European Review for Medical and Pharmacological Sciences 2019; 23: 6588-6595

Long non-coding RNA (lncRNA) small nucleolar RNA host gene 7 (SNHG7) promotes breast cancer progression by sponging miRNA-381

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Abstract. – OBJECTIVE: The abnormal expression of lncRNA small nucleolar RNA host gene 7 (SNHG7) has been found in various kinds of cancers but its expression and role in breast cancer are unknown. We conducted this study to identify the expression, the function, and to underline the mechanism of SNHG7 in breast cancer.

PATIENTS AND METHODS: The expression of SNHG7 was evaluated in clinical breast cancer tissues and adjacent normal tissues by qPCR assays. The expression was also detected in breast cancer cell lines and normal cell line. CCK8 assays were used to determine the biological functions of SNHG7 on breast cancer cells' proliferation. The transwell assays were applied for the exploration of the effects of SNHG7 on breast cancer cells' invasion. The direct target of SNHG7 was predicted by bioinformatics algorithm and verified by the Luciferase reporter assays.

RESULTS: SNHG7 was found to be significantly upregulated in breast cancer tissues when compared with normal tissues. Breast cancer cell lines showed higher levels of SNHG7 than normal breast epithelial cell line. The knockdown of SNHG7 by siRNA could remarkably repress breast cancer cell proliferation and invasion. Moreover, miRNA-381 was newly confirmed as a direct target of SNHG7 and it mediated the suppressing effects of SNHG7 on breast cancer cells.

CONCLUSIONS: SNHG7 was significantly upregulated in breast cancer and acted as an oncogene to promote breast cancer cell proliferation and invasion by directly sponging miRNA-381.

Key Words:
Small nucleolar RNA host gene 7, Breast cancer, Progression, MiRNA-381.

Introduction

Breast cancer is the most common type of malignant tumors and is one of the leading causes of cancer related deaths in women all over the world[1,2]. It is estimated that there are about 1.3 million women newly diagnosed as breast cancer, so it brings a huge public health burden[3]. Even the diagnostic methods and treatment measures including surgery, radiotherapy, and chemotherapy have greatly developed in the past ten years, the 5 year overall survival rates, and the prognosis of advanced breast cancer remain poor[4]. Therefore, it is of great importance to identify the mechanisms of tumor carcinogenesis and develop new therapeutic target for breast cancer[5].

Non-coding RNA is a category of RNAs which do not translate into a protein[6]. The family of non-coding RNAs contains microRNA (miRNA), long non-coding RNA (lncRNA), circular RNA (cirRNA) and other non-coding RNAs[7]. Recently it was found that most long non-coding RNAs (lncRNAs) play an important role in the process of physiology and pathology[8]. The abnormal expression of some specific lncRNAs has been found in some type of tumors such as breast cancer, gastric cancer, and liver cancer. For example, lncRNA ZFAS1 was found to be upregulated in bladder cancer and associated with the prognosis of bladder cancer[9]. Wang et al[10] demonstrated that lncRNA DNACR was elevated in osteosarcoma tissue specimens and it accelerated ROCK1-mediated proliferation and metastasis of osteosarcoma.

The specific lncRNA, small nucleolar RNA host gene 7 (SNHG7), was recently identified and it was located on chromosome 9q34.3[11]. The full length of SNHG7 is 2176 bp and some investigations[12-14] have suggested that it exerted important function in bladder cancer, osteosarcoma and, esophageal cancer. However, its expression type and biological function in breast cancer remain largely to be elucidated. In the present study, we tried to investigate the expression of SNHG7 in

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breast cancer tissues and cell lines. The biological function and the mechanism of how SNHG7 works also were identified.

Materials and Methods

Clinical Tissues Collection

30 patients who had breast cancer surgery were enrolled in this study. After surgery we collected their breast cancer tissues and adjacent normal tissues. The tissues were stored in liquid nitrogen immediately. The informed consents were obtained from each of the enrolled patients. The protocol of this study was reviewed and approved the Ethics Committee Board of Nanfang Hospital, Southern Medical University.

