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RESEARCH ARTICLE

lncRNA SNHG3 facilitates acute myeloid leukemia cell growth via the regulation of miR-758-3p/SRGN axis

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Abstract

Small nucleolar RNA host gene 3 (SNHG3) is a newly identified long non-coding RNA whose dysregulation has been reported in several cancers. However, the details about clinical significances and biological functions of SNHG3 on acute myeloid leukemia (AML) remain covered. In this study, we revealed increased SNHG3 expression in AML samples and cells and its high potential as a prognostic biomarker for AML patients. Likewise, serglycin (SRGN), which plays an important role in granule-mediated apoptosis, was previously verified to be upregulated in AML and confirmed again by the present study, and its upregulation predicted poor outcomes in AML. Furthermore, knockdown of SNHG3 or SRGN inhibited cell proliferation and induced cell apoptosis. Besides, silencing SNHG3 noticeably decreased the expression of SRGN in AML cells. Moreover, we uncovered that SNHG3 modulated SRGN expression by competitively binding with miR-758-3p. Importantly, both miR-758-3p suppression and SRGN overexpression could mitigate the inhibitory effects of SNHG3 depletion on AML cell growth. Intriguingly, the higher SRGN expression in AML samples with a higher SNHG3 level exhibited an enhanced Ki67 level but a reduced caspase 3 level. To sum up, SNHG3 elicits a growth-promoting function in AML via sponging miR-758-3p to regulate SRGN expression, providing a new therapeutic road for AML patients.

KEYWORDS

AML, cell growth, miR-758-3p, SNHG3, SRGN

1 | INTRODUCTION

Acute myeloid leukemia (AML) is the most aggressive malignant disease of the hematopoietic system with the characteristic of clonal proliferation of leukemia progenitor cells, which eventually leads to dysfunction in producing normal blood cells.[1] Genetic abnormalities and epigenetic alterations, which play key roles in processes such as cell self-renewal, differentiation, and proliferation, are the leading causes of AML occurrence and development.[2] Hence, it is necessary to find the molecular targets for AML.

Long non-coding RNAs (lncRNAs) are a set of non-coding RNAs longer than 200 nucleotides and play crucial roles in modulating pathological and physiological cellular processes of many diseases, including cancers, cardiovascular diseases, lung diseases, and so on.[3-5] Aberrantly expressed lncRNAs have been discovered in various malignancies,[6-8] including leukemia.[9]

Peng and Zhang are co-first authors.

Recently, increasing evidence has identified that lncRNAs, including MEG3, CCDC26, FTX, and HOTAIR, play a role in leukemogenesis.[10-13] Small nucleolar RNA host gene 3 (SNHG3) is a newly recognized lncRNA, which has been revealed to be an oncogene in several cancers.[14-17] Nevertheless, whether SNHG3 also functions in leukemia, especially in AML, still needs to be understood.

Serglycin (SRGN) is a hematopoietic cell granule proteoglycan, which has been identified to be a marker to draw a distinction between myeloid leukemia and lymphoid leukemia.[18] Recently, SRGN has been reported to play an important role in certain malignancies.[19-22] What's more, SRGN has been reported to be upregulated in AML.[23] However, the functional role of SRGN in AML is still unclear.

In the current study, we explored the role of both SNHG3 and SRGN in AML cell growth, and revealed the relationship and regulatory mechanism among SNHG3, SRGN, and leukemogenesis.

2 | MATERIALS AND METHODS

2.1 | Patients and clinical samples

Bone marrow samples were obtained from 62 AML patients and healthy volunteers at Baoji People's Hospital Shaanxi Province. After bone marrow puncture, a total of 3 to 5 mL of the bone marrow was collected followed by the extraction of mononuclear cells in bone marrow using lymphocyte separation medium (Hao Yang Bio, Tianjin, China). After that, the cells were maintained at −80°C for using in next experiments. These samples were obtained in accord with the Helsinki declaration. Informed consent was obtained from all patients and volunteers. This study was approved by the Medical Ethics Committee of Baoji People's Hospital Shaanxi Province.

2.2 | Cell lines and cell culture

The human AML cell line HL-60 and THP-1 (ATCC, Manassas, VA), KG-1 (European Collection of Cell Cultures Wiltshire, UK), NB4 (Institutes for Biological Science, Shanghai, China), and MOLM-14 (Leibniz-Institut DSMZ-Deutsche Sammlung von 133 Mikroorganismen und Zellkulturen GmbH, Germany), were grown in RPMI-1640 medium (Sigma-Aldrich) with 10% fetal bovine serum (v/v; Life Technologies, Grand Island, NY). Besides, $CD34^+$ cells sorted from bone marrow aspirates of four healthy controls were applied as controls to these AML cell lines. All cells were cultured in a humidified air containing 5% CO_2 at 37°C.

