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Research Article
LncRNA SNHG1 Expression Changes and Mechanism Regulating in Breast Cancer

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Abstract

Background and Objective: Breast cancer is one of the most common malignant tumours in women. In recent years, the incidence of this disease in China has been increasing significantly. This study aimed to preliminarily inquire into the expression and mechanism of LncRNA SNHG1 (SNHG1) in Breast Cancer (BC) to see if there is a treatment benefit. **Materials and Methods:** The expression of SNHG1 and its relationship with tumour diseases were preliminarily screened by ENCORI, an online biological information analysis website. Paired cancerous tissues and adjacent normal tissues were obtained from 50 BC patients who received treatment in the First Central Hospital of Baoding from December, 2017-June, 2018. The measurement of SNHG1 expression in BC tissues employed qRT-PCR. SNHG1 overexpression vector (sh-SNHG1 group) and inhibitory expression vector (si-SNHG1 group) were transfected into BC cells and a blank control group (NC group) was set up. The transfection efficiency was determined by qRT-PCR. Measurements of BC cell multiplication, apoptosis, migration and invasiveness as well as Caspase-3 and MMP-2 protein expression adopted MTT assay, flow cytometry, transwell and western blot, respectively. **Results:** In ENCORI database, SNHG1 was mostly up-regulated, moreover, the prognostic analysis revealed higher prognostic mortality in those with high SNHG1 levels. In this study, SNHG1 was significantly higher in cancerous tissues than in their noncancerous counterparts ($p<0.05$). In the si-SNHG1 group, cells showed reduced multiplication, viability and MMP-2 protein expression, while increased apoptosis and Caspase-3 protein expression ($p<0.05$). While the opposite results were observed in the sh-SNHG1 group ($p<0.05$). **Conclusion:** SNHG1 is upregulated in BC tissues. Downregulation of SNHG1 inhibits the malignant behaviours of BC cells and enhances apoptosis.

Key words: Breast cancer, LncRNA SNHG1, invasiveness, apoptosis, proliferation

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Breast Cancer (BC) is a common malignancy that affects females, with an increasing incidence in China in recent years[1]. The survey shows that worldwide, there are approximately 300,000-500,000 newly diagnosed BC patients yearly and more than 1-3% of women have a potential risk of BC[2,3]. In addition, due to the high concealment of BC, there are no obvious clinical symptoms at the initial stage of the disease[4]. Because of this, patients often miss the optimal treatment timing. When BC shows obvious symptoms, the tumour has usually reached the middle and later stage, which directly leads to a very poor prognosis of BC[5]. Studies have shown a five-year relative survival rate exceeding 80% in women with early-stage BC, dropping to 20-30% in those at advanced stages[6]. Therefore, it is considered that effectively improving the early detection rate of BC is the key to ensuring patients' life and health in clinical practice[7]. Currently, however, BC screening still mainly relies on traditional markers, imaging technology, etc. and the only diagnostic gold standard is pathological biopsy[8]. It is still difficult to achieve rapid, effective, accurate and large-scale early detection. Because of this, researchers at home and abroad are constantly committed to finding a new way to achieve this significant clinical breakthrough.

With the increasing number of BC patients, the study of BC related genes has become the research hotspot[9]. Besides, BC is a multifactorial disease, whose initiation and development were meditated by plenty of intrinsic and extrinsic factors. Currently, the molecular pathological mechanisms of BC have not been fully clarified[10]. The progression of BC is regulated by abnormal activation of its oncogenes and abnormal deletion or inactivation of tumour-suppressor genes. Besides, these oncogenes and tumour-suppressor are aberrantly expressed in different stages of cell carcinogenesis[11]. Referring to previous studies, we found that LncRNA SNHG1 (SNHG1) is a gene that play a vital part in the development of neoplastic diseases and has been proved to regulate the activity of tumour cells such as cervical cancer, prostate cancer[12,13]. LncRNA SNHG1, located on the chromosome, has been shown to function as an oncogene in the human body[14]. When Taherian-Esfahani *et al.*[15] screened for abnormal genes in BC, they found that SNHG1 was also present. Therefore, this study hypothesize that SNHG1 may also interfere with the development of BC, which carries great implications for evaluating the disease. Given the current lack of research on SNHG1 concerning BC, we explored the expression changes and function of SNHG1 in BC tissues, intending to render novel references and guidance for diagnosing and treating BC in the clinic.

MATERIALS AND METHODS

Study area: This research project was conducted in Baoding First Hospital Lab China, from December, 2020-October, 2021.

Patient clinical data: This research was approved by the First Central Hospital of Baoding and followed the Declaration of Helsinki. Signed informed consent was obtained from all subjects. Fifty BC patients admitted to the First Central Hospital of Baoding who underwent surgical resection were selected as the study subjects. After obtaining the consent of patients before surgery, BC tissues and their non-cancerous counterparts (5 cm from the tumour edge confirmed by 2 pathologists) were obtained.