Cell Culture

We used four human breast cancer cell lines and one normal breast epithelial cell line in the current study. We obtained human breast cancer cell lines (ZR-75-1, HCC-1973, MDA-MB-231, and MDA-MB-468) from the American Type Culture Collection (ATCC, Manassas, VA, USA) and normal breast epithelial cell line MCF-10A from Shanghai Institutes for Biological Sciences of Chinese Academy of Sciences (Shanghai, China). The above cell lines were all cultured in Dulbecco's Modified Eagle's Medium (DMEM; high glucose medium; Gibco, CA, USA). The medium was added with 10% fetal bovine serum (FBS), 1% penicillin, and 1% streptomycin (Gibco, CA, USA). The condition of the humidified incubator was set at 37°C and filled with 5% CO_2.

RNA Extraction and Real Time-PCR

For the total RNA extraction, the TRIzol reagent (Invitrogen, Carlsbad, CA) was used according to the manufacturer's protocol. The RNA concentration of the clinical samples and the cell lines were measured and used for reverse transcription and quantitative Real Time-PCR (qRT-PCR). We detected the RNA expression of SNHG7 and miRNA-381 in the clinical samples. GAPDH and U6 were used as controls. The detections were performed on Applied Biosystems Real Time-PCR platform (Applied Biosystems, Carlsbad, CA). The specific primers of SNHG7 were: forward 5'-CGATCGATATGCTAGCTAGC-3', reverse 5'-CGTAGCTAGCGTAGCGTAT-3'; the specific primers of GAPDH were: 5'-CGTCGCTAGCGATCGTTACA-3', reverse 5'-CTAAATGCTAGTCTTTACGA-3'.

Cell Transfection

Three small interfering RNAs for SNHG7 (si-SNHG7#1, si-SNHG7#2, and si-SNHG7#3) and the negative control (si-control) were obtained from Ribobio (Guangzhou, China). The miRNA-381 mimic (miR-381), mimic control (miR-control), miRNA-381 inhibitor (in-miR-381), and inhibitor control (in-miR-control) were purchased from Ribobio (Guangzhou, China). The above regents were transfected into the breast cancer cells. After 48 h of transfection, the cells were harvested for further experiments.

Colony Formation Assays

After transfection, the cells were harvested and counted. 2×10^3 cells were planted on the 6 well culture plates. After 4 weeks of culture, the colonies were formatted. Then, the cells were fixed by polyoxymethylene and stained with Giemsa. The numbers of colonies were counted under the microscope.

Cell Counting Kit-8 Assays

The transfected cells were counted and were planted on the 96 well culture plates. The Cell Counting Kit-8 (CCK8) reagent was added into the plates. After 4 h incubation, the absorbance on 450 nm of each well was measured using the micro-plate reader.

Cell Invasion Assays

For cell invasion assays, the transwell inserts (Corning Costar, MA, USA) were used. The chambers of inserts were coated with matrigel matrix (BD, NJ, USA) before use. The breast cancer cells were digested and counted. 1×10^4 cells were put into the upper chamber with 300 μg DMEM without FBS. Then, the lower chambers of inserts were filled with 400 μg DMEM with FBS. After 48 h incubation, the cells invaded into the lower chamber were stained with methanol. 0.1% crystal violet was used for the cell dyeing. The numbers of invaded cells were calculated under a light microscope.

Dual-Luciferase Reporter Assays

We synthesized the sequences of SNHG7 which contained the predicted miRNA-381 and the interacting site or mutant site. The synthesized sequences were then inserted into the pmirGLO vector (Promega, Madison, WI, USA). The cells were then transfected with vectors and miR-381 or miR-control. After transfection, the Luciferase activities were detected by the Dual-Luciferase

reporter detection system (Promega, Madison, WI, USA). The Luciferase activity was normalized to Renilla Luciferase activity.

Statistical Analysis

We presented all the data as mean ± standard deviation (SD). GraphPad Prism 7.0 (GraphPad Software Inc., La Jolla, CA, USA) was used for photo drafting and statistical analysis. The statistical analysis method including the Student's *t*-test (2-tailed), Pearson's correlation analysis, Analysis of Variance (ANOVA) followed by the Dunnett test were used in this study. $p < 0.05$ was considered as statistically significant.

Results

LncRNA SNHG7 Was Notably Upregulated in Breast Cancer

We enrolled 30 patients who underwent breast cancer surgery in our hospital and collected breast cancer tissues and adjacent normal tissues. Using qRT-PCR, the expression of lncRNA SNHG7 was measured. Compared with the adjacent normal tissues, the expression of SNHG7 was significantly upregulated in breast cancer tissues (Figures 1A and 1B). Moreover, we measured the expression of SNHG7 in the normal breast epithelial cell line MCF-10A and four human breast cancer cell lines including ZR-75-1, HCC-1973, MDA-MB-231, and MDA-MB-468. It was found that the level of SNHG7 was remarkably upregulated in breast cancer cell lines than in normal breast epithelial cell line (Figure 1C). These results indicated that lncRNA SNHG7 was notably upregulated in breast cancer.