2.3 | Cell transfection

The short hairpin RNAs (shRNAs) targeting SNHG3 (shSNHG3 and shSNHG3#2) or SRGN (shSRGN and shSRGN#2), as well as their corresponding negative controls were all purchased from GenePharma (Shanghai, China). The full-length sequence of SRGN was synthesized by Invitrogen (Carlsbad, CA) and then subcloned into the pcDNA3.1 vector (Invitrogen) to obtain pcDNA3.1/SRGN, with the empty vector as the negative control. Also, miR-758-3p inhibitors, miR-758-3p mimics, and their controls were constructed by Invitrogen. These plasmids were transfected into HL-60 and KG-1 cells as needed by using Lipofectamine 2000 (Invitrogen) as per the manufacturer's protocols.

2.4 | RNA extraction and quantitative real-time PCR

Total RNA was extracted using the Trizol reagent (Invitrogen) and cDNAs were obtained using PrimeScript RT reagent kit (TaKaRa, Dalian, China) except that of miR-758-3p by TaqMan Advanced miRNA cDNA synthesis kit (Waltham, MA). Polymerase chain reaction (PCR) was then performed using SYBR Green (Takara), and real-time PCR was conducted using Thermal Cycler Dice Real-Time PCR System (Takara, Japan). Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and U6 were used as endogenous controls. The relative levels of genes were calculated by the $2^{-\Delta\Delta C_t}$ method. The sequences of primers used were as follows: SNHG3: 5′-AGT GGT CGC TTC TTC TCC TTG-3′ (Forward) and 5′-GAT TGT CAA ACC CTC CCT GTT A-3′ (Reverse); SRGN: 5′-GGT TAT CCT ACG CGG AGA GC-3′ (Forward) and 5′- CAA GTC CTG GCT GTC TGA GG-3′ (Reverse); miR-758-3p: 5′- ACA CTC CAG CTG GGT TTG TGA CCT GGT CCA-3′ (Forward) and 5′- TGG TGT CGT GGA GTC G-3′ (Reverse); GAPDH: 5′-GAA GGT GAA GGT CGG AGT C-3′ (Forward) and 5′-GAA GAT GGT GAT GGG ATT TC-3′ (Reverse); U6: 5′-ATT GGA ACG ATA CAG AGA AGA TT-3′ (Forward) and 5′-GGA ACG CTT CAC GAA TTT G-3′ (Reverse).

2.5 | MTT assays

The HL-60 and KG-1 cells were resuspended and then seeded into 96-well plates (1×10^5 cells/well). Afterward, the cells were cultured for 0, 24, 48, 72, and 96 hours at 37°C. The viability of HL-60 and KG-1 cells was evaluated using MTT assay. Briefly, 10 μL of 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (MTT; Sigma-Aldrich) was added to all wells, and the plates were maintained at 37°C for 4 hours. Then the absorbance at

490 nm was read with a microplate reader (Thermo Fisher Scientific). The assays were conducted in three replicates.

2.6 | Cell apoptosis analysis

After cultured for 48 hours, the stably transfected cells were harvested and resuspended by cold phosphate buffer saline (PBS). Before the experiment, transfected cells were modulated to a density of 1×10^6 cells/mL. After that, the cells were stained using an Annexin V-FITC/propidium iodide (PI) apoptosis detection kit (Multisciences, Shanghai, China). Then cell apoptosis was assessed by a flow cytometer (BD Biosciences). All experiments were performed three times independently.

2.7 | Western blot analysis

Cells were lysed by RIPA buffer and the concentration of extracted protein was measured using BCA protein assay kit (Pierce Biotechnology, Rockford, IL) following the manufacturer's instructions. After that, 10% sodium dodecyl sulfate polyacrylamide electrophoresis gel was used to separate proteins, and then the proteins were transferred onto polyvinylidene fluoride (PVDF) membranes (Millipore, Billerica, MA). After being blocked, the membranes were incubated with primary antibodies at 4°C overnight, washed, and finally incubated with secondary antibodies for 2 hours. Target bands were detected by the ECL chemiluminescent detection system (Thermo Fisher Scientific , Rochester, NY). The primary antibodies used were as follow: Bax (50599-2-Ig; Proteintech); Bcl-2 (ab32124; Abcam, Britain); Cleaved caspase 3 (ab13847; Abcam); SRGN (EL908815-100; EterLife, Britain); GAPDH (60004-1-Ig; Proteintech).

2.8 | Luciferase reporter assay

The full-length SNHG3 (SNHG3-WT) was inserted into a pmirGLO Dual-luciferase miRNA Target Expression Vector (Promega, Madison, WI), and mutant-type SNHG3 was implanted into the vector to construct SNHG3-Mut. Similarly, the SRGN sequences containing the binding sites of miR-758-3p (SRGN-WT) and its mutation without the binding sites (SRGN-Mut) were built as before. After that, HEK-293T cells were transfected with different plasmids as appropriate. Lipofectamine 2000 was used for transfection. Then the transfected cells were grown for 48 hours and harvested for luciferase detection by using luciferase reporter assay system (Promega). Each of the experiment was performed three times. Data were represented as the mean ± SD.

