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# SNHG7 mediates cisplatin-resistance in non-small cell lung cancer by activating PI3K/AKT pathway

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**Abstract. – OBJECTIVE: The aim of this study was to clarify the function of long noncoding ribonucleic acids (lncRNAs) small nucleolar RNA host gene 7 (SNHG7) in cisplatin-resistant non-small cell lung cancer (NSCLC), and to explore the potential mechanism.**

**PATIENTS AND METHODS: SNHG7 expression in NSCLC and para-cancerous tissues was determined by quantitative real-time polymerase chain reaction (qRT-PCR). Meanwhile, the correlation between SNHG7 expression with clinical stage and cisplatin-resistance in NSCLC patients was analyzed. After transfection of si-SNHG7 or p-complementary deoxyribonucleic acid (pcDNA)-SNHG7, changes in cellular behaviors of A549/DDP cells were evaluated, including cell viability, apoptosis, migration, invasion and cell cycle. The regulatory effects of SNHG7 on the expressions of genes were determined by qRT-PCR as well. Furthermore, Western blot was conducted to determine the protein expressions of drug-resistance genes minimal residual disease1 (MRD1), P-glycoprotein (P-gp), BCRP and relative genes in phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway.**

**RESULTS: Compared with adjacent normal tissues, SNHG7 was highly expressed in NSCLC tissues. Moreover, SNHG7 expression was significantly higher in advanced-stage NSCLC patients than those in early-stage. SNHG7 level remained significantly higher in DDP-resistant NSCLC tissues and cell lines as well. Knockdown of SNHG7 remarkably enhanced cisplatin-resistance in NSCLC cells, manifesting as decreased cell viability, migratory and invasive rates, DNA synthesis capacity, and promoted apoptosis. Meanwhile, SNHG7 knockdown down-regulated the mRNA levels of matrix metalloprotein2 (MMP2), MMP7 and MMP9 in vitro. After SNHG7 knockdown, the expressions of drug-resistant and relative genes in the PI3K/AKT pathway were notably down-regulated.**

**CONCLUSIONS: SNHG7 induces the development of cisplatin-resistance in NSCLC through upregulating MRD1 and BCRP via PI3K/AKT pathway.**

*Key Words:*
Non-small cell lung cancer (NSCLC), Cisplatin-resistance, SNHG7, PI3K/AKT pathway.

## Introduction

Lung cancer is a common malignancy with the highest morbidity and mortality worldwide. As the major histological type, non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases[1]. Currently, platinum-based combination chemotherapy is the first-line treatment for NSCLC[2]. However, due to the development of primary and secondary drug-resistance, the efficacy of platinum-based chemotherapy is greatly restricted. It is reported that about 70% of NSCLC patients may develop platinum-based chemotherapy resistance within 4-6 months, eventually leading to treatment failure[3]. Therefore, prevention and reversion of platinum-based drug resistance are of great significance to improve the prognosis of NSCLC patients.

Long non-coding ribonucleic acids (lncRNAs) are a class of non-coding RNAs containing over 200 nt in length. They are mostly transcribed from RNA polymerase II[4]. Some lncRNAs have 5' cap and 3' poly (A) tails that are involved in splicing process[5]. In comparison with small non-coding ribonucleic acids (ncRNAs), lncRNAs are lowly conserved. However, important functional regions of lncRNAs, such as the promoter region, tend to be highly conserved. Highly conserved promoter sequences and lowly conserved transcripts of lncRNAs allow their crucial functions[6]. Multiple cellulars and molecular biological processes are regulated by lncRNAs. Among them, lncRNAs are closely related to the occurrence and development of malignant tumors. Recent studies have shown that there is a close relationship between abnormal expres-

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sion of lncRNAs and tumor cell resistance. For example, the expression of lncRNA HOTAIR is significantly up-regulated in cisplatin-resistant A549/DDP cell line relative to cisplatin-sensitive cell line. Down-regulation of HOX transcript antisense RNA (HOTAIR) reverses the sensitivity of A549 cells to cisplatin through arresting the cell cycle in the $G_0/G_1$ phase and inducing apoptosis *via* up-regulating p21 (WAF1/CIP1)[7]. LncRNA MEG3 is lowly expressed in A549/DDP cells relative to parental cells. Meanwhile, up-regulation of MEG3 enhances cisplatin-resistance in lung cancer cells; however, the specific mechanism remains unknown[8]. Similarly, Xia Y. et al[9] have confirmed the regulatory effect of MEG3 on cisplatin-resistance of lung cancer cells *via* the activated Wnt/β-catenin pathway. LncRNA small nucleolar RNA host gene 7 (SNHG7) has been proved to promote the development of NSCLC[10,11]. However, its exact role in cisplatin-resistant NSCLC has not been fully elucidated. This research aimed to study the regulatory effect of SNHG7 on cisplatin-resistant NSCLC and the specific mechanism.