Knockdown of LncRNA SNHG7 Repressed Breast Cancer Cell Proliferation and Invasion

In order to determine whether SNHG7 exerted any function in breast cancer, we synthetized three siRNAs (si-SNHG7#1, si-SNHG7#2, and si-SNHG7#3). The siRNAs were then transfected into breast cancer cell lines ZR-75-1 and MDA-MB-231. The knockdown effects of the three siRNAs on SNHG7 were verified. It was found that si-SNHG7#2 could profoundly inhibit the SNHG7 expression (Figures 2A and 2B). The si-SNHG7#2 has been defined as si-SNHG7 and selected for further experiments. We transfected the breast cancer cells with si-SNHG7 or si-control and explored their functions. The findings of CCK8 assays showed that the knockdown of SNHG7 could significantly increase the OD values of ZR-75-1 and MDA-MB-231 cells (Figure 2C). As showed, the colony numbers of breast cancer cells in si-SNHG7 groups were significantly less than si-SNHG7 groups, which suggested that the knockdown of SNHG7 suppressed colony formation (Figure 2D). Moreover, the transwell invasion assays indicated that the knockdown of SNHG7 could notably suppress the invaded abilities of ZR-75-1 and MDA-MB-231 cells (Figure 2E). These results illustrated that lncRNA served as an oncogene in breast cancer.

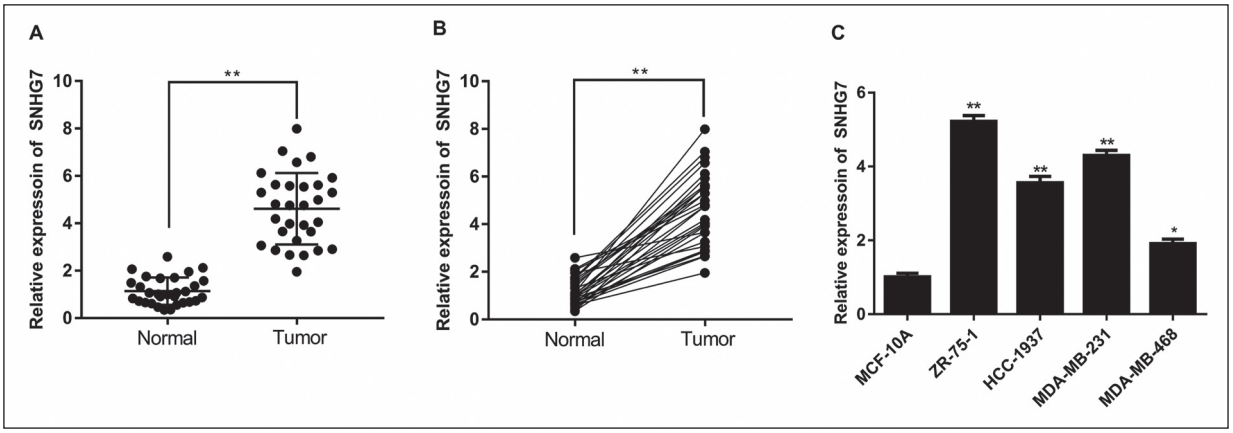

Figure 1. The lncRNA SNHG7 was notably upregulated in breast cancer. ***A,*** The expression of SNHG7 was measured in breast cancer and adjacent normal tissues. ***B,*** The results indicated that SNHG was significantly upregulated in breast cancer tissues. ***C,*** The level of SNHG7 was detected in breast cancer cell lines and normal breast epithelial cell line. $^{**}p<0.01$.