2.9 | RNA pull down assay

Pierce RNA 3′ End Desthiobiotinylation Kit (20163, Thermo Fisher Scientific, Rockford, IL) was used to label miRNA. Then 50 pmol of biotin-labeled miRNAs were mixed with AML cell lysates overnight, followed by the addition of Streptavidin-Dyna beads (Dyna beads M-280 Streptavidin, #11205D; Invitrogen). After discarding the supernatant, the beads were washed and the levels of SNHG3 and SRGN in the pulldown samples were measured using quantitative real-time PCR (qRT-PCR) and normalized using GAPDH as an internal reference.

2.10 | Statistical analyses

All statistical analyses were conducted by SPSS 20.0 software (SPSS Inc.). Data were exhibited using the mean ± SD. Differences between groups were analyzed by Student *t*-test or one-way analysis of variance as needed. Spearman's correlation analysis was utilized to analyze relationships among the expression level of SNHG3, SRGN, miR-758-3p. Overall survival curves were determined by using Kaplan–Meier analysis and the log-rank test. Statistical significance was defined as $P < .05$.

3 | RESULTS

3.1 | Upregulated SNHG3 and SRGN predict poor outcome in adult AML patients

To demonstrate the biological significance of SNHG3 in AML, the messenger RNA (mRNA) levels of SNHG3 in bone marrow cells from 62 AML patients and 20 healthy patients were detected using qRT-PCR. The results suggested that SNHG3 was significantly increased in patients with AML in comparison with healthy controls (Figure 1A). The markedly upregulated SNHG3 in AML patients necessitated an investigation into its clinical relevance in patients with AML. As shown in Table 1, the level of SNHG3 only had strong correlations with white blood cell count ($P = .01$) and platelet count ($P = .021$). Furthermore, the Kaplan–Meier curve revealed that patients with higher SNHG3 level seemed to have shorter survival time (Figure 1B). Finally, only white blood cell count ($P = .035$) and SNHG3 level ($P = .02$), but not the remaining clinical features, were found to be used as prognostic indicators of AML (Table 2).

Similarly, to understand the role of SRGN in AML, we examined its level in bone marrow samples from AML patients and healthy controls. As illustrated in Figure 1C, SRGN was remarkably upregulated in AML samples compared to healthy controls, which was consistent with