Eligibility criteria

Inclusion criteria: The included patients were all females, aged >18 years old, with BC diagnosis by pathological examination, complete clinical data and no prior treatment such as radiotherapy, chemotherapy or endocrine therapy.

Exclusion criteria: Those with other cardio-cerebrovascular diseases, neurological diseases, malignant tumours, liver and kidney dysfunction, communication disorders or drug allergies were excluded.

Reagents and equipment: The RPMI 1640 medium and p+s antibiotics were purchased from Sigma (USA). FBS was purchased from Gibco (USA). Lipofectamine 2000 and Trizol were supplied by Invitrogen (USA). SNHG1-WT and SNHG1-MUT for transfection was obtained from Hanbio (China). Annexin V-FITC/PIkit was bought from Keygentec (China). MTTkit was obtained from Sangon (China). The Transwell chambers were supplied by Corning (USA). PCR primers were designed by Genescript (China). SYBR® Premix ExTaqTMII and Transcriptor First Strand cDNA Synthesis Kit was purchased from Solarbio (China). miRNA reverse transcription kit was supplied by Takara (China). SYBR Green Realtime PCR Master Mix was bought from Thermo (USA). Rabbit anti-MMP-2 and Cleaved Caspase-3 antibodies were ordered from CST (USA).

Biological information analysis: The expression of SNHG1 and its relationship with tumour diseases were preliminarily screened using ENCORI (https://starbase.sysu.edu.cn/), an online biological information analysis website.

Table 1: Primer sequences

Genes	Primer sequences
SNHG1	
Forward	5′-CCTAAAGCCACGCTTCTTG-3′
Reverse	5′-TGCAGGCTGGAGATCCTACT-3′
GAPDH	
Forward	5′-ACCCAGAAGACTGTGGAGG-3′
Reverse	5′-TTCTAGACGGCAGGTCAGGT-3′

Expression of SNHG1 in BC by qRT-PCR: Trizol reagent was utilized for extracting RNA from samples to be tested and specific primers and other related reagents were added according to kit instructions. qRT-PCR reaction conditions (40 cycles): 95°C, 5 min, 95°C, the 30 sec, 60°C, 30 sec, 72°C, 30 sec and 72°C for 5 min. The expression of SNHG1 relative to GAPDH was analyzed using the $2^{-\Delta\Delta Ct}$ method. The primer sequences used in the experiment showed in Table 1.

Cell culture and transfection: MDA-MB-231 cells ordered from the cell bank of the Chinese Academy of Science Shanghai Branch were inoculated in RMPI-1640 containing 10% FBS and 100 U mL^{-1} p+s antibiotics. Cell transfection was carried out when cell convergence was 50% under the microscope. SNHG1 overexpression vector and SNHG1 inhibitory expression vector were transfected into MDA-MN-231, respectively and set as SNHG1-sh group and SNHG1-Si group. In addition, MDA-MB-231 cells treated with equal normal saline were set as the NC group. Follow-up experiments were performed 48 hrs after transfection.

MTT assay: The cells were treated with trypsin and transferred into 96-well plates at 5000 cells/well 48 hrs after transfection, MTT solution was placedat10 µL/well for 4 hrs of cultivation. After discarding the supernatant, 150 µL DMSO was added and mixed for 10 min. The OD value at 490 nm was read with the use of a microplate reader.

Flow cytometry (FCM): Cell digestion was performed 48 hrs after transfection with trypsin. After centrifugation and supernatant removal, the cells were rinsed with PBS and centrifuged again. Thereafter, combination buffer solution, annexin V-FITC and PI staining solution (Keygentec, China), with a volume of 500, 5 and 5 µL, respectively, were subsequently applied to the samples for 15 min of light-tight incubation at 26°C. The apoptotic rate was analyzed using a flow cytometer.

Transwell assay: To detect cell invasiveness, the matrigel and culture solution without serum was mixed at 1:9 and applied into the apical chamber to cover the PC membrane. The matrigel was condensed after 4 hrs of maintenance at 37°C. The residue was removed and the chamber was refreshed using culture solution. 100 µL suspension was added to the upper chamber at a density of 4×10^5 cell mL^{-1}. 500 µL culture medium containing serum was transferred into the lower chamber. Two days later, the cells were washed with PBS, followed by treated with paraformaldehyde (4%) immobilization for 20 min and crystal violet dyeing. Cells that remained at the upper surface were discarded by swabs. The cells were counted under the microscope at 400×. The detection procedure of cell migration was similar to cell invasiveness but without the application of matrigel.

Western blot: GAPDH served as the internal control to detect the levels of proteins. The film was scanned by the scanner and the bands grey values were obtained using quantity one software:

$$\text{Protein expression level} = \frac{\text{Target protein gray value}}{\text{GAPDH gray value}}$$

Statistical processing: Each experiment was repeatedly determined 3 times and the collected data were processed using SPSS v21.0 and represented by Mean±SD. The statistical methods were student's t-test, one-way ANOVA and SNK-q test and the statistical significance was defined as a $p<0.05$.