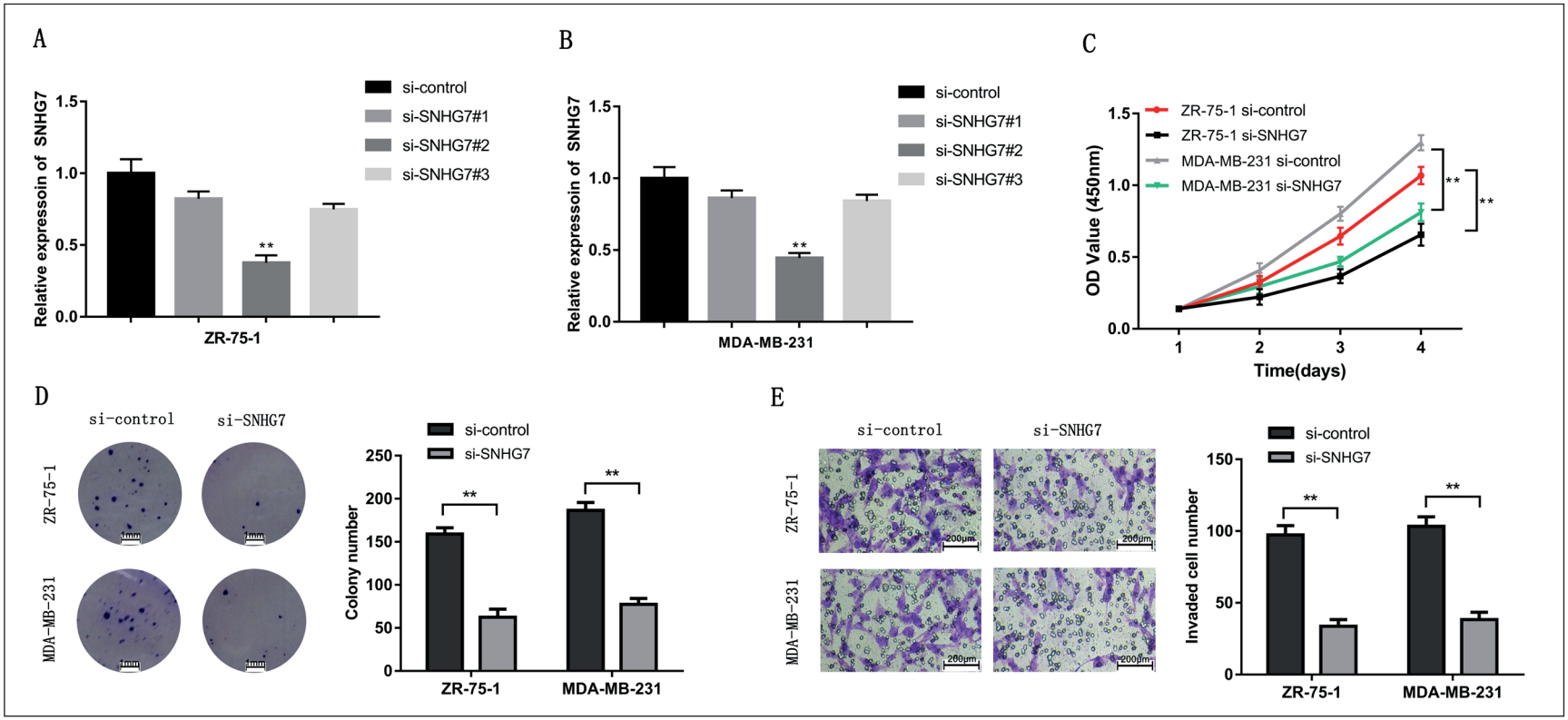

Figure 2. Knockdown of lncRNA SNHG7 repressed breast cancer cell proliferation and invasion. ***A, B,*** The knockdown effects of three siRNAs of SNHG7 in ZR-75-1 and MDA-MB-231 cell lines. ***C,*** The results of CCK8 assays on breast cancer cells which were transfected with si-SNHG7 or si-control. ***D,*** The results of the colony formation assays on breast cancer cells which were transfected with si-SNHG7 or si-control (10× magnifications). ***E,*** The results of invasion assays on breast cancer cells which were transfected with si-SNHG7 or si-control (200× magnifications). $^{**}p<0.01$.

MiRNA-381 Was a Direct Target of LncRNA SNHG7

To determine the underlying molecular mechanism of how lncRNA SNHG7 exerted its function, the online target prediction algorithm StarBase 2.0 was applied. As presented, it was predicted that miRNA-381 was a direct target of lncRNA SNHG7 (Figure 3A). We then measured the expression of miRNA-381 on breast cancer cells with si-SNHG7. Compared with the control group, the breast cancer cells with SNHG7 knockdown presented a higher level of miRNA-381 (Figure 3B). We also transfected breast cancer cells with miR-381 and miR-control (Figure 3C).