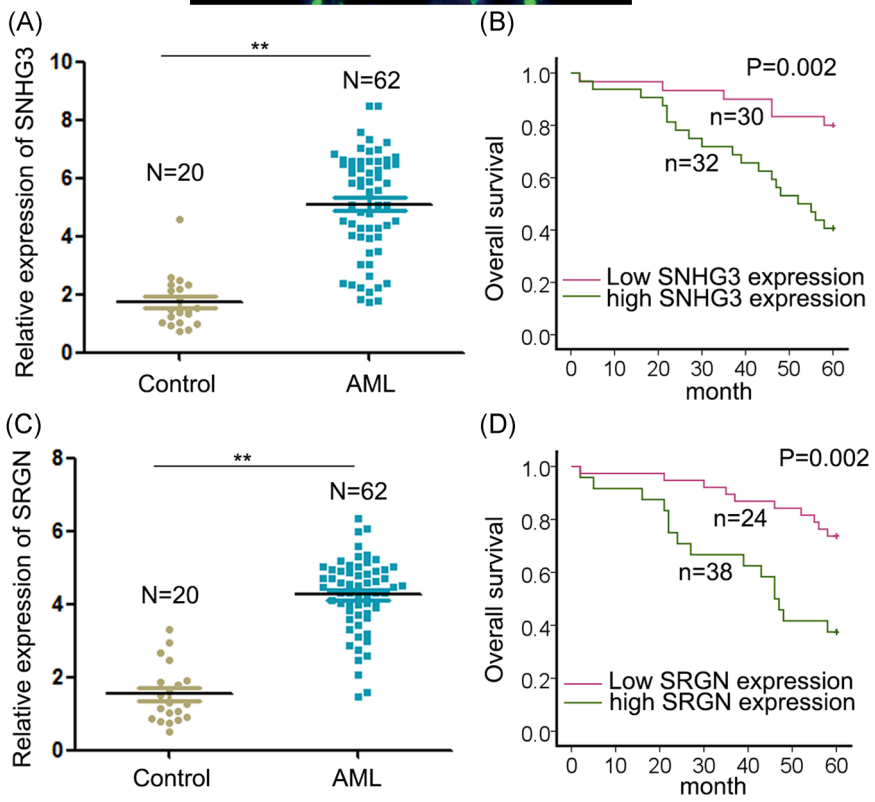

FIGURE 1 Upregulated SNHG3 and SRGN predict poor outcome in AML patients. A, qRT-PCR results of SNHG3 in 62 AML samples and 20 healthy controls. B, Kaplan–Meier curve determined the association between SNHG3 level and overall survival (OS) in AML patients. C, SRGN expression in in AML samples and healthy controls was analyzed using qRT-PCR. D, Kaplan–Meier curve of OS in AML patients with high or low expression of SRGN. AML, acute myeloid leukemia; qRT-PCR, quantitative real-time PCR; SNHG3, small nucleolar RNA host gene 3; SRGN, serglycin

TABLE 1 Correlation between SNHG3 expression and clinical features. ($n = 62$)

	SNHG3 expression		
Variable	**Low**	**High**	***P*-value**
Age			
<60	18	21	.793
≥60	12	11	
Gender			
Male	13	15	.804
Female	17	17	
WBC ($\times 10^9$/l)			
<100	20	10	.010
≥100	10	22	
HB (g/l)			
<60	18	17	.617
≥60	12	15	
PLT ($\times 10^9$/l)			
<30	19	10	.021
≥30	11	22	
Bone Marrow Blasts (%)			
<60	16	16	.805
≥60	14	16	
Risk Stratification Based On Karyotype			
Better/Intermediate	20	19	.606
Poor	10	13	

Note: Low/high by the sample median. Pearson χ^2 test. $P < .05$ was considered statistically significant.
Abbreviations: HB, hemoglobin; PLT, platelets; SNHG3, small nucleolar RNA host gene 3; WBC, whitewhite blood cell

TABLE 2 Multivariate analysis of prognostic parameters in AML patients by Cox regression analysis

Variable	**Category**	***P*-value**
Age		
	<60	.199
	≥60	
Gender		
	Male	.057
	Female	
WBC ($\times 10^9$/l)		
	<100	.035*
	≥100	
HB (g/l)		
	<60	.500
	≥60	
PLT ($\times 10^9$/l)		
	<30	.451
	≥30	
Bone Marrow Blasts (%)		
	<60	.475
	≥60	
SNHG3 Level	Low	.020*
	High	

Note: Proportional hazards method analysis showed a positive, independent prognostic importance of SNHG3 expression ($P = .02$).
Abbreviations: AML, acute myeloid leukemia; HB, hemoglobin; PLT, platelets; WBC, whitewhite blood cell.
*$P < .05$ was considered statistically significant.