RESULTS

Biological information analysis of SNHG1: The ENCORI database shows that the expression level of SNHG1 in rectum adenocarcinoma tissue is higher than that in adjacent tissues (Fig. 1a). The ENCORI database shows that the expression level of SNHG1 in lung adenocarcinoma tissue is higher than that in adjacent tissues in (Fig. 1b). While the expression level of SNHG1 in colon adenocarcinoma tissue is higher than that in adjacent tissues in (Fig. 1c). Besides, the expression level of SNHG1 in esophageal carcinoma tissue is higher than that in adjacent tissues in (Fig. 1d). Further study showed that the survival rate of patients with kidney renal clear cell carcinoma with high expression of SNHG1 was significantly reduced in (Fig. 1e). Moreover, the prognostic analysis indicated that in bladder and kidney cancers, the high expression of SNHG1 predicted higher prognostic mortality. The result showed in (Fig. 1f).

Elevated SNHG1 expression in BC tissues: At first, SNHG1 expression in cancerous tissues and their normal tissues were determined by qRT-PCR. The results showed that the

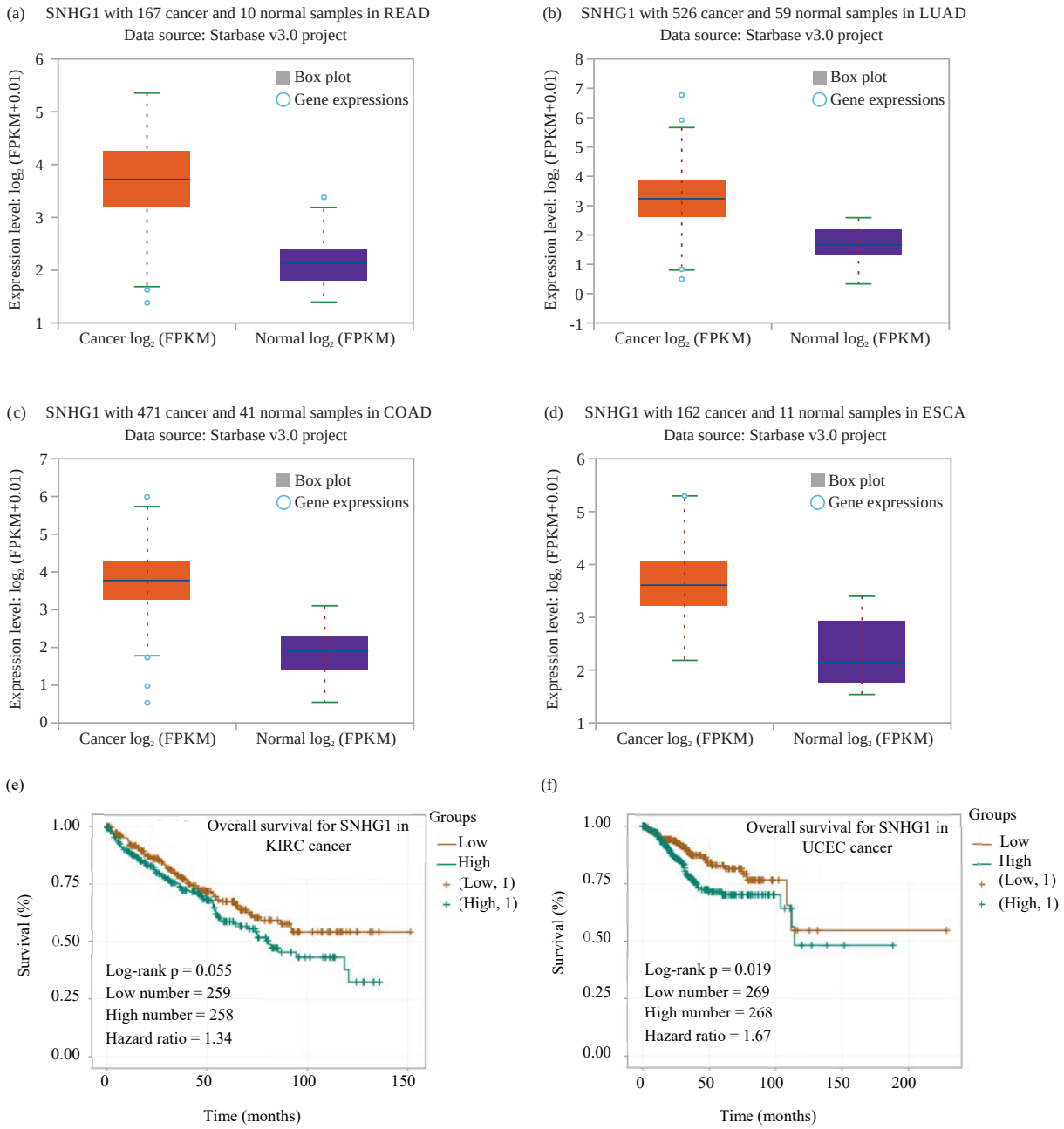

Fig. 1(a-f): Biological information analysis of SNHG1, (a) ENCORI database analyzes the expression of SNHG1 in rectum adenocarcinoma, (b) ENCORI database analyzes the expression of SNHG1 in lung adenocarcinoma, (c) ENCORI database analyzes the expression of SNHG1 in colon adenocarcinoma, (d) ENCORI database analyzes the expression of SNHG1 in esophageal carcinoma, (e) ENCORI database analyzes the relationship between SNHG1 and the prognosis of kidney renal clear cell carcinoma and (f) ENCORI database analyzes the relationship between SNHG1 and the prognosis of uterine corpus endometrial carcinoma

