Original Article

LncRNA MVIH knockdown inhibits the malignancy progression through downregulating *miR-505* mediated *HMGB1* and *CCNE2* in acute myeloid leukemia

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Background: This study aimed to investigate the regulatory role of *long non-coding RNA associated with microvascular invasion in hepatocellular carcinoma* (*lnc-MVIH*) in the progression of acute myeloid leukemia (AML) and the underlying mechanism.

Methods: *Lnc-MVIH* expression was detected in AML cell lines AML-193, KG-1, HL-60, OCI-AML2 and primary normal bone marrow mononuclear cells (BMMC). The effect of *lnc-MVIH* knockdown on cell proliferation, apoptosis and *miR-505* expression were detected by transfection of *lnc-MVIH* shRNA and control shRNA into KG-1 cells. And the effect of *miR-505* knockdown on *lnc-MVIH*, cell proliferation, cell apoptosis as well as potential *miR-505* target genes [*high mobility group box 1* (*HMGB1*) and *cyclin E2* (*CCNE2*)] in *lnc-MVIH* knockdown treated KG-1 cells was assessed by transfection of *lnc-MVIH* shRNA and *lnc-MVIH* shRNA & *miR-505* shRNA into KG-1 cells.

Results: *Lnc-MVIH* expression was elevated in AML-193, KG-1, OCI-AML2 cell lines, but similar in HL-60 cell line compared with primary normal BMMC. *Lnc-MVIH* knockdown inhibited cell proliferation but promoted cell apoptosis in KG-1 cells, meanwhile *miR-505* expression was increased by *lnc-MVIH* knockdown in KG-1 cells. And in rescue experiments, *miR-505* knockdown had no effect on expression of *lnc-MVIH*, while it increased the expressions of *HMGB1* and *CCNE2*, promoted cell proliferation, inhibited cell apoptosis in *lnc-MVIH* knockdown treated KG-1 cells.

Conclusions: *Lnc-MVIH* knockdown inhibits cell proliferation but promotes cell apoptosis via regulating *miR-505* mediated *HMGB1* and *CCNE2* in AML.

Keywords: Acute myeloid leukemia (AML); apoptosis; *long non-coding RNA associated with microvascular invasion in hepatocellular carcinoma* (*lnc-MVIH*); *miR-505*; proliferation

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Introduction

Acute myeloid leukemia (AML) is a hematological malignancy characterized by malignant transformation of clonal neoplastic hematopoietic stem cells as well as the impaired normal hematopoiesis in the bone marrow and peripheral blood (1). Current therapies for AML commonly consist of intensive induction chemotherapy, stem cell transplantation and post-remission consolidation, which contributes to the complete remission of approximately 50–70% of adults with AML. However, only 20% of

patients with AML enjoy long-term disease-free survival, and refractory or relapsed AML is the main cause of AML mortality (2,3). Existing evidence indicates that insight into genetic background of AML that foster the extensive understanding of AML pathology might lead to development of specific targeted therapy (4,5). Therefore, it is necessary to investigate the mechanism underlying the development and progression of AML to explore new therapeutic strategies.

Long non-coding RNAs (lncRNA) are defined as RNAs longer than 200 nucleotides, which participate in multiple stages of gene regulation including chromatin modification, regulation of protein modification, chromatin structure, and so on (6,7). Increasing number of researches reveal that lncRNAs also play important roles in diverse human diseases, especially cancers, and some lncRNAs, such as *lnc-CCAT1*, *lnc-HOTAIR*, are reported to exert functions through interacting with microRNA (miRNA) at the post-transcriptional level in AML (6,8,9). Recently, increasing studies indicate that *lncRNA associated with microvascular invasion in hepatocellular carcinoma* (*lnc-MVIH*) is upregulated and participates in the progression and development of several solid cancers, such as breast cancer, non-small cell lung cancer and hepatocellular carcinoma (10-13). However, little is known about its role in hematological malignancies. In addition, *lnc-MVIH* contains target sites for *miR-505* as retrieved from miRanda database analysis (www.miranda.org), which is a tumor suppressor in several malignancies including chronic myeloid leukemia (14-16). Therefore, we hypothesized that *lnc-MVIH* might interact with *miR-505* as well as *miR-505* downstream target genes and regulate AML progression. In the present study, we investigated the regulatory role of *lnc-MVIH* in AML progression and the underlying mechanism, aiming to provide a novel insight of potential therapeutic targets in AML (17,18).