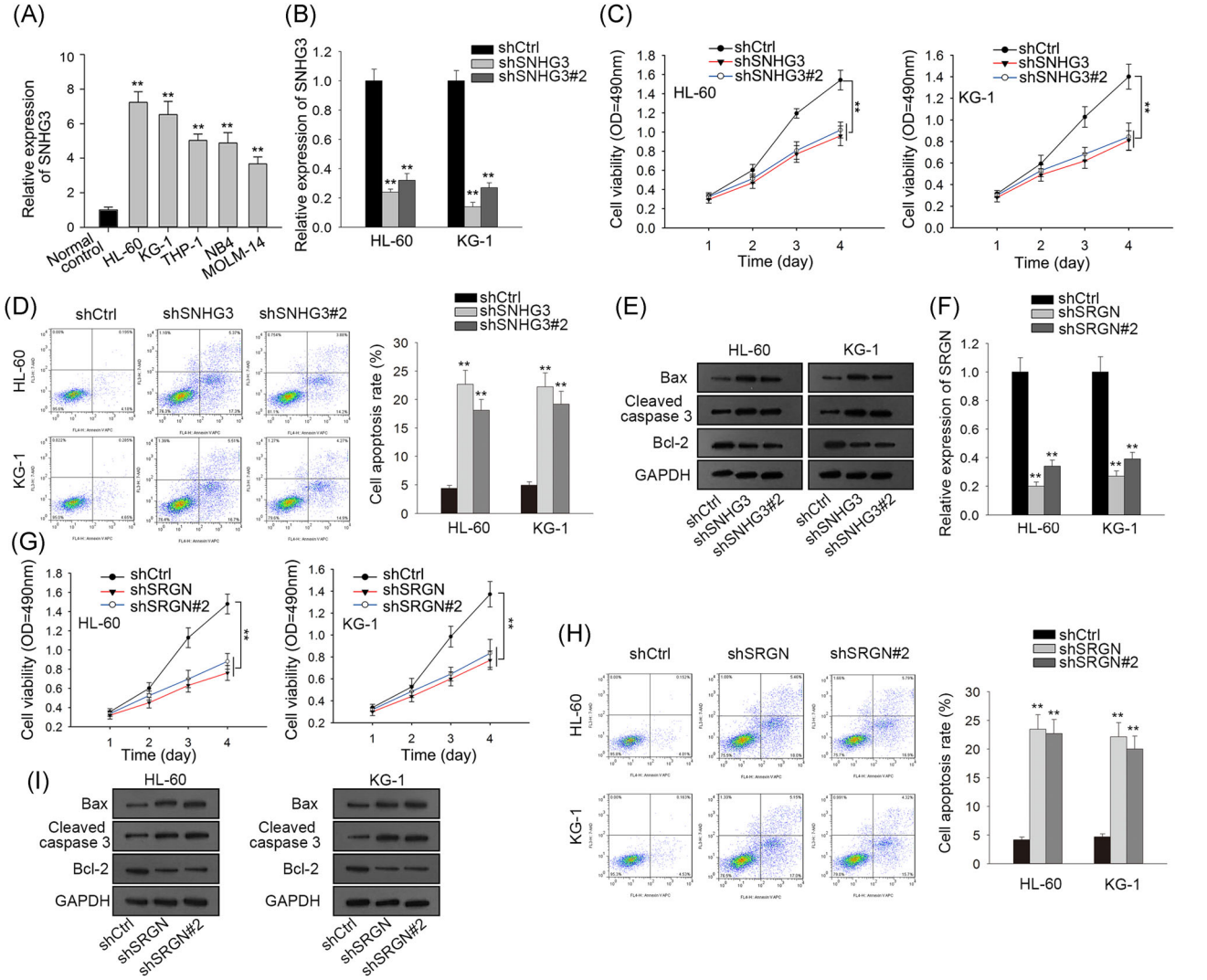

FIGURE 2 Knockdown of SNHG3 or SRGN exerts inhibitory effects on AML cell growth. A, Relative expression of SNHG3 in AML cell lines was tested by qRT-PCR. B, qRT-PCR results of SNHG3 level in HL-60 and KG-1 cells after transfection. C-D, Impacts of SNHG3 silence on cell proliferation and apoptosis in two AML cells was analyzed by MTT assay and flow cytometry analysis respectively. E, Western blot analysis was utilized to determine the level of apoptosis related genes in HL-60 and KG-1 cells with or without SNHG3 knockdown. F, qRT-PCR results of SRGN level in HL-60 and KG-1 cells after transfection. G-I, Silencing SRGN led to inhibited cell proliferation (MTT assay) and enhanced cell apoptosis (H: flow cytometry analysis; I: Western blot analysis) in AML cells. AML, acute myeloid leukemia; qRT-PCR, quantitative real-time PCR; SNHG3, small nucleolar RNA host gene 3; SRGN, serglycin

a previous study.[23] Then the Kaplan–Meier curve showed that higher SRGN level in AML patients always led to poorer outcomes (Figure 1D). In sum, SNHG3 and SRGN are upregulated in AML, and both of them predict clinical outcomes.

3.2 | Silencing SNHG3 or SRGN results in suppressed cell growth in AML cells

Due to the abnormal expression of SNHG3 in clinical AML samples, we suspected that SNHG3 might play a role in AML progression. First of all, we tested the NSHG3 expression in five AML cell lines (HL60, KG-1, THP-1, NB4, and MOLM-14) and the normal control. As shown in Figure 2A, SNHG3 was highly expressed in all five cell lines compared with control. To assess its role in the growth of AML cells, two shRNAs against SNHG3 were constructed and transfected into HL-60 and KG-1 cells. As a result, the expression level of SNHG3 was overtly silenced in HL-60 and KG-1 cells with the transfection of either shSNHG3 or shSNHG3#2 (Figure 2B). Moreover, we discovered that SNHG3 knockdown by shSNHG3 or shSNHG3#2 reduced cell viability but enhanced cell apoptosis in both HL-60 and KG-1 cells (Figure 2C,D). Accordantly, the protein levels of pro-apoptosis gene such as Bax, Cleaved caspase 3, were

elevated, whereas that of anti-apoptostic Bcl-2 was declined under SNHG3 suppression (Figure 2E). Likewise, the function of SRGN in AML was also evaluated in vitro. As illustrated in Figure 2F, SRGN was successfully silenced in the two AML cells transfected with shSRGN or shSRGN#2. SRGN knockdown caused a remarkable inhibition in cell viability but a significant increase in cell apoptosis in AML cells (Figure 2G-I). The results above suggested that SNHG3 as well as SRGN plays a growth-promoting role in AML cells.