expression level of SNHG1 in cancerous tissues was 1.12±0.21, which was significantly higher than that of 0.54±0.13 in adjacent normal tissues ($p<0.05$). Figure 2, indicating elevated SNHG1 expression in BC tissues.

Influences of SNHG1 on BC cell proliferation: First, the transfection success rate was confirmed by PCR. SNHG1 expression was found to be the highest in the sh-SNHG1 group (2.48±0.12), followed in descending order by the NC

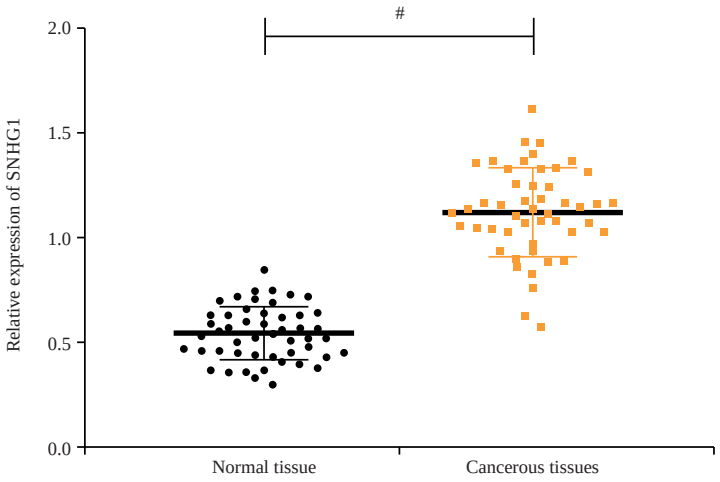

Fig. 2: qRT-PCR was used to detect the expression level of SNHG1 in cancerous tissues and adjacent tissues
Compared with adjacent tissues, the expression level of SNHG1 in cancer tissues was significantly higher and #p<0.05

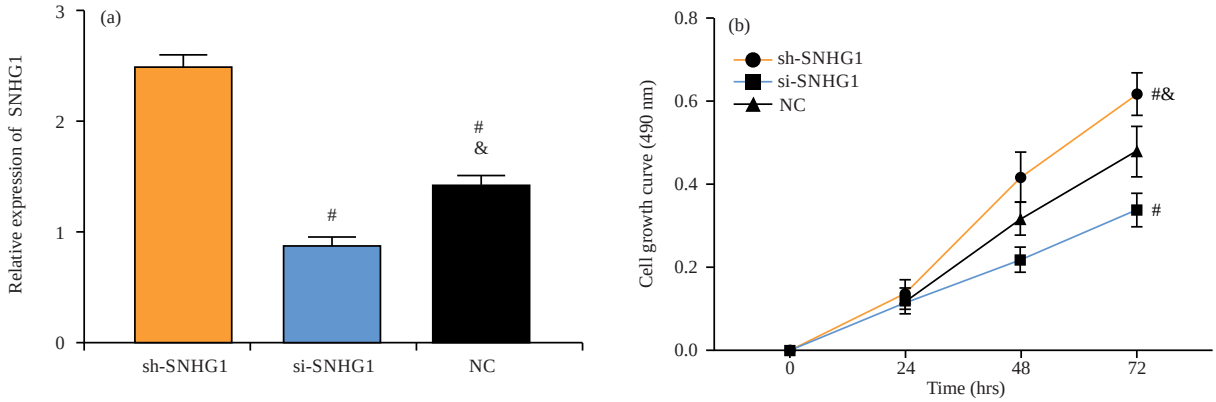

Fig. 3(a-b): Transfection success rate confirmed by qRT-PCR and MTT experiments to detect cell proliferation ability, (a) qRT-PCR verified the success rate of transfection and (b) Cell growth curve
sh-SNHG1 group cell proliferation ability is higher than si-SNHG1 group and NC group, while si-SNHG1 group cell proliferation ability is lower than NC group, compared with sh-SNHG1, #p<0.05, compared with si-SNHG1, p<0.05

group (1.42±0.09) and si-SNHG1 group (0.87±0.08) (p<0.05) Fig. 3a, confirming the success of transfection. MTT assay results identified that at 72 hrs, BC cell multiplication was the highest in the sh-SNHG1 group (0.62±0.05), followed in descending order by the NC group (0.48±0.06) and si-SNHG1 group (0.34±0.04) (p<0.05) (Fig. 3b), suggesting that SNHG1 down-regulation suppressed BC cell multiplication.