## Patients and Methods

### Sample Collection

Tumor and para-cancerous tissues (n=26) were collected from NSCLC patients in Xinjiang Uygur Autonomous Region People's Hospital from June 2013 to June 2016. None of these patients received pre-operative anti-tumor therapy. Cisplatin (DDP)-resistant patients developed drug resistance after first-line cisplatin-based combination chemotherapy. Enrolled patients denied other diseases. Collected tissues were immediately placed in RNase-free cryotubes (Invitrogen, Carlsbad, CA, USA) and preserved in liquid nitrogen within 15 min of *ex vivo*. Signed written informed consents were obtained from all participants before the study. This study was approved by the Ethics Committee of Xinjiang Uygur Autonomous Region People's Hospital.

### Cell Culture and Transfection

Cell lines used in this study were provided by American type culture collection (ATCC), (Manassas, VA, USA). All cells were cultured in Roswell Park Memorial Institute-1640 (RPMI-1640) medium containing 10% fetal bovine serum (FBS), 100 U/mL L-penicillin and 100 μg/mL streptomycin (Gibco, Rockville, MD, USA). DDP-resistant cell line (A549/DDP) was established by cisplatin induction in our laboratory and cultured in RPMI 1640 containing 0.9 ng/mL cisplatin (Gibco, Rockville, MD, USA).

One day prior to transfection, cells were seeded into 6-well plates (Corning, Corning, NY, USA) at a density of $1\times10^5$ cells per well. Cell transfection was performed at 60-70% of confluence for 48 h, according to the instructions of Lipofectamine™ 2000 (Invitrogen, Carlsbad, CA, USA). Fresh medium was replaced 6 h later. Transfection plasmids were provided by GenePharma (Shanghai, China).

### Quantitative Real Time-Polymerase Chain Reaction (qRT-PCR)

Total RNA was extracted from tissues using TRIzol reagent (Invitrogen, Carlsbad, CA, USA), and quantified using NanoDrop 2000 spectrophotometer. RNA samples with 1.8-2.0 of D260/D280 were considered qualified. Subsequently, these RNA samples were reverse transcribed into complementary deoxyribonucleic acid (cDNA) using Primescript RT Reagent (TaKaRa, Otsu, Shiga, Japan). Obtained cDNA was further amplified by real-time quantitative PCR using SYBR®Premix Ex Taq™ (TaKaRa, Otsu, Shiga, Japan). Relative expression levels of genes were quantitatively analyzed using the $2^{-\Delta\Delta Ct}$ method. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal reference. Primer sequences used in this study were as follows: SNHG7, F: CAACTGCCTGAAACCCCATCT, R: CGGGTTCAAGCGATTCTCCT; MDR1, F: CTGAAATCCAGCGGCAGA, R: TGTATCGGAGTCGCTTGGTGAG; BCRP, F: GCTGCAAGGAAAGATCCAAG, R: TTCCTGAGGCCAATAAGGTG; GAPDH, F: CGCTCTCTGCTCCTCCTGTTC, R: ATCCGTTGACTCCGACCTTCAC.

### Cytotoxicity Assay

Transfected cells were first seeded into 96-well plate with $2.0\times10^3$ cells per well, followed by incubation with 0, 2, 4, 6, 8 and 10 mg/mL cisplatin, respectively. 3 replicates were set for each concentration. Optical density (OD) at 450 nm was recorded using cell counting kit-8 (CCK-8) (Dojindo Laboratories, Kumamoto, Japan). Finally, the viability curve was plotted, and the $IC_{50}$ was calculated.

### Cell Apoptosis

48 h after transfection, the cells were incubated with 1 μg/mL cisplatin for another 48 h. Subse-

quently, the cells were re-suspended in 500 μL of binding buffer, followed by incubation with 5 μL of Annexin V-FITC (fluorescein isothiocyanate) and 10 μL of Propidium Iodide (PI; Biosciences, San Jose, CA, USA) in the dark for 30 min. Cell apoptosis was determined by flow cytometry (Beckman Coulter, Miami, FL, USA) within half an hour.