3.3 | SNHG3 modulates SRGN expression via sponging miR-758-3p

Many studies have reported that lncRNAs function as ceRNAs to regulate certain proteins.[24] Bioinformatics analysis predicted that miR-758-3p was a shared partner of both SNHG3 and SRGN. Meanwhile, we observed that the expression of miR-758-3p was distinctly enhanced while that of SRGN drastically reduced in SNHG3-silenced AML cells, whereas the level of SNHG3 was never affected by SRGN inhibition (Figure S1A-C). Furthermore, SNHG3 suppression markedly decreased both the mRNA and protein levels of SRGN in both HL-60 and KG-1 cells (Figure 3A,B). Therefore, we speculated that SNHG3 might regulate SRGN through a ceRNA mechanism. The bioinformatics analysis predicted that miR-758-3p was a shared partner of both SNHG3 and SRGN. The luciferase reporter assay uncovered that only the luciferase activity of SNHG3-WT, instead of SNHG3-Mut, was reduced by miR-758-3p mimics but not miR-NC (Figure 3C). Subsequently, we observed a marked enrichment of SNHG3 in the pullet pulled down by Bio-miR-758-3p-WT (Figure 3D). Moreover, miR-758-3p was down-regulated in AML samples in comparison to healthy controls and inversely correlated with SNHG3 expression (Figure 3E,F).

Analogously, we uncovered that miR-758-3p interacted directly with SRGN and that SNHG3 regulated