Influences of SNHG1 on BC cell apoptosis: The apoptosis rate of the 3 groups of cells was detected by FCM and the results are shown in (Fig. 4a). FCM showed that the apoptotic rate was the lowest in the sh-SNHG1 group (5.84±0.87%) among the three groups, while the apoptotic rate in the si-SNHG1 group (18.63±2.63%) was higher than that in the NC group (8.54±1.34%) (p<0.05) (Fig. 4b). It can be seen that increasing SNHG1 can inhibit cell apoptosis while silencing SNHG1 promotes cell apoptosis.

Influences of SNHG1 on BC cell Caspase-3 protein: Caspase-3 is a pro-apoptotic factor related to apoptosis. The western blot map of Caspase-3 is shown in (Fig. 5a). Western blot detection showed that Caspase-3 protein expression was the lowest in the sh-SNHG1 group (0.19±0.04) among the 3 groups, while that in the si-SNHG1 group (0.86±0.08) was higher compared with the NC group (0.58±0.06) (p<0.05) (Fig. 5b). It can be seen that increasing the expression of SNHG1 in BC cells can inhibit the expression of Caspase-3 protein and silencing SNHG1 can promote the expression of Caspase-3 protein.

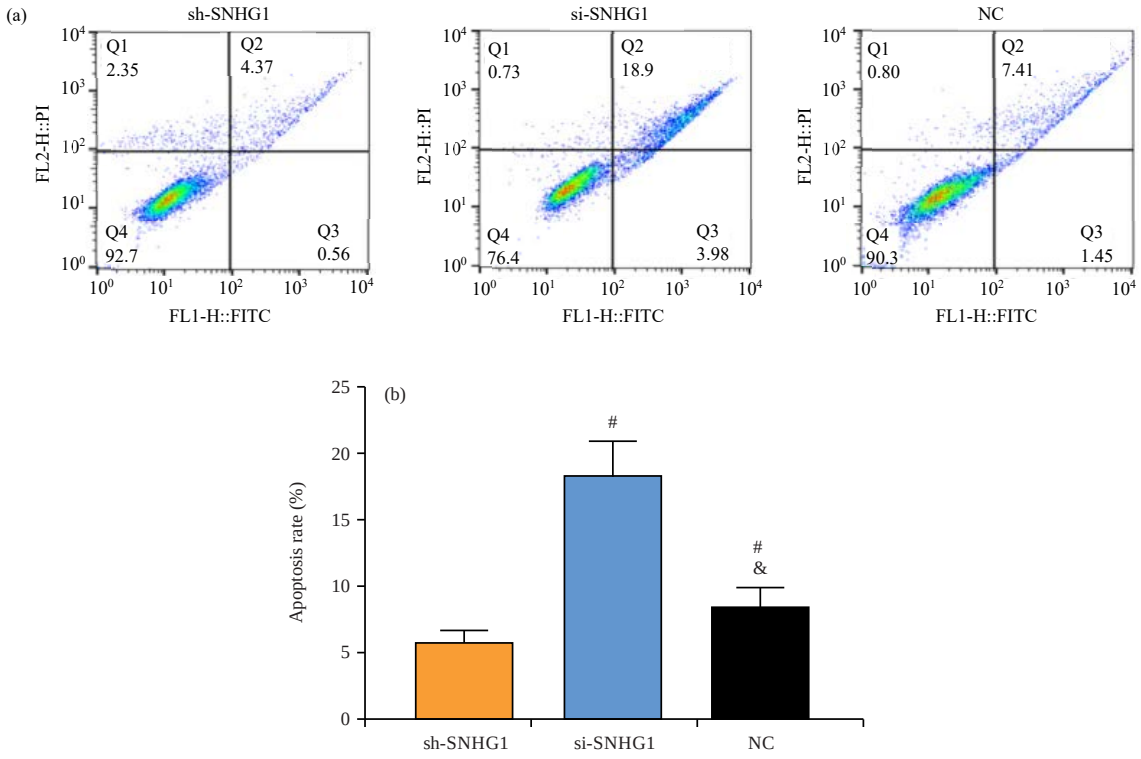

Fig. 4(a-b): FMC detects the effect of SNHG1 on the apoptosis rate of BC cells, (a) FMC results and (b) Apoptosis rate

Apoptosis rate of the sh-SNHG1 group was lower than that of the si-SNHG1 group and NC group and the apoptosis rate of the si-SNHG1 group was higher than that of the NC group, compared with sh-SNHG1, #p<0.05, compared with si-SNHG1 and p<0.05