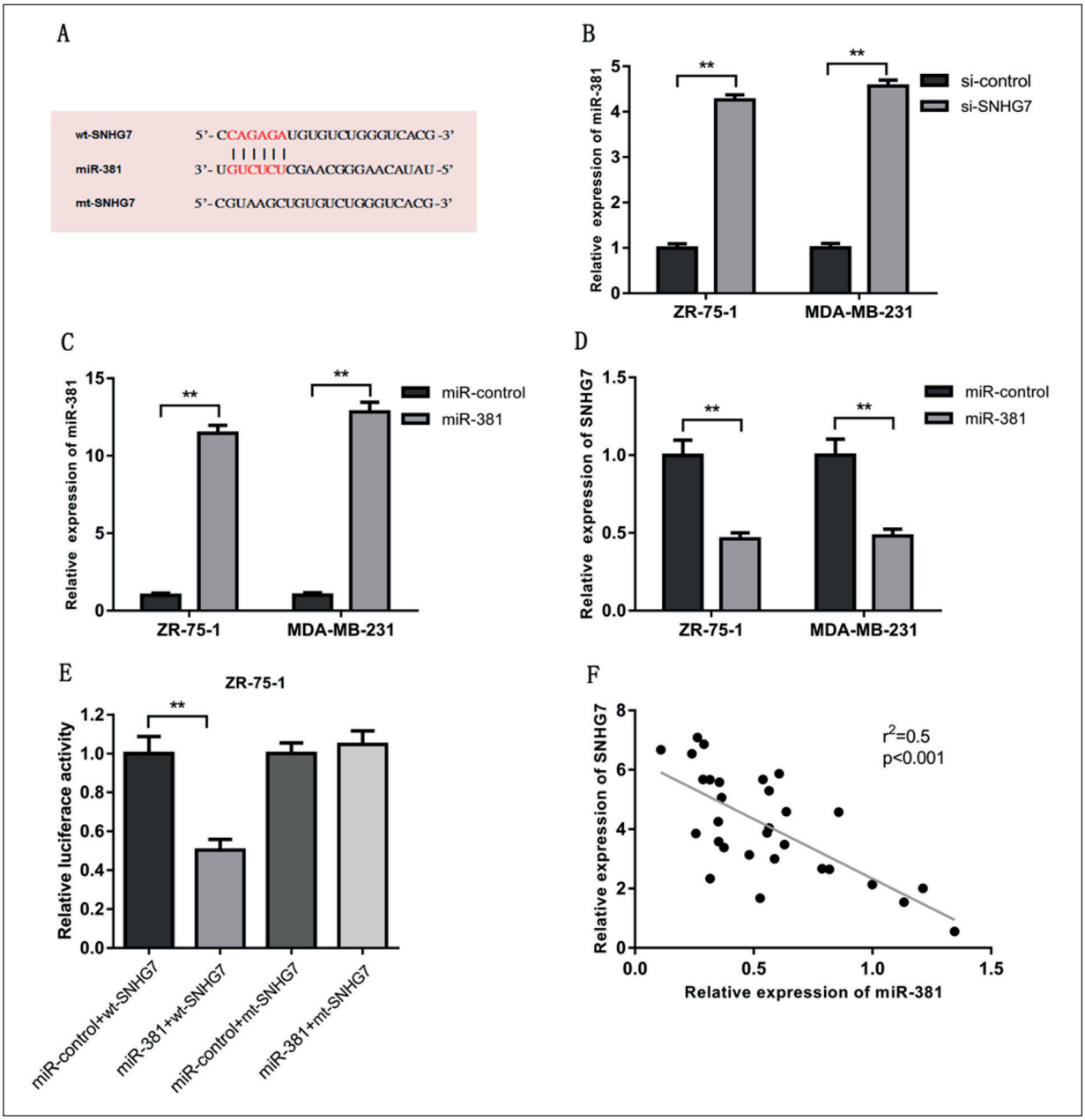

Figure 3. MiRNA-381 was a direct target of lncRNA SNHG7. ***A,*** The binding site between miRNA-381 and SNHG7 was presented. ***B,*** Knockdown of SNHG7 in breast cancer cells repressed the expression of miRNA-381. ***C,*** The overexpression of miRNA-381 was validated by qRT-PCR. ***D,*** The repressing effect of miRNA-381 on SNHG7 was validated. ***E,*** The sponging effects were determined by dual-luciferase reporter assays. ***F,*** There were negative correlation between miRNA-381 and SNHG7. $^{**}p<0.01$.