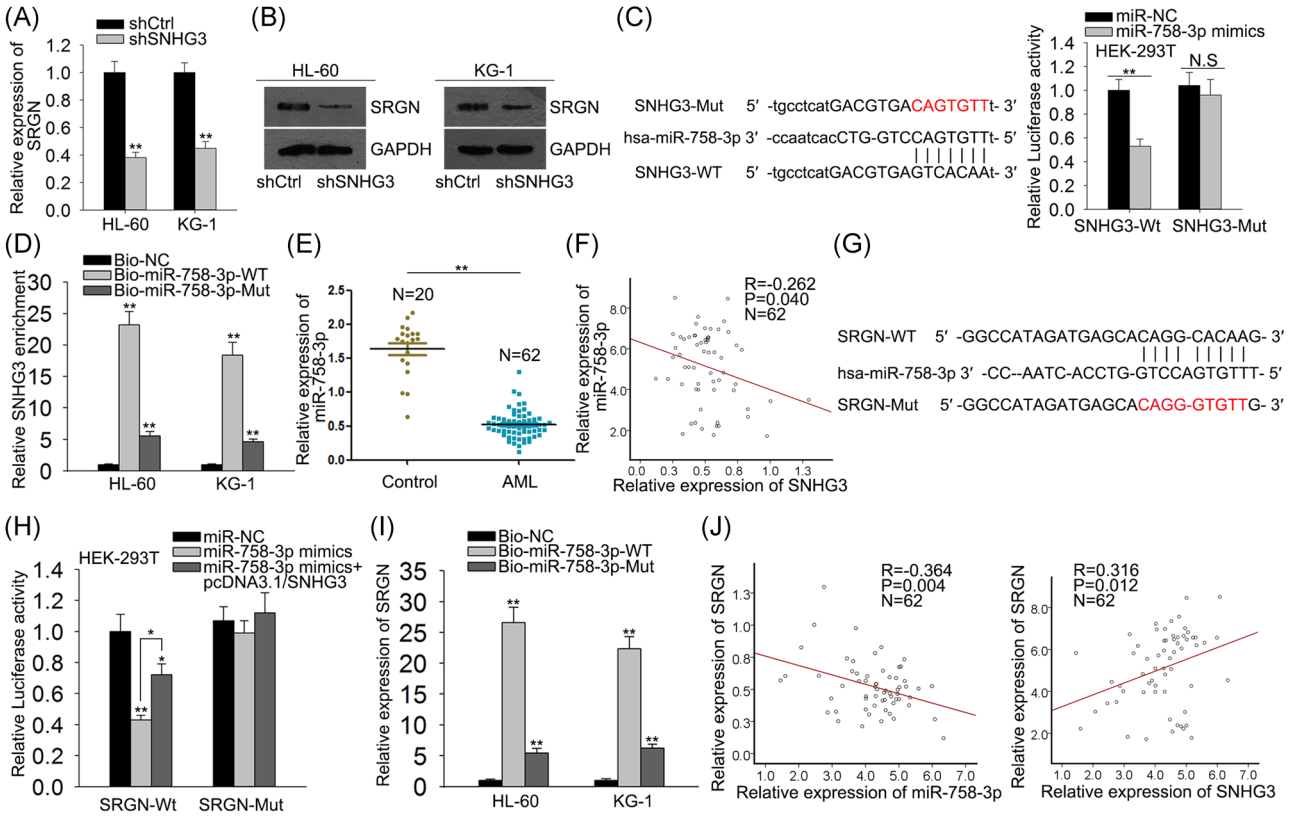

FIGURE 3 SNHG3 regulates SRGN via sponging miR-758-3p. A-B, Effects of SNHG3 knockdown on mRNA and protein level of SRGN in HL-60 and KG-1 cells were estimated by qRT-PCR analysis or Western blot analysis respectively. C-D, The putative binding sites between miR-758-3p and SNHG3, and their interactions were confirmed using luciferase reporter assay (C) and RNA pull down assay (D). E, The expression of miR-785-3p in clinical samples was evaluated by qRT-PCR analysis. F, Spearman's correlation analysis indicated the negative association between the expression of miR-758-3p and SNHG3 in these samples. G-I, The predicted binding sites between miR-758-3p and SRGN (G), and then luciferase reporter assay (H) and RNA pull down assay (I) were conducted to validate their interactions. J, Spearman's correlation analysis results of the correlations among SRGN, miR-758-3p and SNHG3 expression in AML samples. AML, acute myeloid leukemia; mRNA, messenger RNA qRT-PCR, quantitative real-time PCR; SNHG3, small nucleolar RNA host gene 3; SRGN, serglycin