Methods

Cell sources and culture

Human AML cell lines AML-193, KG-1, HL-60 and OCI-AML2 were purchased from Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures (Braunschweig, German). AML-193 cells were cultured in 90% Iscove's Modified Dulbecco's Medium (Gibco, USA) and 10% fetal bovine serum (Gibco, USA); KG-1 and HL-60 cells were cultured in 90% Roswell Park Memorial Institute (RPMI) 1640 Medium (Gibco, USA) and 10% fetal bovine serum (Gibco, USA); OCI-AML2 were cultured in 90% Minimum Essential Medium (MEM) (Gibco, USA) and 10% fetal bovine serum (Gibco, USA).

Lnc-MVIH expression in AML cell lines and primary normal bone marrow mononuclear cells (BMMC)

Lnc-MVIH expression in AML cell lines AML-193, KG-1, HL-60 and OCI-AML2 was detected using real-time quantitative polymerase chain reaction (RT-qPCR). Besides, primary normal human BMMC was purchased from American type culture collection (Manassas, USA) and lnc-MVIH in BMMC was detected by RT-qPCR as control.

Lnc-MVIH expression in CD34$^+$ AML cells and wild AML cell lines

CD34$^+$ AML cells were separated from wild AML cell lines (AML-193, KG-1, HL-60, OCI-AML2) using Dynabeads CD34$^+$ Positive Isolation Kit (Thermo, USA) according to the instructions of the manufacture, and *lnc-MVIH* expression in CD34$^+$ AML cells and wild AML cells was detected using RT-qPCR.

Effect of lnc-MVIH knockdown on cell proliferation, apoptosis and potential target miR-505

Control shRNA [Control(–) group] and *lnc-MVIH* shRNA [lnc-MVIH(–) group] were constructed by Shanghai GenePharma Bio-Tech Company (Shanghai, China) using pGPH1 vector and transfected into KG-1 cells. *Lnc-MVIH* expression was detected at 24 h by RT-qPCR, cell proliferation was detected at 0, 24, 48, and 72 h by Counting Kit-8 (CCK-8) (Dojindo, Japan), cell apoptosis rate was detected at 24 h by Annexin V-FITC Apoptosis Detection Kit (BD, USA), potential target *miR-505* was predicted using miRanda database analysis (www.miranda.org) and detected at 24 h by RT-qPCR, respectively.

Effect of miR-505 knockdown on attenuating lnc-MVIH knockdown functions

Lnc-MVIH shRNA [Lnc-MVIH(–) group], and *lnc-MVIH* shRNA plus *miR-505* shRNA [Lnc-MVIH(–)&miR-505(–) group] were constructed by Shanghai GenePharma Bio-Tech Company (Shanghai, China) using pGPH1 vector and transfected into KG-1 cells. *Lnc-MVIH* and *miR-505* expressions were detected at 24 h by RT-qPCR, *miR-505*

Table 1 Primers applied in qPCR

Gene	Forward primer (5'-3')	Reverse primer (5'-3')
Lnc-MVIH	AATTTTGCACATCTGAACAGCC	TTCAAAATCCCACTACGCCCA
HMGB1	TTCTTCCTCTTCTGCTCTGAGTATC	TTCATAAGGCTGCTTGTCATCTG
CCNE2	GCTGCTGCCTTGTGCCATT	GTGCTCTTCGGTGGTGTCATAA
GAPDH	GACCACAGTCCATGCCATCAC	ACGCCTGCTTCACCACCTT
MiR-505	ACACTCCAGCTGGGGGGAGCCAGGAAGTAT	TGTCGTGGAGTCGGCAATTC
U6	CGCTTCGGCAGCACATATACTA	ATGGAACGCTTCACGAATTTGC

Table 2 Antibodies applied in Western blot

Antibody	Company	Dilution
Primary antibody		
Rabbit monoclonal to HMGB1	Abcam (UK)	1:2,000
Rabbit monoclonal to Cyclin E2	Abcam (UK)	1:2,000
Rabbit monoclonal to GAPDH	Abcam (UK)	1:3,000
Secondary antibody		
Goat anti-rabbit IgG H&L (HRP)	Abcam (UK)	1:5,000

target genes including *high mobility group box 1* (*HMGB1*) and *cyclin E2* (*CCNE2*) were detected at 24 h by RT-qPCR and Western Blot, cell proliferation was detected at 0, 24, 48, and 72 h by CCK-8 (Dojindo, Japan), cell apoptosis rate was detected at 24 h by Annexin V-FITC Apoptosis Detection Kit (BD, USA).

