

LINC00963 facilitates acute myeloid leukemia development by modulating miR-608/MMP-15

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ABSTRACT

Despite continuous improvements of AML therapy, the prognosis of AML patients remains unsatisfactory. Recently, lncRNAs have been reported to participate in the development of AML. Our data demonstrated that MMP15 and LINC00963 were upregulated and miR-608 was decreased in AML cells (THP-1, HL-60, HEL and MOLM-13) compared to HS-5 cells. RT-qPCR results showed that LINC00963 levels were higher in the serum and bone marrow of AML cases than in controls. Moreover, overexpression of LINC00963 promoted AML cell growth and EMT progression in both THP-1 and HL-60 cells. Furthermore, miR-608 levels were downregulated in the serum and bone marrow of AML cases compared with controls, and Pearson's correlation analysis indicated that LINC00963 was negatively correlated with miR-608 in the serum and bone marrow of AML samples. In addition, we demonstrated that LINC00963 sponged miR-608 expression and that MMP-15 was a target of miR-608 in AML cells. Finally, rescue experiments indicated that ectopic expression of LINC00963 accelerated cell growth and EMT development by modulating MMP-15. These data demonstrated that LINC00963 acted as an oncogene and may be a potential target for AML treatment.

INTRODUCTION

Acute myeloid leukemia (AML) remains the most prevalent hematological tumor [1–3]. AML is characterized by impaired interference and apoptosis, uncontrolled proliferation and differentiation in leukemic cells [4–6]. Several risk factors, including age, white blood cell count, cytogenetic risk and gene mutations, have been reported to be related to AML development [5, 7–9]. Despite progress in the treatment of AML, the overall survival rate is still unsatisfactory [10–12]. Thus, there is a need to identify novel molecular mechanisms and treatment targets for AML.

LncRNAs are widely found in mammals and are a group of noncoding RNA transcripts longer than 200 nt with little or no protein-coding ability [13–18]. Growing studies have illustrated that lncRNAs can act as

oncogenes or cancer suppressor genes in most tumors, including osteosarcoma, glioblastoma, gastric tumor, gallbladder carcinoma and AML [19–24]. Studies have suggested that lncRNAs play vital roles in a variety of cell activities, such as cell metabolism, invasion, differentiation and migration [25–30]. Recently, LINC00963, a newly discovered lncRNA, has been reported to be involved in the development of several tumors, such as breast cancer, ovarian tumors, esophageal tumors, cutaneous carcinoma, melanoma, hepatocellular carcinoma and prostate cancer [31–37]. However, the clinical relevance and cell function of LINC00963 in AML are still poorly characterized.

We first measured LINC00963 in AML cells, and RT-qPCR analysis demonstrated that LINC00963 was upregulated in AML cells (THP-1, HL-60, HEL and MOLM-13) compared to HS-5 cells. RT-qPCR analysis

showed that LINC00963 levels were higher in the serum and bone marrow of AML cases than in controls. Furthermore, overexpression of LINC00963 promoted AML cell growth and EMT progression in both THP-1 and HL-60 cells.

RESULTS

MMP15, LINC00963 and miR-608 levels in AML cells

First, RT-qPCR analysis was utilized to determine MMP15, LINC00963 and miR-608 levels in AML cells. MMP15 was overexpressed in AML cells (THP-1, HL-60, HEL and MOLM-13) compared with HS-5 cells

(Figure 1A). LINC00963 was upregulated in AML cells (THP-1, HL-60, HEL and MOLM-13) compared to HS-5 cells (Figure 1B). Moreover, miR-608 was decreased in AML cells (THP-1, HL-60, HEL and MOLM-13) compared to HS-5 cells (Figure 1C).

LINC00963 level in AML specimens

Then, we measured LINC00963 in the serum and bone marrow of AML cases and controls. The data illustrated that LINC00963 levels were higher in the bone marrow of AML cases than in controls (Figure 2A). Moreover, LINC00963 levels were upregulated in the serum of AML cases compared with controls (Figure 2B).