### Cell Cycle Determination

48 h after transfection, the cells were incubated with 1 μg/mL cisplatin for another 48 h. Then, the cells were fixed in pre-cooled ethanol overnight. Subsequently, the cells were subjected to incubation with 10 μL of PI in the dark for 1 h. Cell cycle was finally determined by flow cytometry.

### Transwell Cell Migration and Invasion Assay

48 h after transfection, the cells were incubated with 1 μg/mL cisplatin for another 48 h and adjusted to the concentration of $2.0\times10^5$/mL. 200 μL/well cell suspension was seeded into the upper Matrigel-coated (diluted in serum-free medium with 1:10) Transwell chamber (Millipore, Billerica, MA, USA). Meanwhile, 500 μL of medium containing 10% FBS (Gibco, Rockville, MD, USA) was seeded into the lower chamber. After 48 h of incubation, invasive cells were fixed in 4% paraformaldehyde, dyed with crystal violet and observed using a microscope. Penetrating cells were counted in 5 randomly selected fields per sample (magnification 10×). Transwell migration assay was conducted with the same procedures except for Matrigel pre-coating.

### Western Blot

Total protein in cells was extracted using radioimmunoprecipitation assay (RIPA: Invitrogen, Carlsbad, CA, USA). The concentration of extracted protein was quantified by the bicinchoninic acid (BCA: Sigma-Aldrich, St. Louis, MO, USA) method. Subsequently, protein samples were separated by electrophoresis and transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). After blocking them with 5% skim milk for 2 hours, the membranes were incubated with primary antibodies at 4°C overnight. On the next day, the membranes were incubated with corresponding secondary antibodies for 2 h. Immuno-reactive bands were exposed by enhanced chemiluminescence (ECL) and analyzed by Image Software (Silver Springs, MD, USA).

### Statistical Analysis

Statistical Product and Service Solutions (SPSS) 19.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Data were expressed as mean ± standard deviation. Intergroup difference was analyzed by *t*-test. $p<0.05$ was considered statistically significant.

## Results

### SNHG7 was Highly Expressed in Cisplatin-Resistant NSCLC Patients

We first examined SNHG7 expression in NSCLC and para-cancerous tissues by qRT-PCR. Compared with adjacent normal tissues, SNHG7 was highly expressed in NSCLC tissues (Figure 1A). Moreover, its expression in advanced-stage of NSCLC patients was significantly higher than those in early-stage (Figure 1B). These results indicated that SNHG7 might participate in the progression of NSCLC. In comparison with DDP-sensitive NSCLC patients, SNHG7 level remained significantly higher in DDP-resistant patients (Figure 1C). Therefore, we speculated that SNHG7 might be the regulator of cisplatin-resistance in NSCLC. Subsequently, A549/DDP cells showed significantly higher IC50 for cisplatin than parental cells (Figure 1D). Meanwhile, SNHG7 level in A549/DDP cells was remarkably higher than that of A549 cells, which was consistent with its expression pattern in NSCLC tissues (Figure 1E).

### Knockdown of SNHG7 Enhanced Cisplatin-Resistance in NSCLC Cells

To explore the role of SNHG7 in cisplatin-resistant NSCLC, we first verified the transfection efficacy of constructed si-SNHG7 in A549/DDP cells (Figure 2A). A significantly decreased cell viability and lower IC50 for cisplatin were observed in A549/DDP cells transfected with si-SNHG7 (Figure 2B). Flow cytometry indicated that apoptosis was markedly induced in drug-resistant cells with SNHG7 knockdown (Figure 2C). After transfection of si-SNHG7 in A549/DDP cells, the number of cells in S phase significantly decreased, suggesting a reduction in DNA synthesis capacity (Figure 2D). Meanwhile, both the migratory and invasive rates of cells were significantly reduced after SNHG7 knockdown (Figure 2E, 2F). Matrix metalloproteinases (MMPs) can promote cancer cells to invade and metastasize. MMP2 and MMP9 can hydrolyze