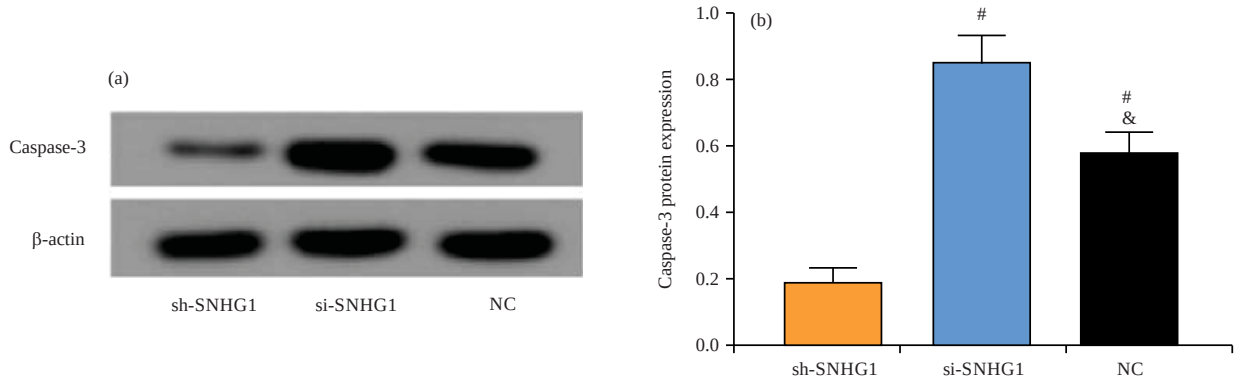

Fig. 5(a-b): Western blot was used to detect the effect of SNHG1 on the expression of Caspase-3 protein in BC cells, (a) Western blot map and (b) Caspase-3 protein expression in BC cells

#p<0.05, compared with si-SNHG1 and p<0.05

Influences of SNHG1 on BC cell invasiveness: The results of transwell staining are shown in Fig. 6a. Transwell assay showed that the number of invaded cells was the highest in the sh-SNHG1 group (124.63±8.11), followed in descending order by the NC group (96.14±8.41) and si-SNHG1 group (67.14±6.09) (p<0.05) (Fig. 6b). It can be seen that increasing the expression of SNHG1 can promote the invasion ability of BC cells and silencing SNHG1 can inhibit the invasion ability of BC cells.

Influences of SNHG1 on BC cell migration: The results of transwell staining are shown in Fig. 7a. Similarly, the

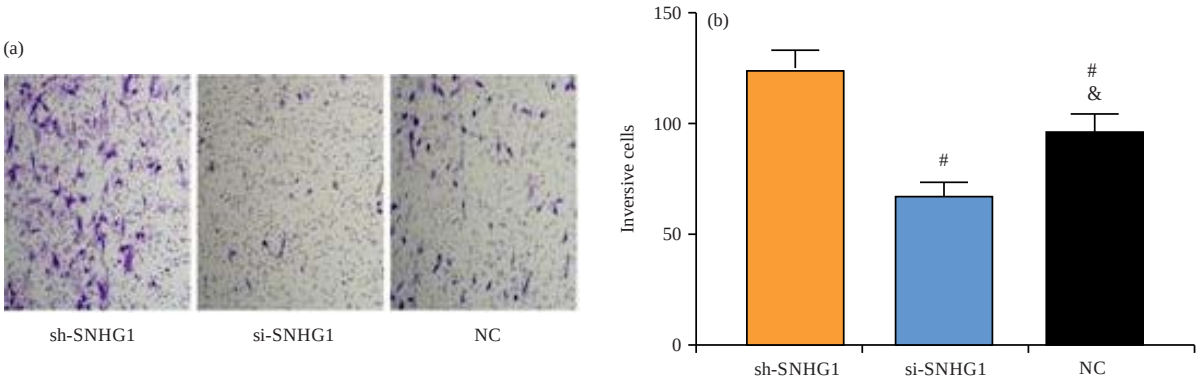

Fig. 6(a-b): Transwell experiment detects the effect of SNHG1 on the invasion ability of BC cells, (a) Stained image of invaded cells in transwell experiment and (b) Number of invaded cells in the transwell experiment