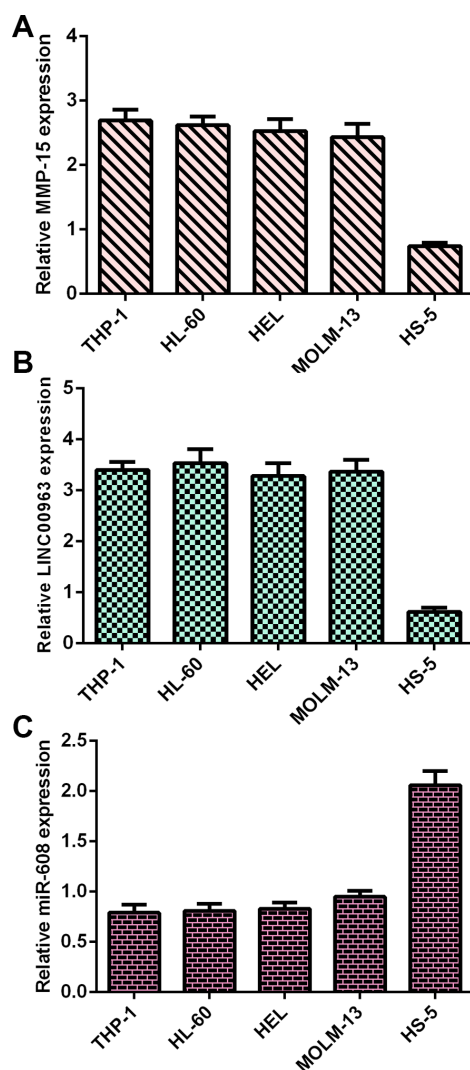


Figure 1. MMP15, LINC00963 and miR-608 levels in AML cells. (A) MMP15 was overexpressed in AML cells (THP-1, HL-60, HEL and MOLM-13) compared with HS-5 cells. GAPDH was used as the internal control. (B) The expression of LINC00963 was determined by RT-qPCR analysis. GAPDH was used as the internal control. (C) miR-608 was decreased in AML cells (THP-1, HL-60, HEL and MOLM-13) compared to HS-5 cells. U6 was used as the internal control for miR-608.

miR-608 level in AML specimens

Furthermore, we measured miR-608 in the serum and bone marrow of AML cases and controls. The results demonstrated that miR-608 levels were lower in the bone marrow of AML cases than in controls (Figure 3A). Pearson's correlation analysis indicated that LINC00963 was negatively correlated with miR-608 in the bone marrow of AML samples (Figure 3B). Moreover, miR-608 levels were downregulated in the serum of AML cases compared with controls (Figure 3C). Pearson's correlation analysis showed that LINC00963 was negatively correlated with miR-608 in the serum of AML samples (Figure 3D).

Overexpression of LINC00963 promoted AML cell growth and EMT progression

The level of LINC00963 was significantly upregulated in both AML cell lines THP-1 and HL-60 after treatment with pcDNA-LINC00963 (Figure 4A). The CCK-8 assay indicated that overexpression of LINC00963 accelerated cell growth in both THP-1 and

HL-60 cells (Figure 4B). Elevated expression of LINC00963 upregulated ki-67 expression in both THP-1 and HL-60 cells (Figure 4C). RT-qPCR assays illustrated that elevated expression of LINC00963 increased PCNA levels in both THP-1 and HL-60 cells (Figure 4D). Moreover, ectopic expression of LINC00963 enhanced Vimentin, N-cadherin and ZEB1 expression and decreased E-cadherin expression in both THP-1 and HL-60 cells (Figure 4E).

LINC00963 inhibited miR-608 expression in AML cells

An online database (starBase) predicted that miR-608 was a potential target of LINC00963 (Figure 5A). The level of miR-608 was significantly upregulated in THP-1 cells after treatment with the miR-608 mimic (Figure 5B). Luciferase reporter assays verified that elevated expression of miR-608 decreased the luciferase value in the LINC00963-wt group but did not change the luciferase value in the LINC00963-mut group (Figure 5C). Overexpression of LINC00963 suppressed miR-608 levels in THP-1 cells (Figure 5D).