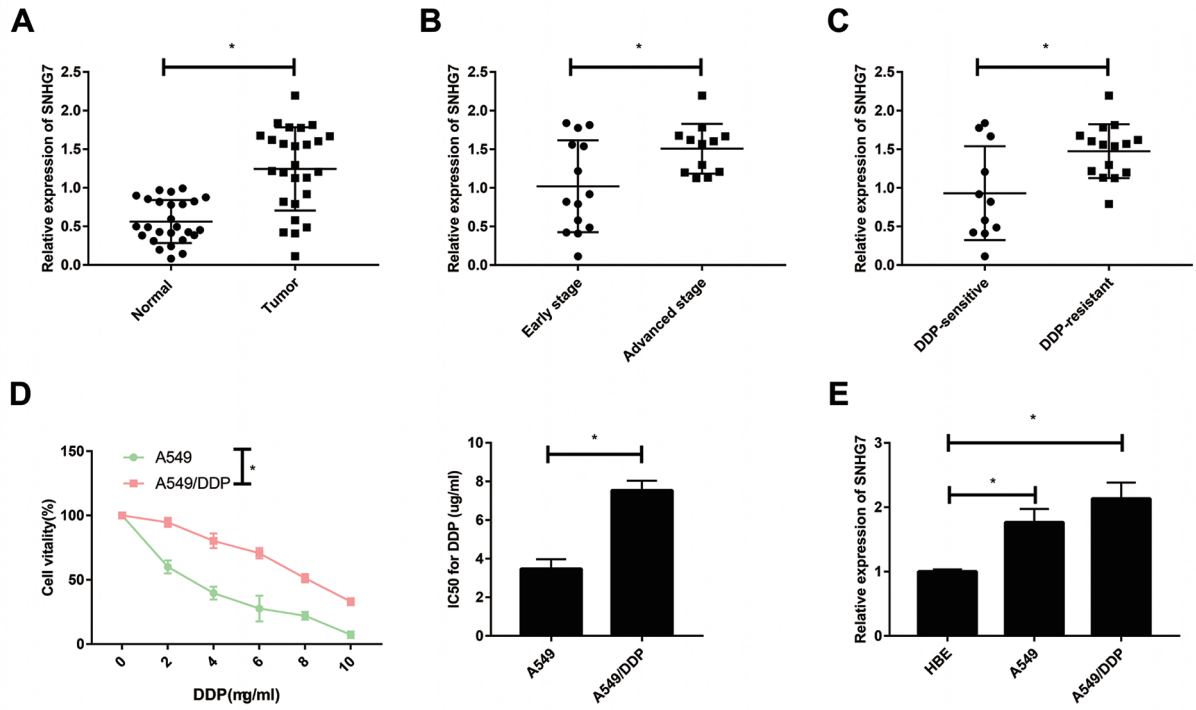


**Figure 1.** SNHG7 was highly expressed in cisplatin-resistant NSCLC patients. ***A,*** SNHG7 was highly expressed in NSCLC tissues compared with adjacent normal tissues (n=26). ***B,*** SNHG7 expression in advanced-stage NSCLC was significantly higher than those in early-stage. ***C,*** SNHG7 expression was significantly higher in DDP-resistant patients than DDP-sensitive patients. ***D,*** A549/DDP cells showed remarkably higher $IC_{50}$ to cisplatin than parental cells. ***E,*** SNHG7 expression was higher in A549/DDP cells than that of A549 cells.

various components such as type IV collagen in ECM, which are pronounced in the progression of malignant tumors[12]. MMP7 induces invasive cell growth by breaking through the limitations of basement membrane and extracellular matrix[13,14]. In this study, RT-PCR results revealed that the levels of MMP2, MMP7, and MMP9 were significantly down-regulated in A549/DDP cells transfected with si-SNHG7 (Figure 2G). The above experimental results suggested that cisplatin-sensitivity increased significantly in A549/DDP cells with SNHG7 knockdown.

### *Overexpression of SNHG7 Decreased Cisplatin-Resistance in NSCLC Cells*

Conversely, SNHG7 expression was significantly up-regulated after transfection of p-complementary deoxyribonucleic acid (pcDNA)-SNHG7 (Figure 3A). Cell viability and IC50 for cisplatin were markedly higher in A549/DDP cells over-expressing SNHG7 (Figure 3B). The percentage of apoptotic cells remarkably decreased after SNHG7 over-expression (Figure 3C). Meanwhile, after SNHG7 up-regulation, the number of A549/DDP cells in the S phase increased, showing an enhanced DNA synthesis capacity (Figure 3D). Transwell assay indicated that migratory and invasive rates of cells were remarkably enhanced after SNHG7 overexpression (Figure 3E, 3F). Finally, up-regulated levels of MMP2, MMP7 and MMP9 were observed in A549/DDP cells transfected with pcDNA-SNHG7 (Figure 3G).