RT-qPCR

Total RNA was extracted from cells using TRIzol™ Reagent (Invitrogen, USA) and then reversely transcribed to cDNA using RT-PCR Quick Master Mix (Toyobo, Japan). Following that, RT-qPCR was performed using SYBR® Green Realtime PCR Master Mix (Toyobo, Japan) to quantify *lnc-MVIH*, *miR-505*, *HMGB1* and *CCNE2* expressions. The result was calculated using $2^{-\Delta\Delta Ct}$ method with GAPDH as an internal reference. The primers used in RT-qPCR were listed in *Table 1*.

Western blot

Total protein was extracted with RIPA Buffer (Sigma, USA). The protein concentration in each sample was then measured using the Pierce™ Rapid Gold BCA Protein Assay Kit (Thermo, USA). Twenty ug protein samples were added to NuPAGE™ 4–12% Bis-Tris Protein Gels (Thermo, USA) and transferred onto polyvinylidene fluoride membrane (Millipore, German). After blocking with BSA (Thermo, USA) for 2 h, the membranes were incubated with the primary antibodies overnight at 4 ℃. Then, the membranes were incubated with the secondary antibody for 90 min at 37 ℃. EasyBlot ECL kit (Sangon, China) was used to illuminized the bands and X-ray film (Kodak, USA) was used to visualize the result. The antibodies used in this study were summarized in *Table 2*.

Statistics

GraphPad 7.01 (GraphPad Int., USA) was used for statistical analysis and drawing images. Data were mainly presented as mean ± standard deviation, and compared by One-way ANOVA test followed by multiple comparisons test or *t* test. P<0.05 was considered as significant.

Results

The relative expression of lnc-MVIH in AML cell lines and primary normal BMMC

The relative expression of *lnc-MVIH* was elevated in AML-193 (P<0.05), KG-1 (P<0.001), OCI-AML2 (P<0.001) cells, but similar in HL-60 (P>0.05) cells compared with primary normal BMMC (*Figure 1*), indicating that *lnc-MVIH* was upregulated in AML cell lines.

The relative expression of lnc-MVIH in CD34⁺ and wild AML cells

The relative expression of *lnc-MVIH* was elevated in CD34⁺ AML-193 cells compared with wild AML-193 cells (P<0.05),

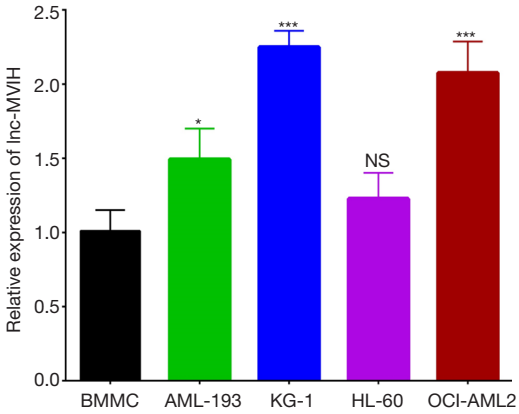

Figure 1 *Lnc-MVIH* expression in AML cells and primary normal BMMC. The comparison of *lnc-MVIH* expression between human AML cell lines and primary normal BMMC was detected by One-Way ANOVA followed by Dunnett's multiple comparisons test, which indicated that *lnc-MVIH* expression was elevated in AML-193, KG-1 and OCI-AML2 cell lines, but similar in HL-60 cell lines compared to primary normal BMMC. P<0.05 was considered significant. NS, non-significant; *, P<0.05; ***, P<0.001. *Lnc-MVIH*, *long non-coding RNA associated with microvascular invasion in hepatocellular carcinoma;* AML, acute myeloid leukemia; BMMC, bone marrow mononuclear cells.

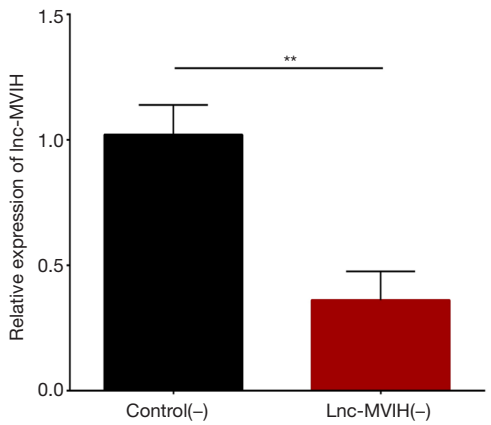

Figure 2 *Lnc-MVIH* knockdown decreased *lnc-MVIH* expression in KG-1 cells. *Lnc-MVIH* knockdown decreased *lnc-MVIH* expression compared to control, which indicated the successful transfection. The comparison of *lnc-MVIH* expression between *lnc-MVIH* shRNA group and control was conducted by *t*-test. P<0.05 was considered significant. **, P<0.01. *Lnc-MVIH*, *long non-coding RNA associated with microvascular invasion in hepatocellular carcinoma*.

and was also increased in $CD34^+$ KG-1 cells compared with wild KG-1 cells (P<0.01), while similar between $CD34^+$ HL-60 cells and wild HL-60 cells (P>0.05), between $CD34^+$ OCI-AML2 cells and wild OCI-AML2 cells (P>0.05) (*Figure S1*).