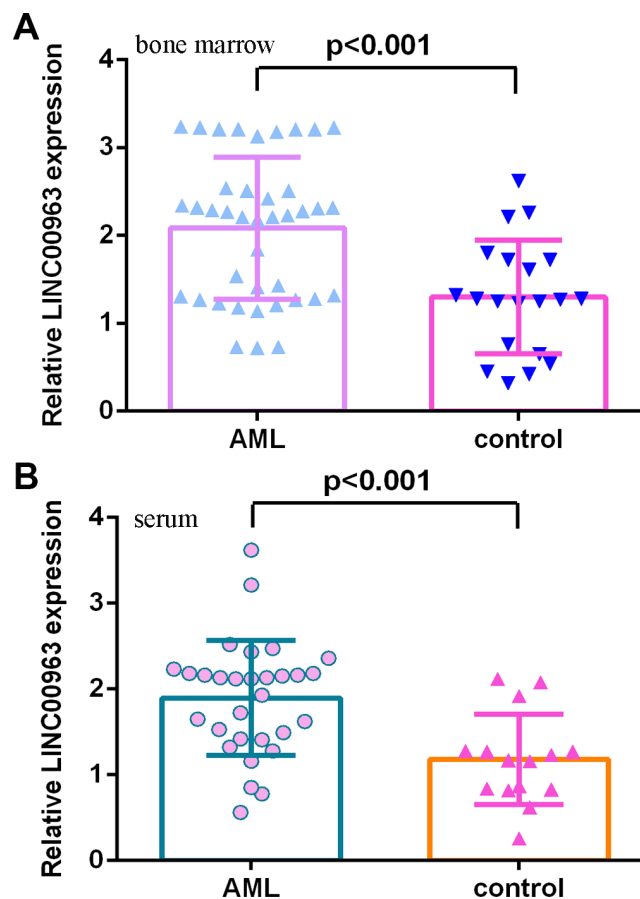


Figure 2. LINC00963 level in AML specimens. (A) LINC00963 levels were higher in the bone marrow of AML cases than in controls. (B) The expression of LINC00963 in the serum of AML cases and controls was measured by RT-qPCR. GAPDH was used as the internal control.

MMP-15 was a target of miR-608

An online database (TargetScan) predicted that MMP-15 was a potential target of miR-608 (Figure 6A). Luciferase reporter analysis verified that elevated expression of miR-608 decreased the luciferase value in the MMP-15-wt group but did not change the luciferase value in the MMP-15-mut group (Figure 6B). Overexpression of miR-608 suppressed MMP-15 levels in THP-1 cells (Figure 6C). Ectopic expression of LINC00963 up-regulated MMP-15 levels in THP-1 cells (Figure 6D).

Ectopic expression of LINC00963 increased cell growth and EMT development by modulating MMP-15

To further study the function of LINC00963 and MMP-15 in AML development, we treated LINC00963-overexpressing THP-1 cells with an siRNA-MMP-15 plasmid. MMP-15 expression was downregulated in THP-1 cells after treatment with the siRNA-MMP-15 plasmid, as demonstrated by RT-qPCR assay (Figure 7A). MMP-15

knockdown inhibited cell growth in LINC00963-overexpressing THP-1 cells (Figure 7B). Knockdown of MMP-15 suppressed ki-67 (Figure 7C) and PCNA levels (Figure 7D) in LINC00963-overexpressing THP-1 cells. Furthermore, downregulation of MMP-15 suppressed Vimentin, N-cadherin and ZEB1 levels and upregulated E-cadherin expression in LINC00963-overexpressing THP-1 cells (Figure 7E).

DISCUSSION

Despite continuous advances in AML therapy, the prognosis of AML patients remains unsatisfactory [38–40]. Recently, lncRNAs have been reported to participate in the development of AML [5, 19, 41–43]. This research explored the role of LINC00963 in the progression of AML. Our data showed that MMP15 and LINC00963 were upregulated and miR-608 was decreased in AML cells (THP-1, HL-60, HEL and MOLM-13) compared to HS-5 cells. RT-qPCR results demonstrated that LINC00963 levels were higher in the serum and bone marrow of AML cases than in controls.