It was found that the overexpression of miRNA-381 could inhibit the expression of SNHG7 which indicated the sponging effect (Figure 3D). The Dual-Luciferase Reporter Assays were performed, and the results demonstrated that miRNA-381 was a direct target of lncRNA SNHG7 (Figure 3E). The expression of miRNA-381 was measured in the clinical samples. The expression of miRNA-381 and SNHG7 showed a significantly negative correlation, which further indicated the sponging effect between miRNA-381 and SNHG7 (Figure 3F).

The Functions of LncRNA SNHG7 on Breast Cancer Were Mediated by MiRNA-381

We co-transfected the breast cancer cells with miRNA-381 inhibitor and si-SNHG7. The rescued experiments including CCK8 assays, colony formation assays, and transwell invasion assays were conducted. The results of CCK8 assays demonstrated that the suppressive effects of si-SNHG7 on breast cancer proliferation could be reversed by a miRNA-381 inhibitor (Figures 4A and 4D). The colony formation assays indicated similar results (Figures 4B and 4E). The findings of the transwell invasion assays also revealed that si-SNHG7 could repress breast cancer cells' invasion but these effects could be reduced by a miRNA-381 inhibitor (Figures 4C and 4F). These results indicated that the functions of lncRNA SNHG7 on breast cancer were mediated by miRNA-381.

Discussion

Many studies revealed that lncRNA, a specific kind of non-coding RNA, could act as pivotal a role in many cellular processes. For instance, it was showed that lncRNA LINC00311 could target delta-like 3 to regulate the Notch-signaling pathway and affected the proliferation and differentiation of osteoclasts[15]. Zhao et al[16] demonstrated that lncRNA Blnc1 was highly induced in both brown and white fats from obese mice and active in preserving metabolic health by orchestrating the homeostatic adipose tissue remodeling. In the pathology processes such as cancer development and progression, there were studies[17-19] illustrating that lncRNA could affect cancer cell growth, migration, and invasion. More and more investigations tried to research the biological functions of lncRNA and its underlying mechanisms on cancer.