The relative expression of lnc-MVIH after transfection

The expression of *lnc-MVIH* was decreased in *lnc-MVIH*(–) group compared with Control(–) group, which indicated the successful transfection of *lnc-MVIH* shRNA (P<0.01) (*Figure 2*).

Effect of lnc-MVIH knockdown on cell proliferation and apoptosis in KG-1 cells

Cell proliferation was decreased in *lnc-MVIH*(–) group at 48 h (P<0.05) and 72 h (P<0.05), but unchanged at 0 h (P>0.05) and 24 h (P>0.05) compared with Control(–) group (*Figure 3A*). Cell apoptosis rate was increased in *Lnc-MVIH*(–) group compared with Control(–) group at 24 h (P<0.01) (*Figure 3B,C*). These data suggested that *lnc-MVIH* knockdown suppressed cell proliferation but promoted cell apoptosis in AML.

The relative expression of miR-505 after transfection in KG-1 cells

The relative expression of *miR-505* was elevated in *lnc-MVIH*(–) group compared with Control(–) group after transfection (P<0.01), which indicated that *lnc-MVIH* knockdown promoted *miR-505* expression in AML (*Figure 4*).

The effect of miR-505 knockdown on HMGB1 and CCNE2 expressions in lnc-MVIH knockdown treated KG-1 cells

The rescue experiments were conducted to explore the effect of *miR-505* knockdown on *HMGB1* and *CCNE2* expressions in lnc-MVIH knockdown treated KG-1 cells. Firstly, we observed that the relative expression of *miR-505* was decreased in *lnc-MVIH*(–) & *miR-505*(–) group compared with *lnc-MVIH*(–) group (P<0.01), which indicated the successful transfection of *miR-505* shRNA (*Figure 5A*). Then the relative expression of *lnc-MVIH* was