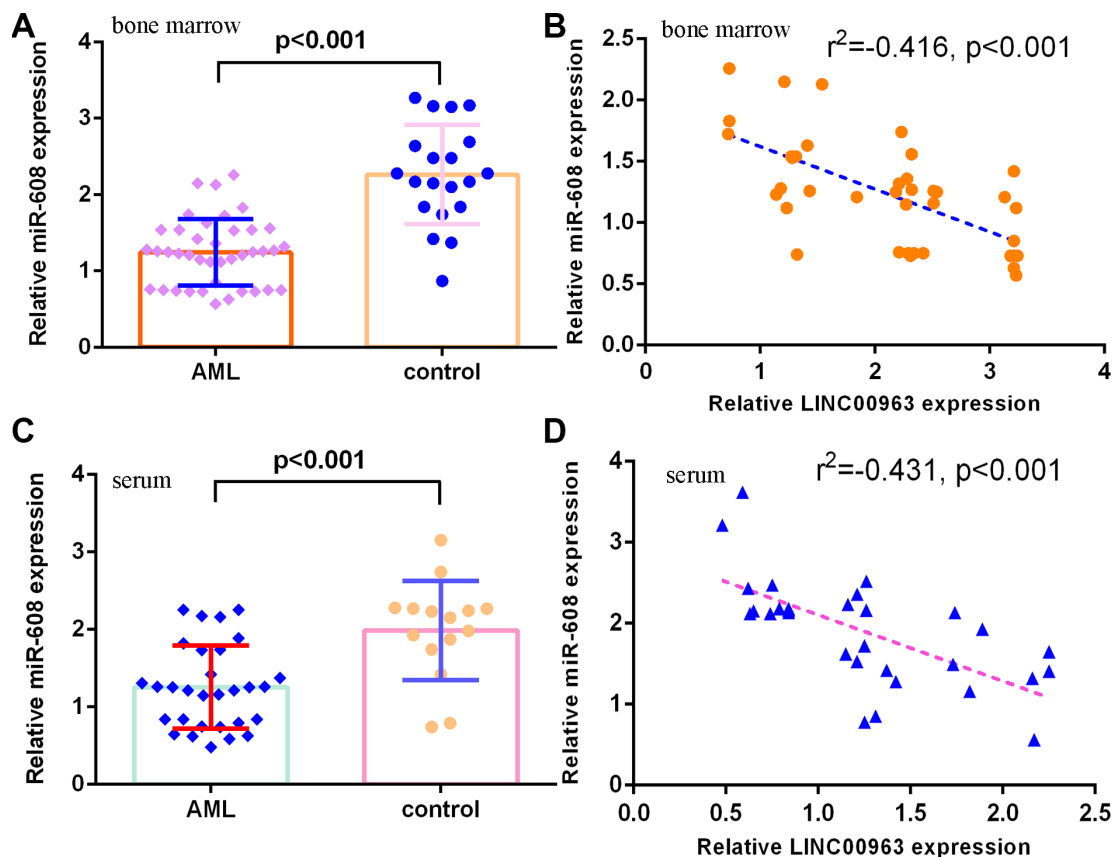


Figure 3. miR-608 levels in AML specimens. (A) The expression of miR-608 in the bone marrow of AML cases and controls was measured by RT-qPCR. (B) Pearson's correlation analysis indicated that LINC00963 was negatively correlated with miR-608 in the bone marrow of AML samples. (C) miR-608 levels were downregulated in the serum of AML cases compared with controls. (D) Pearson's correlation analysis showed that LINC00963 was negatively correlated with miR-608 in the serum of AML samples. U6 was used as the internal control.