### *Knockdown of SNHG7 Inhibited Phosphatidylinositol 3-Kinase (PI3K)/ Protein Kinase B (AKT) Pathway*

Further, we explored the possible mechanism of SNHG7 in cisplatin-resistant NSCLC. Drug-resistance in tumors has been proved to be related to drug-resistance genes MDR1[15], BCRP[16], and PI3K/AKT/mTOR pathway[17]. In this experiment, the mRNA levels of minimal residual disease1 (MRD1) and BCRP were down-regulated in A549/DDP cells after knockdown of SNHG7 (Figure 4A). Meanwhile, the protein levels of MRD1 and BCRP were down-regulated as well. Besides, the expression levels of PI3K, p-AKT, and p-mTOR were also significantly down-regulated by SNHG7 knockdown (Figure 4B).

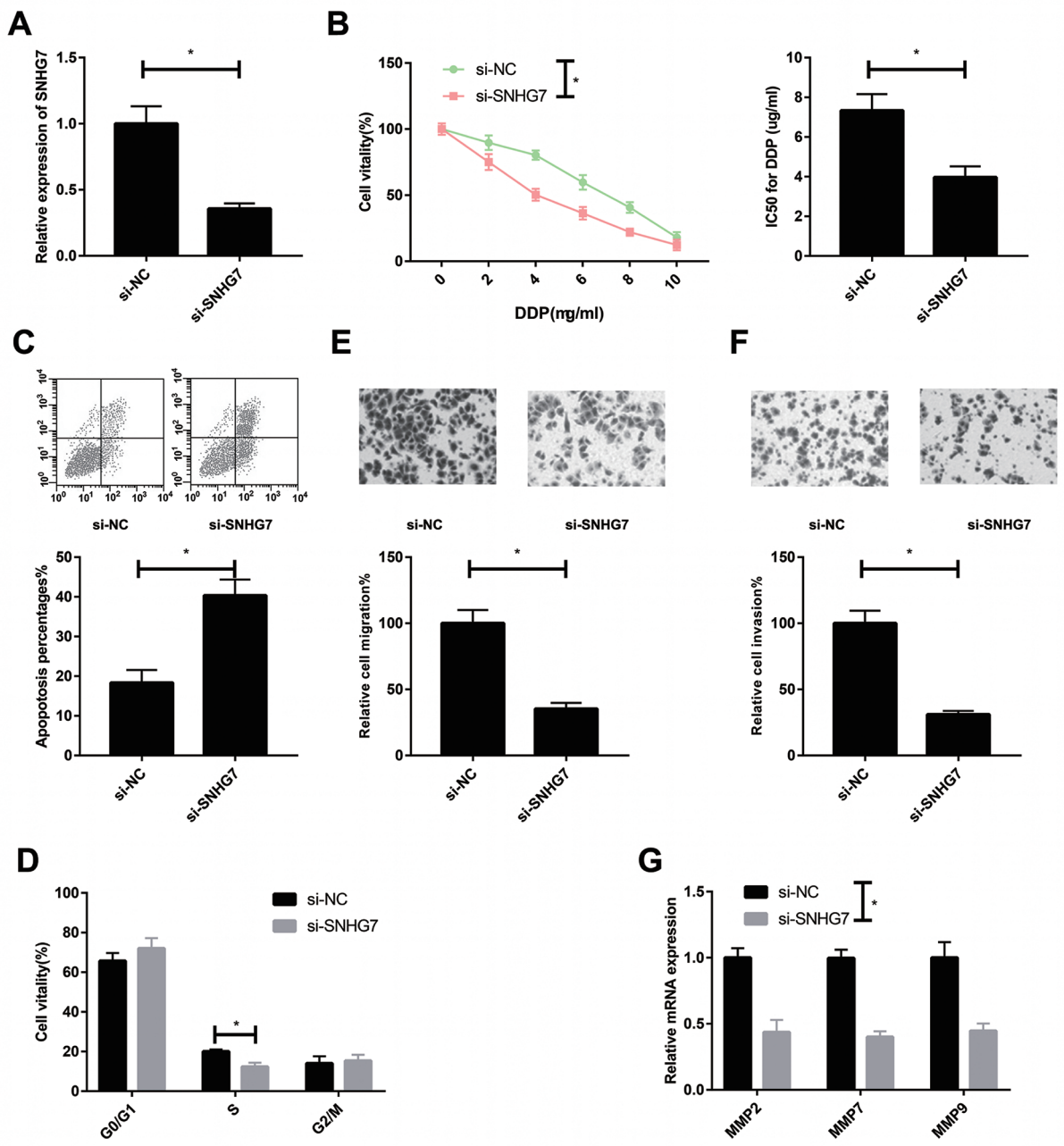


**Figure 2.** Knockdown of SNHG7 enhanced cisplatin-resistance in NSCLC cells. ***A,*** Transfection efficacy of si-SNHG7 in A549/DDP cells. ***B,*** Decreased cell viability and lower $IC_{50}$ for cisplatin were observed in A549/DDP cells transfected with si-SNHG7. ***C,*** Flow cytometry showed that apoptosis was markedly induced in drug-resistant cells with SNHG7 knockdown. ***D,*** Transfection of si-SNHG7 in A549/DDP cells decreased the number of cells in S phase. ***E,*** Transfection of si-SNHG7 in A549/DDP cells decreased the migratory rate. ***F,*** Transfection of si-SNHG7 in A549/DDP cells decreased invasive rate (magnification: 40×). ***G,*** RT-PCR results showed significantly down-regulated levels of MMP2, MMP7 and MMP9 in A549/DDP cells transfected with si-SNHG7.

## Discussion

In this investigation, we first examined SNHG7 expression in NSCLC patients. QRT-PCR data showed that SNHG7 was highly expressed in NSCLC when compared with normal controls. Moreover, advanced-stage or DDP-resistant NSCLC patients showed a significant higher level of SNHG7 relative to early-stage or DDP-sensitive NSCLC patients, respectively. Hence, we