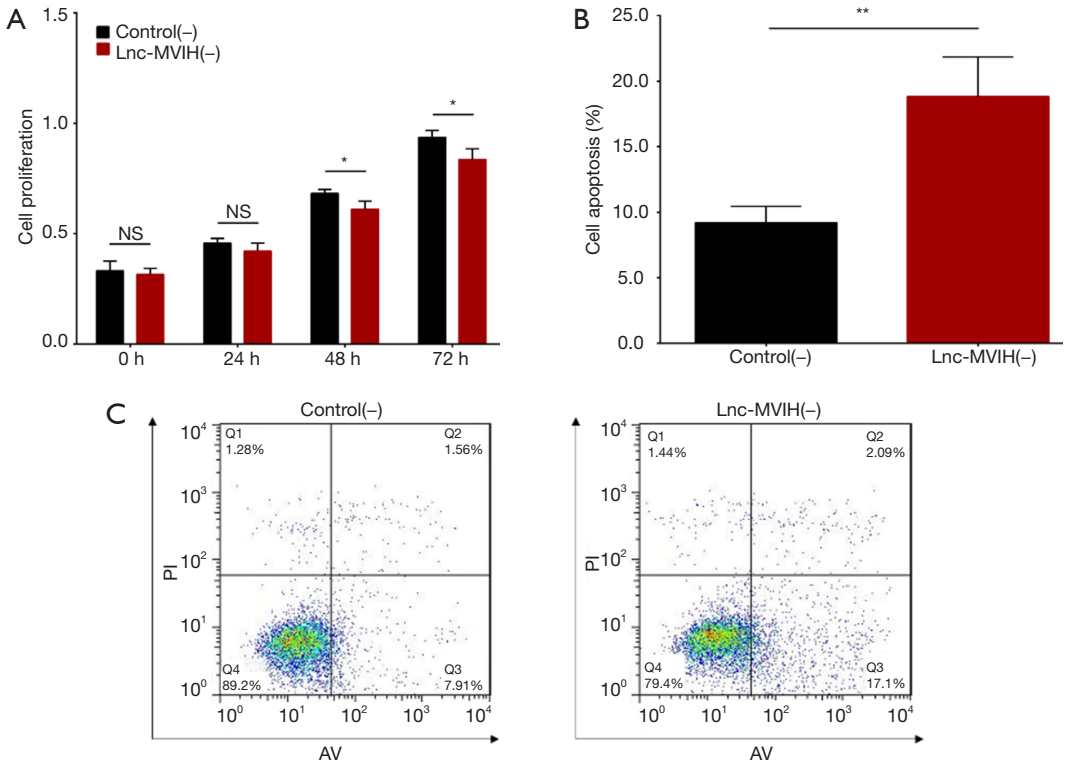

Figure 3 *Lnc-MVIH* knockdown decreased cell proliferation but promoted cell apoptosis in KG-1 cells. *Lnc-MVIH* knockdown had no effect on cell proliferation at 0 and 24 h but decreased cell proliferation at 48 and 72 h (A). *Lnc-MVIH* knockdown increased cell apoptosis (B,C). P<0.05 was considered significant. *, P<0.05. *Lnc-MVIH*, *long non-coding RNA associated with microvascular invasion in hepatocellular carcinoma*; NS, non-significant.

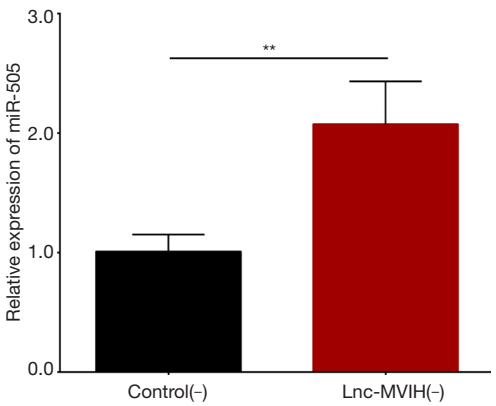

Figure 4 *Lnc-MVIH* knockdown increased *miR-505* expression KG-1 cells. *Lnc-MVIH* knockdown increased *miR-505* expression in AML. The comparison of *miR-505* expression between *lnc-MVIH* knockdown and control was conducted by *t*-test. P<0.05 was considered significant. **, P<0.01. *Lnc-MVIH*, *long non-coding RNA associated with microvascular invasion in hepatocellular carcinoma*; AML, acute myeloid leukemia.

shown to be similar in both *Lnc-MVIH*(–) & *miR-505*(–) group and *Lnc-MVIH*(–) group (P>0.05), which suggested that *miR-505* did not regulate *lnc-MVIH* (*Figure 5B*). Finally, *HMGB1* and *CCNE2*, as the target genes of *miR-505*, were detected, which exhibited that the relative expressions of *HMGB1* (P<0.05) (*Figure 5C*) and *CCNE2* (P<0.05) (*Figure 5D*) were increased in *lnc-MVIH*(–) & *miR-505*(–) group compared with *lnc-MVIH*(–) group. And Western blot also visualized that *HMGB1* and *CCNE2* protein expression was increased in *lnc-MVIH*(–) & *miR-505*(–) group compared with *lnc-MVIH*(–) group (*Figure 5E*). These data suggested that *miR-505* knockdown increased the expressions of *HMGB1* and *CCNE2* in *lnc-MVIH* knockdown treated AML cells.

The effect of miR-505 knockdown on cell proliferation and cell apoptosis in lnc-MVIH knockdown treated KG-1 cells