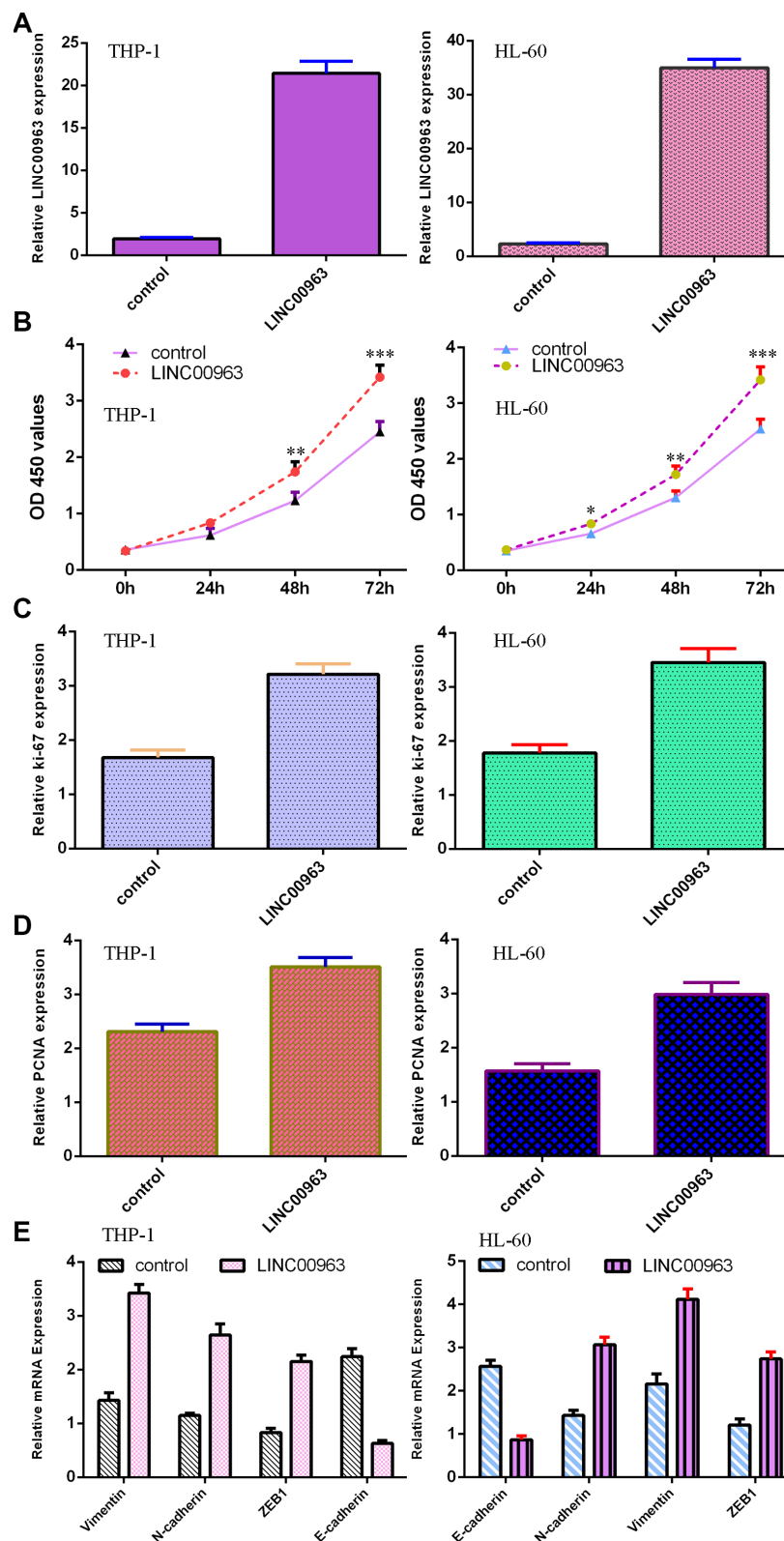


Figure 4. Overexpression of LINC00963 promoted AML cell growth and EMT progression. (A) The expression of LINC00963 was measured by RT-qPCR in both THP-1 and HL-60 AML cells. (B) CCK-8 assay showed that overexpression of LINC00963 accelerated cell growth in both THP-1 and HL-60 cells. (C) Elevated expression of LINC00963 facilitated ki-67 expression in both THP-1 and HL-60 cells. (D) RT-qPCR assay indicated that elevated expression of LINC00963 accelerated PCNA levels in both THP-1 and HL-60 cells. (E) Ectopic expression of LINC00963 enhanced Vimentin, N-cadherin and ZEB1 expression and decreased E-cadherin expression in both THP-1 and HL-60 cells. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$. GAPDH was used as the internal control.

Moreover, overexpression of LINC00963 promoted AML cell growth and EMT progression in both THP-1 and HL-60 cells. Moreover, miR-608 levels were downregulated in the serum and bone marrow of AML cases compared with controls, and Pearson's correlation analysis indicated that LINC00963 was negatively correlated with miR-608 in the serum and bone marrow of AML samples. In addition, we determined that LINC00963 sponged miR-608 expression and that MMP-15 was a target of miR-608 in AML cells. Finally, rescue experiments indicated that ectopic expression of LINC00963 accelerated cell growth and EMT development by modulating MMP-15. These data illustrated that LINC00963 acted as an oncogene and may be a potential target for AML cases.

Recently, LINC00963, a novel lncRNA, has been reported to be involved in the development of several tumors, such as breast cancer, ovarian tumors, esophageal tumors, cutaneous carcinoma, melanoma, hepatocellular carcinoma and prostate cancer [31–37]. Wu et al. [44] noted that LINC00963 was upregulated in breast tumor specimens, and higher levels of LINC00963 were associated with TNM stage, differentiation grade and lymph node metastasis. Knockdown of LINC00963 suppressed cell invasion and proliferation and accelerated apoptosis, partly regulating miR-625/HMGA1. Liu et al. [36] demonstrated that LINC00963 induced ovarian tumor EMT progression and growth by regulating CHI3L1/miR-378g. Liu et al. [35] noted that LINC00963 enhanced esophageal tumor invasion by modulating RAB14/miR-214-5p. Zhou et al. [45] indicated that LINC00963 accelerated osteosarcoma cell invasion and growth by inhibiting miR-204-3p/FN1. However, the

clinical relevance and cell function of LINC00963 in AML are still poorly characterized. We first measured LINC00963 in AML cells, and RT-qPCR analysis illustrated that LINC00963 was upregulated in AML cells (THP-1, HL-60, HEL and MOLM-13) compared to HS-5 cells. Then, we determined LINC00963 levels in the serum and bone marrow of AML cases and controls, and RT-qPCR analysis showed that LINC00963 levels were higher in the serum and bone marrow of AML cases than in controls. Furthermore, overexpression of LINC00963 promoted AML cell growth and EMT progression in both THP-1 and HL-60 cells.