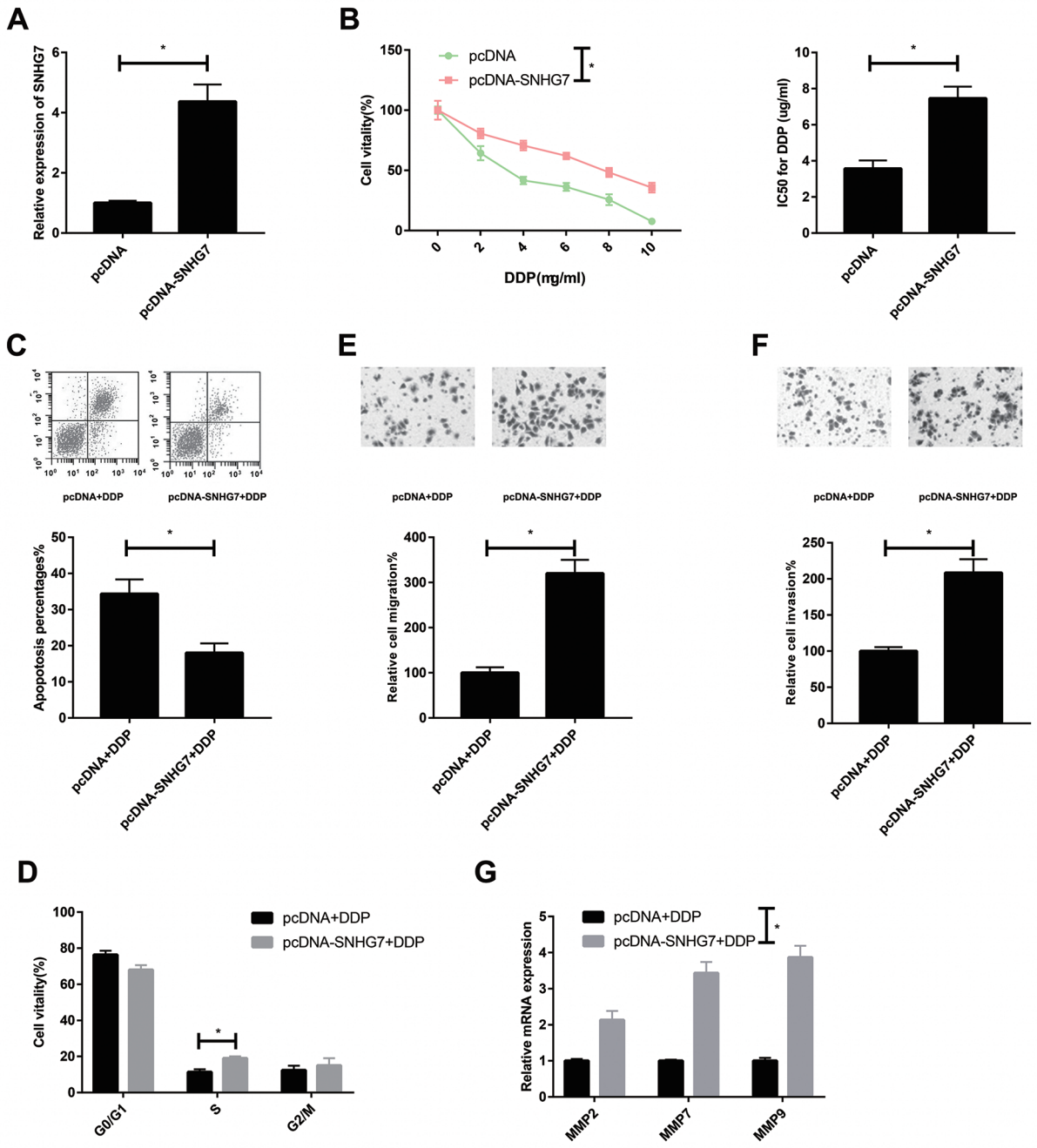


**Figure 3.** Overexpression of SNHG7 decreased cisplatin-resistance in NSCLC cells. ***A,*** Transfection efficacy of pcDNA-SNHG7 in A549/DDP cells. ***B,*** Increased cell viability and higher $IC_{50}$ for cisplatin were observed in A549/DDP cells transfected with pcDNA-SNHG7. ***C,*** Flow cytometry showed that apoptosis was markedly inhibited in drug-resistant cells with SNHG7 overexpression. ***D,*** Transfection of pcDNA-SNHG7 in A549/DDP cells increased the number of cells in S phase. ***E,*** Transfection of pcDNA-SNHG7 in A549/DDP cells increased the migratory rate. ***F,*** Transfection of pcDNA-SNHG7 in A549/DDP cells increased invasive rate (magnification: 40×). ***G,*** RT-PCR results showed significantly up-regulated levels of MMP2, MMP7 and MMP9 in A549/DDP cells transfected with pcDNA-SNHG7.

believed in the potential of SNHG7 to predict clinical stage and drug resistance of NSCLC. Studies have proved that SNHG7 is closely related to tumorigenesis. For example, SNHG7 is highly expressed in lung cancer and is positively correlated with the expression of Fas apoptotic inhibitory molecule 2 (FAIM2). Meanwhile, SNHG7 can promote the proliferative, migratory

and invasive abilities, and inhibit apoptosis of lung cancer cells by down-regulating miR-193b to up-regulate FAIM2[10,11]. In glioma, SNHG7 is also highly expressed. Moreover, it accelerates glioma cells to proliferate, migrate and invade through directly miR-5095 inhibition (inhibiting miR-5095) to up-regulates CTNNB1, thus inhibiting Wnt/β-catenin pathway[18]. In gastric cancer, SNHG7 promotes cell proliferation and reduces cell apoptosis by down-regulating p15 and p16[19]. The crucial functions of SNHG7 in the occurrence and progression of tumors have been widely explored. However, whether SNHG7 is involved in drug-resistance of NSCLC remains unknown. This study yielded the conclusion that SNHG7 served as an oncogene and induced cisplatin-resistance in NSCLC.