Cell proliferation was increased in *lnc-MVIH*(–) & *miR-*

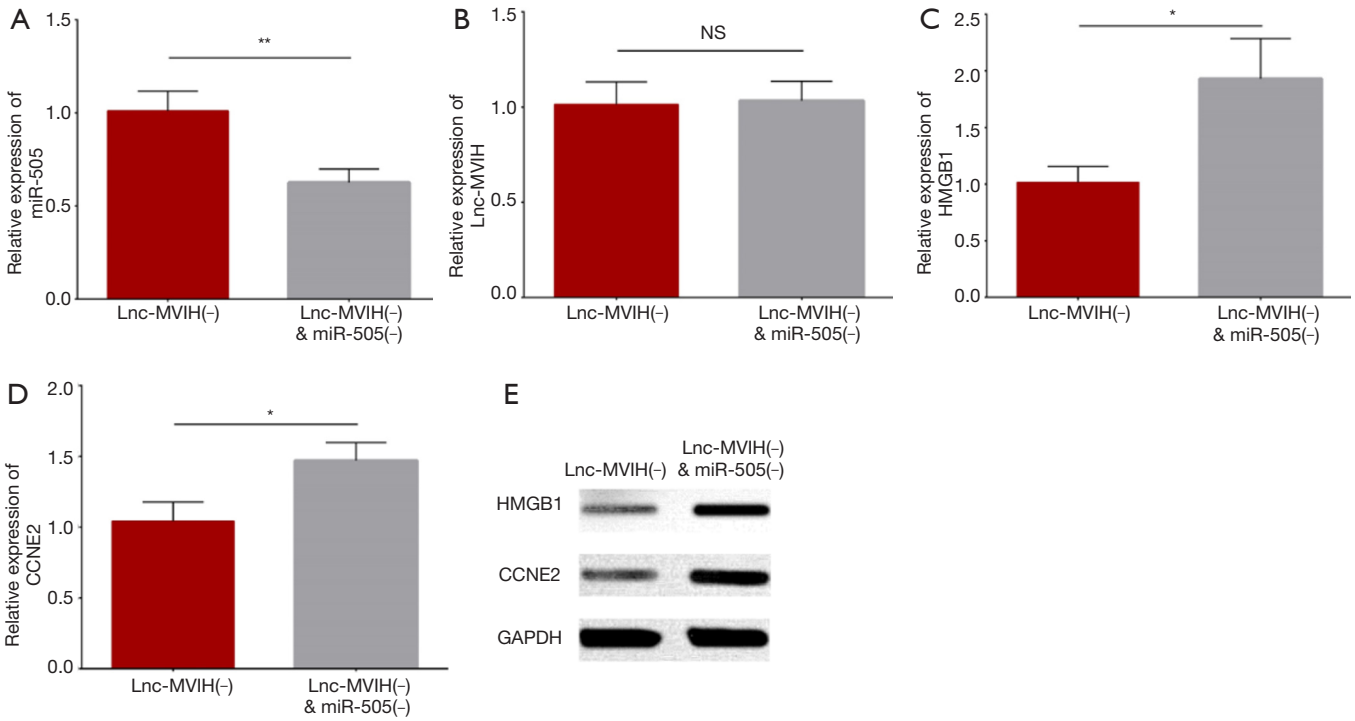

Figure 5 *MiR-505* knockdown increased *HMGB1* and *CCNE2* expressions in *lnc-MVIH* knockdown treated KG-1 cells. *Lnc-MVIH*(–) & *miR-505*(–) group presented decreased expression of *miR-505* compared to *lnc-MVIH*(–) group (A). *Lnc-MVIH*(–) & *miR-505*(–) group and *lnc-MVIH*(–) group showed the similar expression of *lnc-MVIH* (B). *Lnc-MVIH*(–) & *miR-505*(–) group exhibited increased mRNA and protein expressions of *HMGB1* compared to *lnc-MVIH*(–) group (C,E). *Lnc-MVIH*(–) & *miR-505*(–) group also displayed increased mRNA and protein expressions of *CCNE2* compared to *lnc-MVIH*(–) group (D,E). P<0.05 was considered significant. *, P<0.05; **, P<0.01. *Lnc-MVIH*, *long non-coding RNA associated with microvascular invasion in hepatocellular carcinoma*; *lnc-MVIH*(–), *lnc-MVIH* shRNA; *lnc-MVIH*(–) & *miR-505*(–), *lnc-MVIH* shRNA plus *miR-505* shRNA; NS, non-significant.

505(–) group at 48 h (P<0.05) and 72 h (P<0.01), but unchanged at 0 h (P>0.05) and 24 h (P>0.05) compared with *lnc-MVIH*(–) group (*Figure 6A*). Cell apoptosis rate was decreased in *lnc-MVIH*(–) & *miR-505*(–) group compared with *lnc-MVIH*(–) group at 24 h (P<0.01) (*Figure 6B,C*). These data displayed that *miR-505* knockdown compensated the effect of *lnc-MVIH* knockdown on cell proliferation and cell apoptosis in AML. Combining all the data above, we speculated that *lnc-MVIH* knockdown inhibited AML progression possibly via regulating *miR-505* mediated *HMGB1* and *CCNE2* in AML.

Discussion

In the present study, we observed that *lnc-MVIH* was upregulated in AML cell lines compared with primary normal BMMC, and its knockdown suppressed cell proliferation but promoted cell apoptosis via regulating *miR-505* mediated *HMGB1* and *CCNE2* in AML.