A growing number of lncRNAs have emerged as ceRNAs that protect mRNAs from targeting by miRNAs [46, 47]. A previous study showed that LOC285758 induced AML cell invasion by inhibiting miR-204-5p [48]. Tian et al. [5] noted that lncRNA SBF2-AS1 regulated AML cell growth by regulating miR-188-5p. Gan et al. [49] showed that lncRNA ZFAS1 knockdown decreased AML development by modulating the miR-150/Myb/Sp1 pathway. Dong et al. [50] indicated that HOXA-AS2 knockdown inhibited AML chemoresistance by sponging miR-520c-3p/S100A4. Moreover, Jiao et al. [33] demonstrated that overexpression of LINC00963 facilitated melanoma development by sponging miR-608/NACC1. An online database (starBase) predicted that miR-608 was a potential target of LINC00963. Luciferase reporter assays verified that elevated expression of miR-608 decreased the luciferase value in the LINC00963-wt group but did not change the luciferase value in the LINC00963-mut group. These results indicated that LINC00963 inhibited miR-608 expression in AML cells.

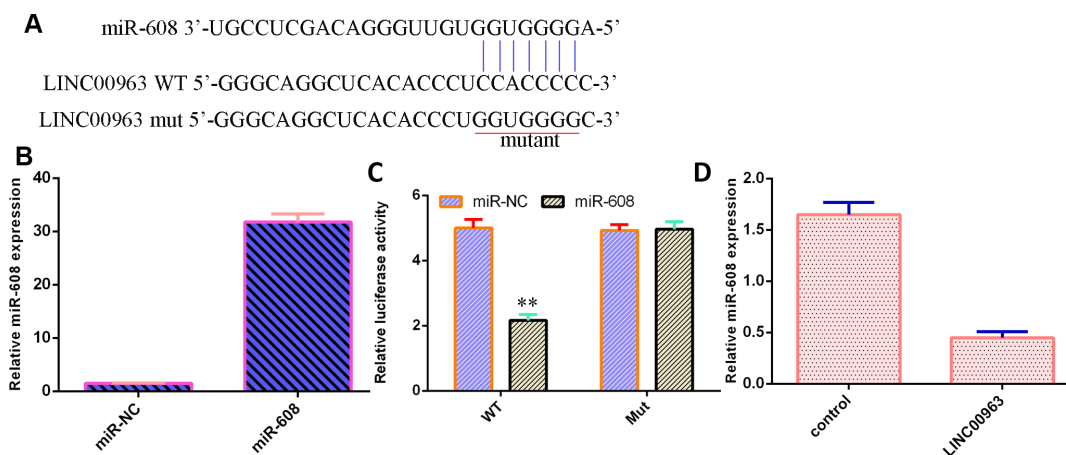


Figure 5. LINC00963 inhibited miR-608 expression in AML cells. (A) An online database (starBase) predicted that miR-608 was a potential target of LINC00963. (B) The level of miR-608 was determined by RT-qPCR. (C) Luciferase reporter assays verified that elevated expression of miR-608 decreased the luciferase value in the LINC00963-wt group but did not change the luciferase value in the LINC00963-mut group. (D) Overexpression of LINC00963 suppressed miR-608 levels in THP-1 cells. ** $p < 0.01$. U6 was used as the internal control.