#p<0.05, compared with si-SNHG1 and p<0.05

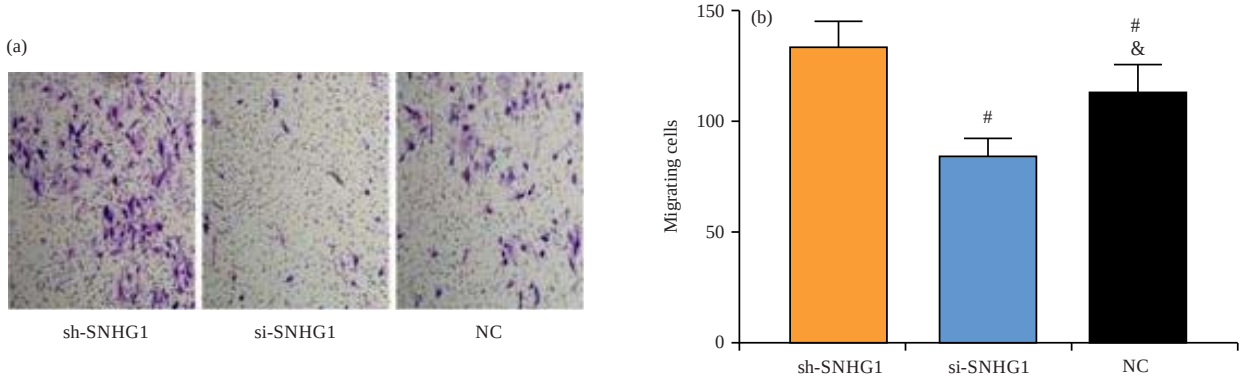

Fig. 7(a-b): Transwell experiment detects the effect of SNHG1 on the migration ability of BC cells, (a) Stained image of migrating cells in the transwell experiment and (b) Number of migrating cells in the transwell experiment

#p<0.05, compared with si-SNHG1 and p<0.05

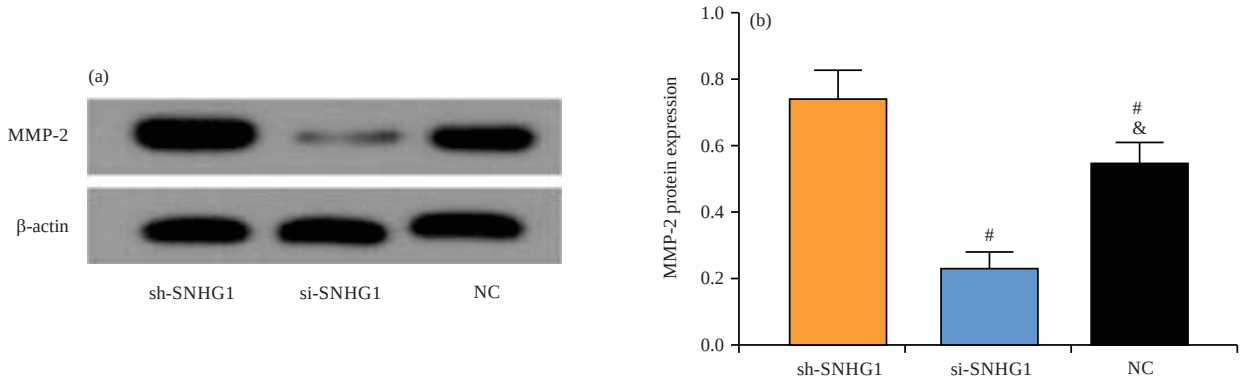

Fig. 8(a-b): Western blot experiment was used to detect the effect of SNHG1 on the expression of MMP-2 protein in BC cells, (a) Western blot map and (b) MMP-2 protein expression level in BC cells

#p<0.05, compared with si-SNHG1 and p<0.05

transwell assay also showed that the number of migrating cells was the highest in the sh-SNHG1 group (134.63±11.57), followed in descending order by the NC group (114.24±12.14) and si-SNHG1 group (85.14±8.61) ($p<0.05$) (Fig. 7b). It can be seen that increasing the expression of SNHG1 can promote the migration ability of BC cells while silencing SNHG1 can inhibit the migration ability of BC cells.

Influences of SNHG1 on BC cell MMP-2 protein: MMP-2 is a matrix metalloproteinase related to cell invasiveness and migration. The western blot map of MMP-2 is shown in Fig. 8a. Western blot analysis showed that MMP-2 protein expression was also the highest in the sh-SNHG1 group (0.75±0.08) among the 3 groups, followed in descending order by the NC group (0.55±0.06) and si-SNHG1 group (0.24±0.05) ($p<0.05$) (Fig. 8b). It can be seen that increasing the expression of SNHG1 can promote the expression level of MMP-2 protein and silencing SNHG1 can inhibit the expression level of MMP-2 protein.

DISCUSSION

As one of the commonly seen malignancies threatening human life and health, BC is correlated with the age, job and genetic factors of patients[16]. With the continuous research on the pathogenesis of BC, it has been found that the onset of BC is linked to the aberrant expression of genes, including miRNAs and LncRNAs[17]. LncRNA played diverse roles in cancers because the long length of nucleotides makes it easier to establish complex molecular structures to exert different functions[18].

SNHG1 is a novel biomarker related to tumours discovered in recent years. Currently, abnormal expression of SNHG1 in lung cancer and hepatocellular carcinoma has been confirmed, but its relationship with BC remains unclear[19,20]. At present, the research on the relationship between lncRNA and tumors is a hotspot and new direction in clinical practice. Its clinical significance lies in that LncRNAs can be used as markers of tumour diseases to assist the early diagnosis and disease evaluation of tumors[21], Moreover, tumour cells can be killed by molecular targeted therapy from the perspective of LncRNAs[22]. Therefore, If the relationship between SNHG1 and BC and the mechanism of action can be clearly understood, it may provide extremely favourable reference and guidance for the clinical treatment of BC in the future.