Lnc-MVIH is located in the intron of the *RPS24* gene and is essential for transcription process of *RPS24* (19). Existing studies demonstrate that it is upregulated and closely related with tumorigenesis and metastasis in some solid tumors (11-13,19). *Lnc-MVIH* is initially found to be upregulated in hepatocellular carcinoma and promotes tumor growth and metastasis by activating tumor-inducing angiogenesis (10). It is also indicated to be overexpressed in MDA-MB-231 breast cancer cell line compared to mammary epithelial cells and lnc-MVIH knockdown inhibits cell proliferation, increases cell apoptosis, elevates the G1–G0 phase cell proportion and decreases the percentage of cells in the S phase in MDA-MB-231 breast cancer cell line (13). In another study, *lnc-MVIH* is upregulated and its knockdown impaires cell proliferation as well as invasion in non-small cell lung cancer (12). Furthermore, the insufficiency of *RPS24* gene,

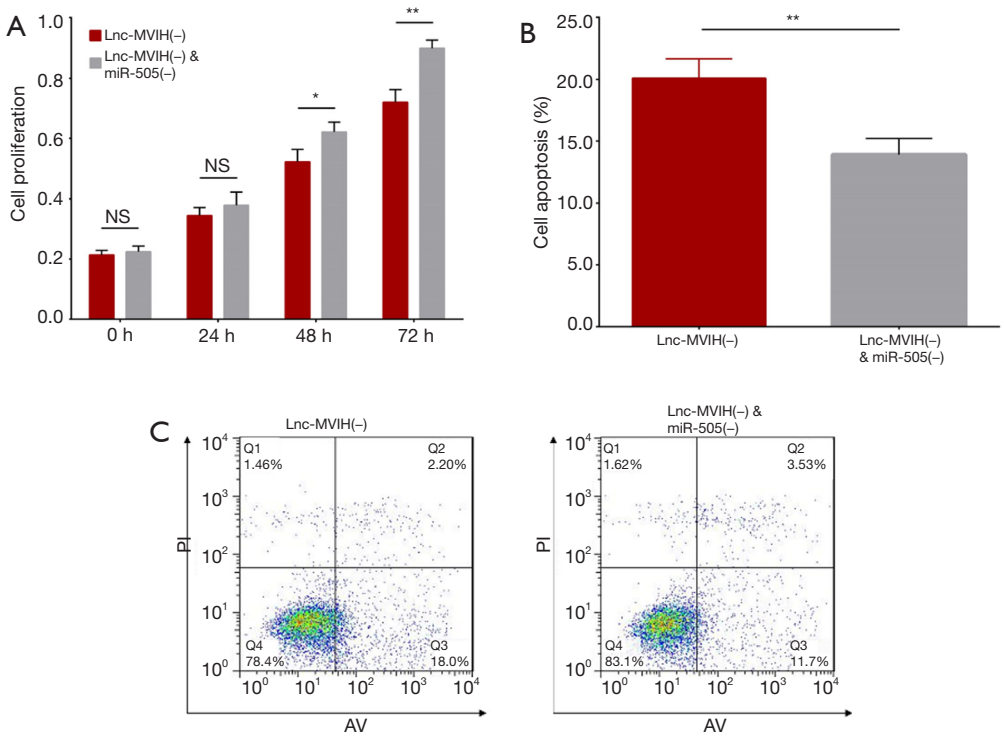

Figure 6 *MiR-505* knockdown promoted cell proliferation but inhibited cell apoptosis in *lnc-MVIH* knockdown treated KG-1 cells. *Lnc-MVIH*(–) & *miR-505*(–) group presented increased cell proliferation at 48 and 72 h, but unchanged at 0 and 24 h compared to lnc-MVIH(–) group (A). *Lnc-MVIH*(–) & *miR-505*(–) group showed decreased cell apoptosis compared to *lnc-MVIH*(–) group (B, C). P<0.05 was considered significant. *, P<0.05; **, P<0.01. *Lnc-MVIH*, *long non-coding RNA associated with microvascular invasion in hepatocellular carcinoma*; *lnc-MVIH*(–), *lnc-MVIH* shRNA; *Lnc-MVIH*(–) & *miR-505*(–), *lnc-MVIH* shRNA plus *miR-505* shRNA; NS, non-significant.

where *lnc-MVIH* is located on, is indicated to cause the cell cycle defects in hematological diseases such as diamond-Blackfan anemia (20). In addition, through the miRanda database analysis we found that *lnc-MVIH* contained several target sites of *miR-505* which was shown to be biomarkers in chronic myeloid leukemia (20). Therefore, we hypothesized that *lnc-MVIH* might participate in the biological processes of AML. In our study, we observed that *lnc-MVIH* was overexpressed in AML cell lines compared with primary normal BMMC, and *lnc-MVIH* knockdown inhibited cell proliferation but promoted cell apoptosis in AML. The possible reasons might include that (I) *lnc-MVIH* might serve as the sponge for miRNA (such as *miR-505*), leading to the inhibitory effect on miRNA target genes (such as *HMGB1* and *CCNE2*), contributing to the AML progression (16). (II) *Lnc-MVIH* knockdown might inactivate the oncogenic pathways such as *WNT* signaling pathway to inhibit the malignant progression (21).