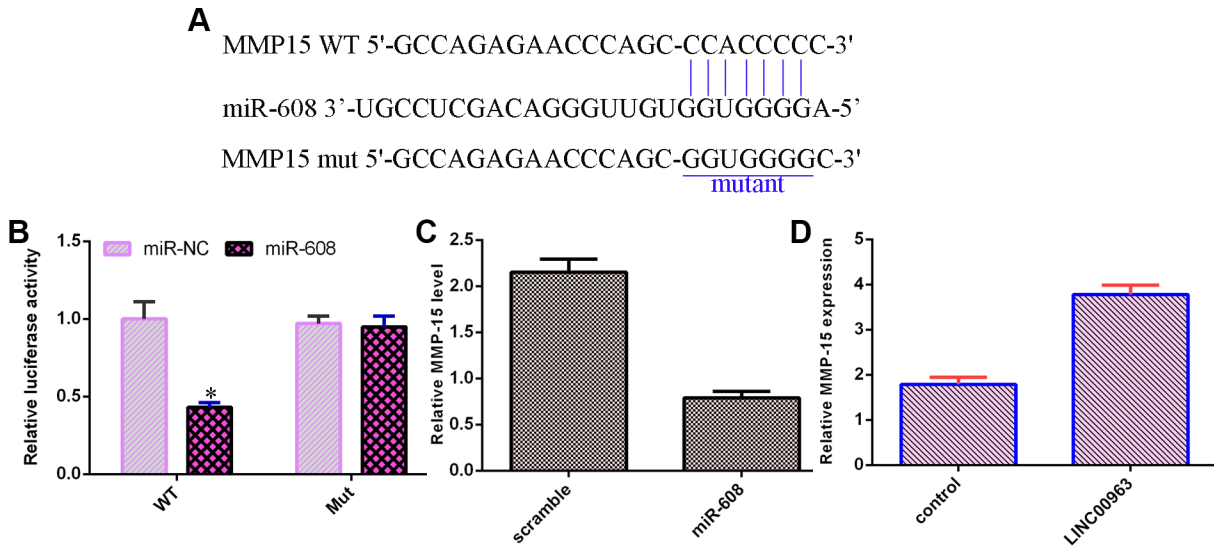


Figure 6. MMP-15 was a target of miR-608. (A) An online database (TargetScan) predicted that MMP-15 was a potential target of miR-608. (B) Luciferase reporter assays verified that elevated expression of miR-608 decreased the luciferase value in the MMP-15-wt group but did not change the luciferase value in the MMP-15-mut group. (C) Overexpression of miR-608 suppressed MMP-15 levels in THP-1 cells. (D) Ectopic expression of LINC00963 upregulated MMP-15 levels in THP-1 cells. * $p < 0.05$. GAPDH was used as the internal control.

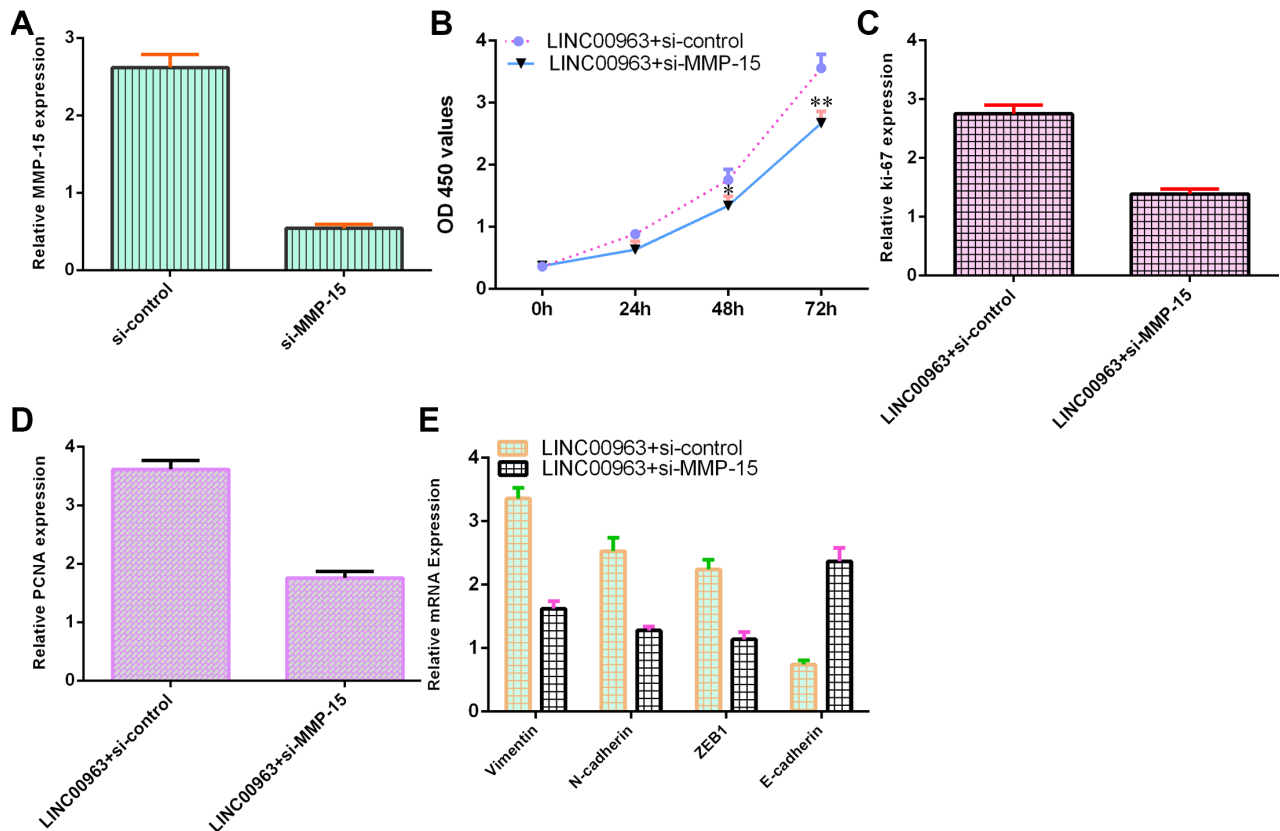


Figure 7. Ectopic expression of LINC00963 increased cell growth and EMT development by modulating MMP-15. (A) The level of MMP-15 was determined by RT-qPCR. (B) CCK-8 assay was performed to detect cell proliferation. (C) The level of ki-67 was measured by RT-qPCR. (D) The expression of PCNA was measured by RT-qPCR. (E) Downregulation of MMP-15 suppressed Vimentin, N-cadherin and ZEB1 levels and upregulated E-cadherin expression in LINC00963-overexpressing THP-1 cells. * $p < 0.05$ and ** $p < 0.01$. GAPDH was used as the internal control.

