. MiR-129-5p is downregulation in breast cancer cells partly due to promoter H3K27m3 modification and regulates epithelial-mesenchymal transition and multi-drug resistance. Eur Rev Med Pharmacol Sci 2016; 20: 4257-4265.

15) Kuo AJ, Cheung P, Chen K, Zee BM, Kioi M, Lauring J, Xi Y, Park BH, Shi X, Garcia BA, Li W, Gozani O. NSD2 links dimethylation of histone H3 at lysine 36 to oncogenic programming. Mol Cell 2011; 44: 609-620.

16) Cai L, Ma X, Huang Y, Zou Y, Chen X. Aberrant histone methylation and the effect of Suv39H1 siRNA on gastric carcinoma. Oncol Rep 2014; 31: 2593-2600.

17) Tan K, Shaw AL, Madsen B, Jensen K, Taylor-Papadimitriou J, Freemont PS. Human PLU-1 Has transcriptional repression properties and interacts with the developmental transcription factors BF-1 and PAX9. J Biol Chem 2003; 278: 20507-20513.

18) Sun LL, Sun XX, Xu XE, Zhu MX, Wu ZY, Shen JH, Wu JY, Huang Q, Li EM, Xu LY. Overexpression of Jumonji AT-rich interactive domain 1B and PHD finger protein 2 is involved in the progression of esophageal squamous cell carcinoma. Acta Histochem 2013; 115: 56-62.

19) Horton JR, Engstrom A, Zoeller EL, Liu X, Shanks JR, Zhang X, Johns MA, Vertino PM, Fu H, Cheng X. Characterization of a linked Jumonji domain of the KDM5/JARID1 family of histone H3 lysine 4 demethylases. J Biol Chem 2016; 291: 2631-2646.

20) Cui Z, Song L, Hou Z, Han Y, Hu Y, Wu Y, Chen W, Mao L. PLU-1/JARID1B overexpression predicts proliferation properties in head and neck squamous cell carcinoma. Oncol Rep 2015; 33: 2454-2460.

21) Roesch A, Vultur A, Bogeski I, Wang H, Zimmermann KM, Speicher D, Korbel C, Laschke MW, Gimotty PA, Philipp SE, Krause E, Patzold S, Villanueva J, Krepler C, Fukunaga-Kalabis M, Hoth M, Bastian BC, Vogt T, Herlyn M. Overcoming intrinsic multidrug resistance in melanoma by blocking the mitochondrial respiratory chain of slow-cycling JARID1B(high) cells. Cancer Cell 2013; 23: 811-825.

22) Su H, Ma X, Huang Y, Han H, Zou Y, Huang W. JARID1B deletion induced apoptosis in Jeko-1 and HL-60 cell lines. Int J Clin Exp Pathol 2015; 8: 171-183.

23) Wang H, Song C, Ding Y, Pan X, Ge Z, Tan BH, Gowda C, Sachdev M, Muthusami S, Ouyang H, Lai L, Francis OL, Morris CL, Abdel-Azim H, Dorsam D, Xiang M, Payne KJ, Dovat S. Transcriptional regulation of JARID1B/KDM5B histone demethylase by Ikaros, histone deacetylase 1 (HDAC1), and Casein Kinase 2 (CK2) in B-cell acute lymphoblastic leukemia. J Biol Chem 2016; 291: 4004-4018.

24) Lin CS, Lin YC, Adebayo BO, Wu A, Chen JH, Peng YJ, Cheng MF, Lee WH, Hsiao M, Chao TY, Yeh CT. Silencing JARID1B suppresses oncogenicity, stemness and increases radiation sensitivity in human oral carcinoma. Cancer Lett 2015; 368: 36-45.

25) Mitra D, Das PM, Huynh FC, Jones FE. Jumonji/ARID1 B (JARID1B) protein promotes breast tumor cell cycle progression through epigenetic repression of microRNA let-7e. J Biol Chem 2011; 286: 40531-40535.

26) Donovan M, Cotter TG. Control of mitochondrial integrity by Bcl-2 family members and caspase-independent cell death. Biochem Biphys Acta 2004; 1644: 133-147.

27) Wei J, Ma LS, Liu DJ, Guo J, Jiang WK, Yu HJ. Melatonin regulates traumatic optic neuropathy via targeting autophagy. Eur Rev Med Pharmacol Sci 2017; 21: 4946-4951.