The mechanism of multi-drug resistance in tumors is very complex. ATP-binding cassette protein (ABC) located on cell membrane exerts a crucial role in multi-drug resistance, including multi-drug resistance-associated protein (MRP1/ABCC1) and multi-drug resistance protein (MDR1/Pgp/ABCB1)[15]. In 1976, the mechanism of tumor resistance was first proposed; it was showed that the drug pumping effect of the transmembrane transporters reduced intracellular concentration of anti-tumor drugs. Furthermore, the presence of cell membrane glycoprotein (Pgp) with 170 kDa was confirmed in MDR cells, known as MDR1[20]. Drugs transported by MDR1 are generally lipophilic compounds with large molecular weight, such as vincristine, taxanes, doxorubicin, etc.[21]. BCRP is the second member of the G subfamily belonging to the ABC family, with a molecular weight of approximately 75 kDa. It is the first MDR-associated transporter found in breast cancer cells[16]. BCRP mainly pumps intracellular drug by hydrolyzing ATP function, reduces intracellular drug concentration and leads to drug resistance[22]. Nakanishi and Ross[23] have shown that BCRP functions as a drug transporter in a dimer manner. In this experiment, we found that SNHG7 knockdown reduced the expressions of MRD1 and BCRP, thus elevating cisplatin-sensitivity in NSCLC.

Recent studies have elucidated the crucial role of the PI3K/AKT pathway in the occurrence and development of tumors. It mainly influences energy metabolism, growth, proliferation, invasion, and apoptosis of tumor cells[24]. The main members in this pathway, including PI3K, AKT, mTOR, and p70s6k, have been utilized as targets for developing anti-tumor drugs. Meanwhile, they have exerted promising aspects in clinical treatment[25,26]. PI3K/AKT pathway is also important in cisplatin-resistant tumor cells. Over-expression of AKT1 leads to cisplatin-resistance in lung cancer cells. Conversely, AKT1 knockdown reverses cisplatin-resistance in A549/DDP cells through mTOR-P70S6K1 pathway[17]. Our study found that SNHG7 knockdown significantly down-regulated

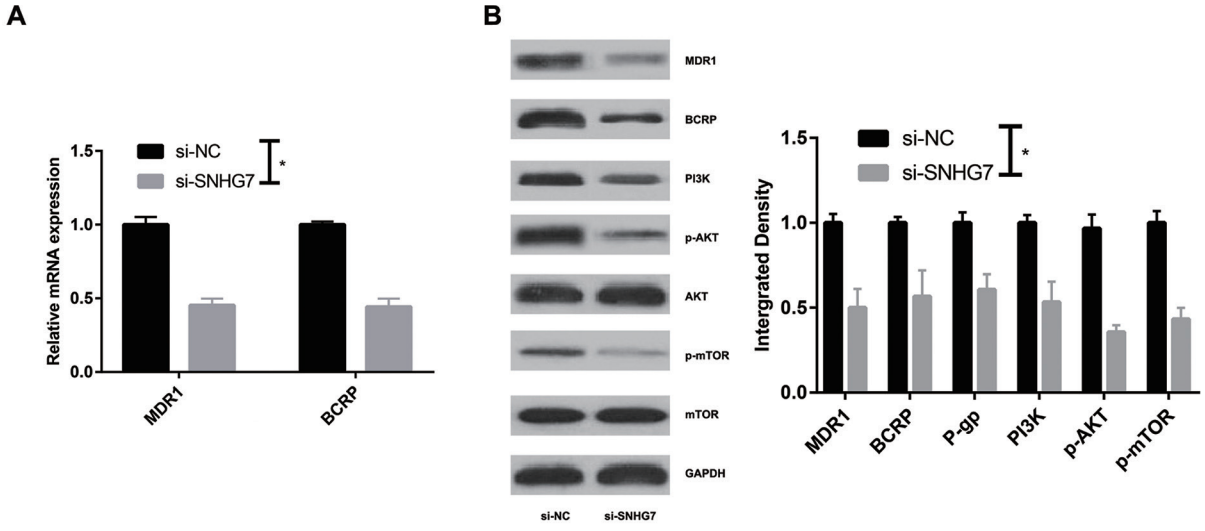


**Figure 4.** Knockdown of SNHG7 inhibited PI3K/AKT pathway. ***A,*** Transfection of si-SNHG7 in A549/DDP cells significantly down-regulated the mRNA levels of MRD1 and BCRP. ***B,*** Transfection of si-SNHG7 in A549/DDP cells significantly down-regulated the protein levels of MRD1, BCRP and relative genes in the PI3K/AKT pathway.

the levels of PI3K, p-AKT, and p-mTOR in cisplatin-resistant NSCLC cells.

## Conclusions

We found that SNHG7 induces the development of cisplatin-resistance in NSCLC through up-regulating MRD1 and BCRP *via* PI3K/AKT pathway.

### Conflict of interest

The authors declare no conflicts of interest.

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