Existing evidence exhibits that *lnc-MVIH* is involved in the regulation of miRNA target genes via serving as miRNA sponge in solid tumors (6). For example, *lnc-MVIH* knockdown inhibits the cell viability and promotes cell apoptosis through upregulating *miR-199a* and *miR-199a* targeted *FZD7* in hepatocellular carcinoma (11). In addition, miRanda database analysis reveals that *miR-505*, which suppresses cell proliferation in hematological malignancies, is the potential target of *lnc-MVIH* (15,16,22). Then we detected the expression of *miR-505* after transfecting *lnc-MVIH* shRNA into KG-1 cells and found that *lnc-MVIH* knockdown upregulated the expression of *miR-505*. Furthermore, *HMGB1* and *CCNE2* are potential target genes of *miR-505*, which are previously shown to be oncogenes in hematological malignancies (22,23). *HMGB1*, as a common oncogene in AML, triggers pro-inflammatory stimulus and activates the immune receptors, leading to the proliferation of AML cells, which is critical for the progression of AML (18,23,24). Besides, *CCNE2* is often regarded as a key gene involved in cell cycle control, whose

overexpression results in the proliferation advantage and malignancy progression in AML (17,25). Therefore, we conducted the rescue experiments to verify whether *lnc-MVIH* knockdown repressed cell activities via regulating *miR-505* mediated *HMGB1* and *CCNE2*, and found that *miR-505* knockdown increased the expression of *HMGB1* and *CCNE2* in *lnc-MVIH* knockdown treated AML cells, meanwhile *miR-505* knockdown compensated the effect of *lnc-MVIH* knockdown on cell proliferation and cell apoptosis in *lnc-MVIH* knockdown treated AML cells. Based on these data, we summarized that *lnc-MVIH* knockdown inhibited cell proliferation but promoted cell apoptosis via regulating *miR-505* mediated *HMGB1* and *CCNE2*. The possible reasons might include that: (I) *lnc-MVIH* knockdown impaired the expression of cell cycle regulatory proteins in the oncogenic pathways (such as Akt pathway, which *CCNE2* participated in) via upregulation of *miR-505*, leading to the blocking effect of oncogenic pathway and inhibited cell proliferation but promoted cell apoptosis in AML (17). (II) *Lnc-MVIH* knockdown reduced the expression of *HMGB1* and inhibited pro-inflammatory stimulus, which decreased proliferation and survival of AML cells (18).

In conclusion, *lnc-MVIH* knockdown inhibits cell proliferation but promotes cell apoptosis via regulating *miR-505* mediated *HMGB1* and *CCNE2* in AML, which suggested that *lnc-MVIH* might serve as a potential therapeutic target for AML.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.10.12). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional ethical approval and individual informed consent were waived due to the nature of the study.

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Supplementary

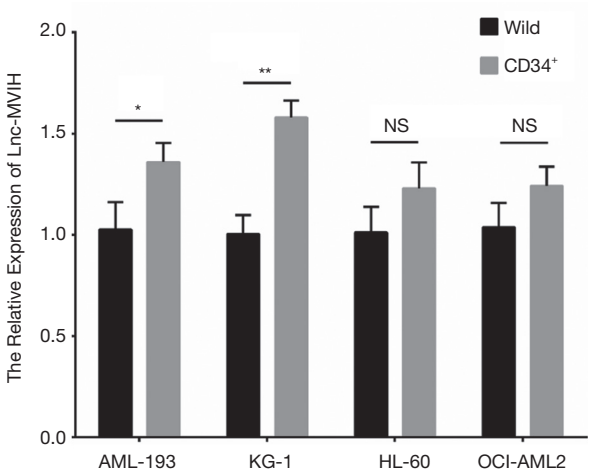

Figure S1 *Lnc-MVIH* expression in $CD34^+$ and wild AML cells. The comparison of *lnc-MVIH* expression between $CD34^+$ and wild AML cells (AML-193, KG-1, HL-60 and OCL-AML2) was detected by *t*-test. P<0.05 was considered significant. *, P<0.05; **, P<0.01. *Lnc-MVIH*, *long non-coding RNA associated with microvascular invasion in hepatocellular carcinoma*; AML, acute myeloid leukemia; NS, non-significant.