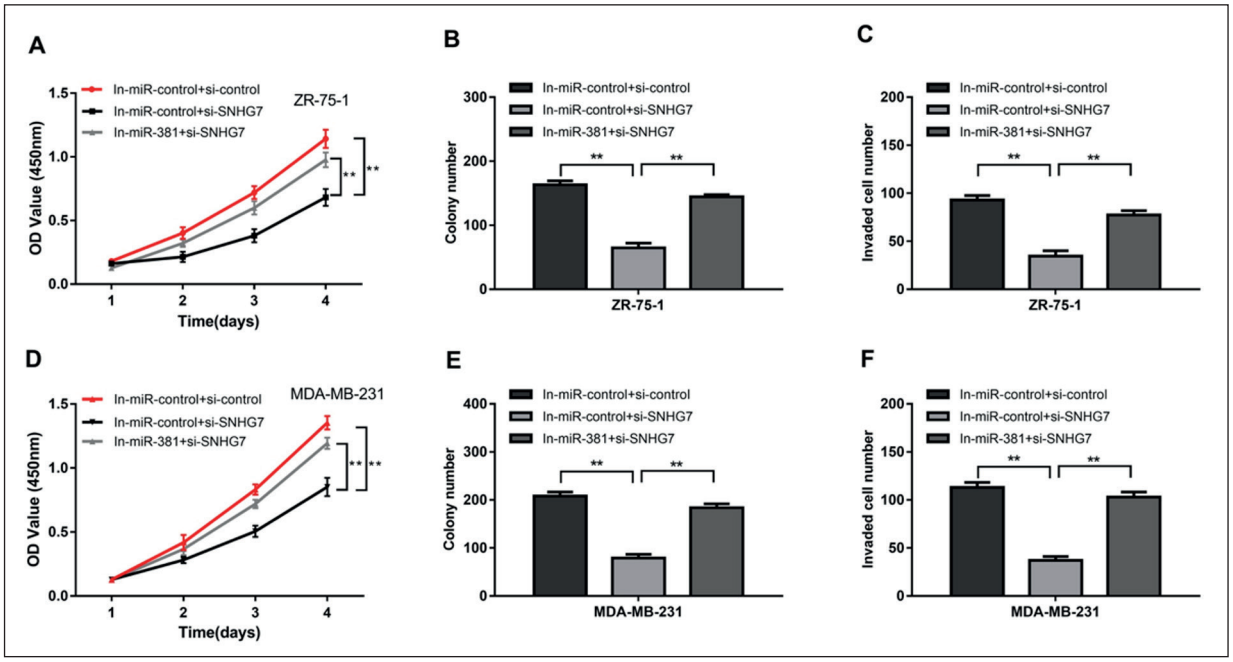

Figure 4. The functions of lncRNA SNHG7 on breast cancer were mediated by miRNA-381. ***A, B, C,*** The results of CCK8, colony formation, and invasion assays demonstrated that the suppressive effects of SNHG7 could be reversed by miRNA-381 in ZR-75-1 cells. ***D, F,*** The results of CCK8, colony formation, and invasion assays revealed that si-SNHG7 could repress breast cancer cells' invasion but receded by miRNA-381 inhibitor in MDA-MB-231 cells. ***p*<0.01.

Previous works have identified the translational sequences, full length, and some functions of SNHG7. Moreover, there are some researches which reveal the abnormal expression of SNHG7 in various kinds of cancers. Studies also found that SNHG could significantly affect the proliferation, migration, invasion, and apoptosis of cancer cells. She et al[20] found that SNHG7 was dramatically upregulated in lung cancer samples compared to adjacent normal samples. Further mechanism analysis revealed that SNHG7 had a positive correlation with FAS apoptotic inhibitory molecule 2 and inhibited lung cancer cell proliferation, migration, and invasion and promoted apoptosis via FAS apoptotic inhibitory molecule 2. Wang et al[21] suggested that the level of SNHG7 was increased in most of the gastric cancer tissues and gastric cancer cells. The altered expression of SNHG7 could significantly affect gastric cancer cell proliferation and apoptosis. However, the expression profile and function of SNHG7 in breast cancer is not clear. In the present study, we enrolled a cohort of breast cancer and collected their breast cancer tissues, as well as adjacent normal tissues. The expression of SNHG7 was determined by qRT-PCR and it suggested that SNHG7 was remarkably upregulated in breast cancer tissues and cell lines. To the best of our knowledge, this is the first study to determine the expression profile of SNHG7 in breast cancer. Herein, we tried to knockdown the expression of SNHG7 in breast cancer cells and observed the change of phenotype. The experimental assays indicated that the knockdown of SNHG7 dramatically repressed breast cancer cell proliferation and invasion, which suggested that SNHG7 acts as an oncogene in breast cancer.

The distinct lncRNAs play roles in the genesis and development of cancer through some exact mechanisms. One of the mechanisms in which lncRNAs exert function is sponging effect. The downstream molecules sponged by SNHG7 which have been discovered including miRNA-34a, miRNA-216b, miRNA-503, and miRNA-5095. Li et al[22] discovered that miRNA-34 was sponged by SNHG7 and thus affected the progression of colorectal cancer via PI3K/Akt/mTOR pathway. MiRNA-216 was found to be a downstream molecule of SNHG7 and mediated the promoting effects of SNHG7 on colorectal cancer growth and progression[23]. Qi et al[24] illustrated that SNHG7 activated the cell growth and cell cycle of prostate cancer by sponging miRNA-503. Ren et al[25] also demonstrated that SNHG7 could inhibit miRNA-5095 to make an influence on glioblastoma progression. By applying the predicted algorithm, we newly confirmed a sponged miRNA of SNHG7, which was miRNA-381. The sponging effects between SNHG7 and miR-381 were further verified by the Dual-Luciferase Reporter Assays and qRT-PCR assays. In addition, this kind of sponging effect was believed to be involved in the change of phenotype by SNHG7 in breast cancer cells. The promoting effects of SNHG7 on breast cancer progression were mediated by miRNA-381. Further studies should focus on the downstream molecules and pathway of SNHG7/miRNA-381.

Conclusions

We firstly determined the expression profile and phenotype of SNHG7 on breast cancer. The results suggested that SNHG7 was upregulated in breast cancer and promoted breast cancer proliferation by sponging miRNA-381. The SNHG7/miRNA-381 axis may provide potential therapy targets for breast cancer in the future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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