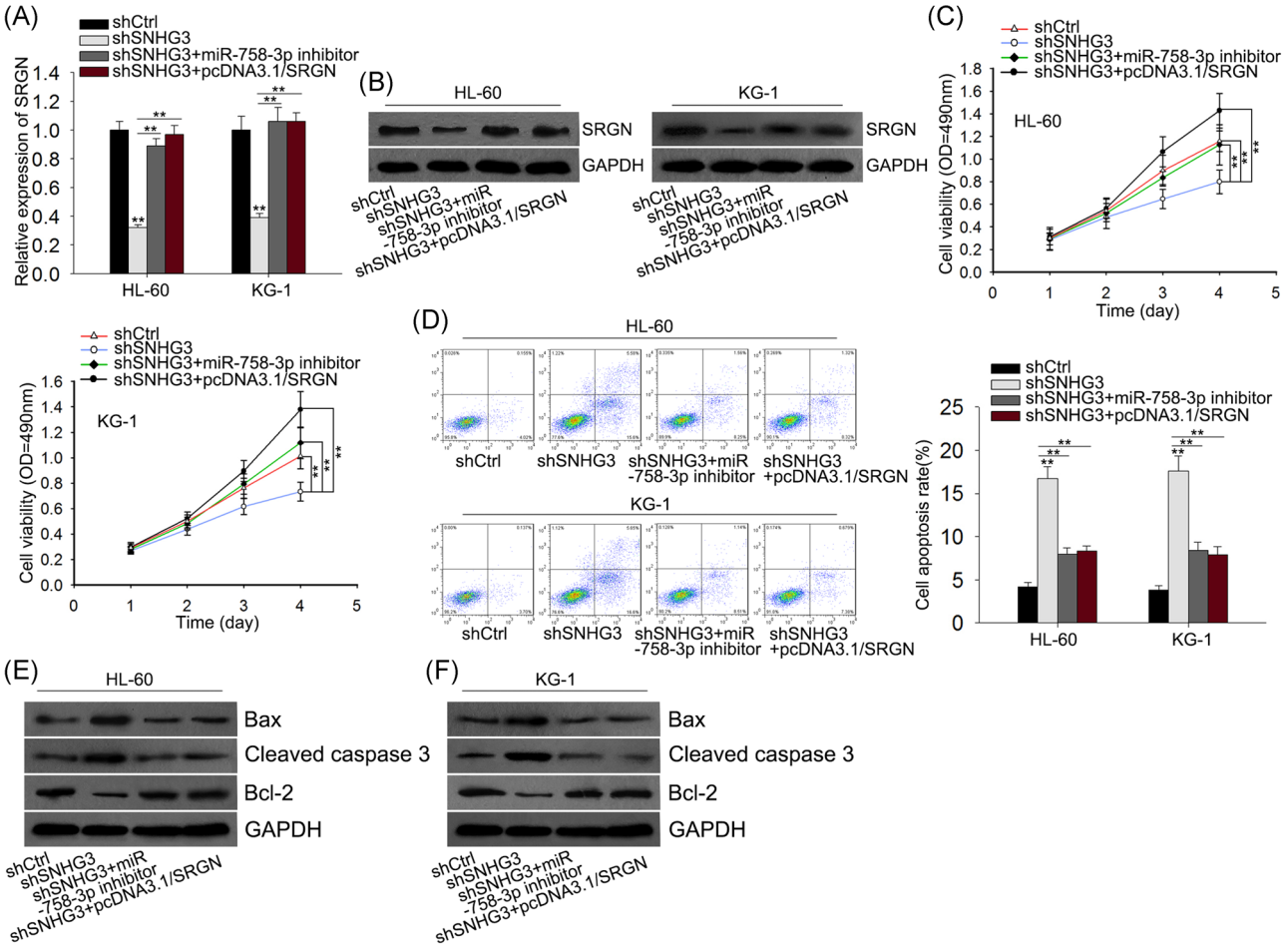

FIGURE 4 miR-758-3p suppression or SRGN overexpression reversed the inhibiting effect of SNHG3 on AML cell growth. A-B, qRT-PCR and Western blot were correspondingly used to examine the alterations in mRNA and protein levels of SRGN in different groups of HL-60 and KG-1 cells. C-D, MTT assay (C) and flow cytometry analysis (D) were respectively utilized to evaluate the changes in cell proliferation ability and apoptosis rate in two AML cells with different transfection. E-F, Western blot analysis was applied to assess changes of protein level of apoptosis-related genes in HL-60 (E) and KG-1 (F) cells after transfection. AML, acute myeloid leukemia; mRNA, messenger RNA; qRT-PCR, quantitative real-time PCR; SNHG3, small nucleolar RNA host gene 3; SRGN, serglycin

SRGN through competitively binding with miR-758-3p (Figure 3G-H). In addition, the interaction between miR-758-3p and SRGN was further confirmed by RNA pull down assay (Figure 3I). Finally, SRGN expression was indicated to be positively associated with SNHG3 level but inversely correlated with miR-758-3p level (Figure 3J). Collectively, these findings demonstrated that SNHG3 acts as a sponge of miR-758-3p to regulate SRGN expression in AML.

3.4 | SNHG3 modulates AML cell growth through regulating miR-758-3p/SRGN axis

To probe the relationships among SNHG3, miR-758-3p and SRGN as well as their impacts on the AML cell growth, the following experiments were conducted. As presented in Figure 4A, the repressed SRGN mRNA level induced by SNHG3 depletion was remarkably elevated by miR-758-3p inhibition or SRGN overexpression, so was its protein level in AML cell lines (Figure 4B). Both the inhibited cell proliferation and the promoted apoptosis under SNHG3 silencing were restored after inhibiting miR-758-3p or overexpressing SRGN (Figure 4C,D). Coincidently, either miR-758-3p suppression or SRGN promotion led to decreased levels of Bax and cleaved caspase 3 but increased levels of Bcl-2 in contrast to the SNHG3-silenced group (Figure 4E,F). Interestingly, we revealed that the higher SNHG3 level in AML samples always led to the higher expression of SRGN (Figure S2A,B), while AML samples with more SRGN protein seemed to express more Ki67 protein and less caspase 3 level (Figure S2C), further intensifying that SNHG3 contributed to AML cell growth via a SRGN-mediated

manner. All in all, these observations elucidated that SNHG3 plays a leukemogenic role in AML via modulating the miR-758-3p/SRGN axis.

4 | DISCUSSION

In the past decade, mounting evidence has shown that lncRNAs also have a significant impact on leukemogenesis and may be potential diagnostic and therapeutic target for leukemia,[25-27] including AML.[11,28,29] In this study, we explored the expression level and functional role of SNHG3 in AML, a reported oncogene in several carcinomas.[14-17,30] We also uncovered that SNHG3 was markedly upregulated in AML samples and cell lines and that its high level was related to poor survival in AML patients. Besides, silencing SNHG3 led to inhibited cell proliferation and enhanced apoptosis in AML cells.

SRGN is an identified marker of AML which is validated to be upregulated in AML previously.[18,23] To date, SRGN has been revealed to exert functions in certain malignancies.[21,31] However, its role in AML had remained unclear until now. Our study demonstrated that upregulated SRGN predicts poor clinical outcome and its knockdown obviously suppressed cell proliferation and promoted cell apoptosis in AML.

Recently, the ceRNA network (lncRNA-miRNA-mRNA regulatory loop) has been increasingly proposed to play important roles in cancers including AML.[11,32] MiRNAs also played a significant part in the ceRNA network through their combining with target mRNAs so as to suppress the action of mRNA expression.[33] Herein, we confirmed the interactions of miR-758-3p with SNHG3 and SRGN as well as the relationships among them in AML samples. Moreover, the rescue assays confirmed the promoting role of the SNHG3/miR-758-3p/SRGN axis in AML cell growth, which was further evidenced by the clinical findings that higher SNHG3 level in AML samples was often accompanied by higher SRGN expression as well as higher Ki67 and lower caspase 3 levels.

In short, our study was the first to reveal the facilitating function of SNHG3 in AML cell growth by regulating the miR-758-3p/SRGN pathway. Besides, we firstly uncovered the promotion effect of SRGN on AML progression and the association of SRGN with SNHG3 as well. Furthermore, this study provided new potential prognostic and therapeutic targets for AML, although more relevant research needs to be done in future.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Linqiang Peng prepared the manuscript and figures. Yanzhi Zhang and Hongli Xin contributed to experiments and tables.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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