In this study, we 1st conducted a preliminary analysis of SNHG1 through the online database. SNHG1 was found to be up-regulated in most tumours and high expression of SNHG1 predicted an increased risk of prognosis and death in patients. Subsequently, we detected the expression of SNHG1 in BC tissues and their noncancerous counterparts and observed up-regulated SNHG1 in BC tissues. In addition, in the analysis of clinicopathological features of BC, we found that patients with higher TNM stage and more severe disease had higher levels of SNHG1, which fully confirmed that SNHG1 was involved in the occurrence and development of BC. Based on the above experimental results, we preliminarily confirmed the expression of SNHG1 in BC. In the studies of Du, Q. and J. Chen[23] and Cai *et al.*[24], SNHG1 was also found to be highly expressed in bladder cancer, glioma, etc., which can also prove our experimental results, indicating that SNHG1 may have relatively consistent disease mechanisms in various diseases. In addition, a previous study revealed that SNHG1 was a marker of poor prognosis in patients with colon cancer and silencing the expression of SNHG1 could inhibit the proliferation, invasion and migration of colorectal cancer cells and enhance their apoptosis, which suggested that SNGH1 can accelerate the development and progression of coloncancer[25]. Moreover, elevated SNHG1 is observed in cervical tissues and cells, After down-regulating SNHG1 in cervical cancer cells by siRNA, the metastasis potential and proliferation rate of cervical cancer cells were reduced, which indicates that SNHG1 may have a suppressive effect on the malignancy and metastasis of cervical cancer[26]. It can be seen that the highly expressed SNHG1 plays a role in the oncogenic gene in most tumour diseases. And combined with the results of our above experiments, we preliminarily speculate that SNHG1 also has a certain activating effect on BC cells. However, no studies have confirmed the mechanism of action of SNHG1 in BC. Therefore, we further regulated the expression of SNHG1 in NC cells by transfection technology. Through MTT, FCM, transwell assay and other experiments, we found reduced capacities of BC cells to proliferate, invade and migrate after down-regulation of SNHG1, as well as weakened apoptosis. However, the biological behaviour of BC cells after overexpression of SNHG1 was opposite, which was consistent with our expectation, indicating that high expression of SNHG1 can promote the proliferation, invasion and migration of BC cells. In addition, the results also suggest that inhibition of SNHG1 expression can resist the malignant phenotype of BC cells, so targeted inhibition of SNHG1 expression may be a potential target for BC treatment. At present, the clinical treatment for BC is still based on surgery combined with or without radiotherapy and chemotherapy. In surgical treatment, complete mastectomy is usually required, which has a great negative impact on the overall appearance and psychology of women[27]. Furthermore, tumour drug resistance is very common in radiotherapy and

chemotherapy, failing to completely kill tumour cells[28]. Therefore, clinical efforts have been committed to finding an effective non-invasive treatment, which can not only completely alleviate the pathological threat of tumour diseases but also guarantee the psychological safety of patients after treatment[29]. However, no breakthroughs have been made so far. The results of this study fully reveal the possibility of successful implementation of molecular targeted therapy from the perspective of SNHG1 in the future, which can completely address the limitations of clinical treatment of BC at the present stage and is of great significance for clinical research of BC.

Western blot analysis also indicated that SNHG1 knockdown increased cleaved Caspase-3 protein expression, which verified the results of FCM and indicated that downregulation of SNHG1 expression can induce BC cell apoptosis. Meanwhile, the protein expression of MMP-2 decreased after SNHG1 down-regulation, which was consistent with the results of the Transwell assay, demonstrating that SNHG1 down-regulation could reduce the metastatic potential of BC and targeted inhibition of SNHG1 expression may be one of the effective ways to inhibit tumour metastasis. Through the repeated verification of the above experiments, can determine the mechanism of SNHG1 in BC and its future clinical application prospect, which will have important significance for the diagnosis and treatment of BC.

However, this study only preliminarily analyzed the role of SNHG1 in BC, while the realization of real clinical application requires more in-depth experimental analysis of SNHG1 in the diagnosis, disease evaluation, prognosis and mechanism of BC. In the future, this study will explore the relationship between SNHG1 and BC on this basis, to provide a more valid and comprehensive reference for clinical practice.

CONCLUSION

In conclusion, SNHG1 is highly expressed in BC, which is in close association with the disease progression. Down-regulation of SNHG1 expression can reduce the capacities of BC cells to proliferate, invade and migrate and enhance apoptosis. However, a more in-depth experimental analysis is needed to explore the mechanism of action of SNHG1.

SIGNIFICANCE STATEMENT

This study discovered that SNHG1 is highly expressed in BC, which is in close association with the disease progression that can be beneficial for therapy the breast cancer. This study will help the researchers to uncover the critical areas of different LncRNA effect the breast cancer therapy that many researchers were not able to explore. Thus a new theory on LncRNA regulating cancer may be arrived at.

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