Furthermore, we identified MMP-15 as a target gene of miR-608 in AML cells. Wu et al. showed that MMP-15 was overexpressed in AML cells and in peripheral blood and bone marrow of AML. Our study demonstrated that ectopic expression of LINC00963 accelerated cell growth and EMT development by modulating MMP-15.

Our results illustrated that LINC00963 was upregulated in AML cells and that LINC00963 levels were higher in the serum and bone marrow of AML cases than in controls. Ectopic expression of LINC00963 accelerated cell growth and EMT development by modulating the miR-608/MMP-15 axis.

MATERIALS AND METHODS

Specimens, cell culture and transfection

Serum and bone marrow samples were obtained from AML patients and control cases at the Affiliated Cancer Hospital of Zhengzhou University. Our research was approved by the Clinical Ethics Committees Board of the Affiliated Cancer Hospital of Zhengzhou University, and written informed consent was obtained from each participant. HS-5 and AML cells (THP-1, HL-60, HEL and MOLM-13) were obtained from ATCC and cultured in RPMI-1640 medium supplemented with antibiotics and FBS. miR-608 mimic, siRNA-MMP-15, pcDNA-LINC00963 and controls were purchased from Genema and transfected using Lipofectamine™2000.

Cell proliferation assays

Cell growth was determined with a CCK-8 assay (Dojindo, Japan). Cells were cultured in 96-well plates and measured at 0, 1, 2 and 3 days. The cell number was determined from the optical density (OD) at 450 nm.

RT-qPCR

Total RNA from all specimens and cells was isolated with a TRIzol kit (Ambion, USA). For mRNA, miRNA and lncRNA expression, RT-qPCR was used on an ABI7500 PCR system (Applied Biosystems, USA) using a SYBR kit (TaKaRa, China). The fold change of these genes was determined with the $2^{-\Delta\Delta C_t}$ method. U6 and GAPDH were used as controls. The primer sequences were as follows: LINC00963, 5'-GGTAA ATCGA GGCC AGAGAT-3' (F), 5'-ACGTG GATGA CAGCG TGTGA-3' (R); GAPDH, 5'-CATGA GAAGT ATGAC AACAG CCT-3' (F), 5'-AGTCC TTCCA CGATAC CAAAGT-3' (R); miR-608 5'-AGGGG TGGTG TTGGG ACAGC-3'; and U6, 5'-GCGCG TCGTG AAGCG TTC-3' (F), 5'-GTGCA GGGTC CGAGG -3' (R).

Luciferase reporter assay

For the luciferase reporter assay, wild-type LINC00963 and wild-type MMP-15 (LINC00963-wt and MMP-15-wt) or sequences with mutant binding sites (LINC00963-mut and MMP-15-mut) were cloned downstream of the Renilla luciferase gene in the pRLTK vector (Promega, USA). Each vector was cotransfected into cells with miR-608 mimic or control (RiboBio, China). Luciferase analysis was carried out with a dual luciferase detection reagent (Promega, USA), and the relative luciferase value was calculated from Renilla luciferase activity.

Statistical analysis

The data values are presented as the mean \pm SD. Analysis of statistical differences was assessed with Student's t-test using SPSS 18.0 (Chicago, USA). The significance level was set at $P < 0.05$. Spearman's correlation analysis was performed to study the correlation.

Editorial note

*This corresponding author has a verified history of publications using a personal email address for correspondence.

AUTHOR CONTRIBUTIONS

Concept and Supervision - Wenli Zuo, Keshu Zhou, Mei Deng; Study Design - Jian Zhou, Yongping Song; Resource and Materials - Yongping Song; Data Collection and/or Processing - Wenli Zuo, Keshu Zhou, Yongping Song; Analysis and/or Interpretation - Wenli Zuo, Keshu Zhou, Yongping Song; Literature Search - Quande Lin, Qingsong Yin, Chunlei Zhang; Writing - Wenli Zuo, Keshu Zhou, Mei Deng; Critical Reviews - Wenli Zuo, Chunlei Zhang, Jian Zhou, Yongping Song.

CONFLICTS OF INTEREST

All the authors in this paper declared that we have no conflicts of interest to this work.

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