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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 d ribonucleic acid (pcDNA)-SNHG7, chan cellular behaviors of A549/DDP cells were al-uated, including cell viability, apoptosis, m tion, invasion and cell cycle. The regulatory fects of SNHG7 on the expres of gen were determined by qRT-PCR. Further more, Western blot was c ucte deter-mine the protein expre ns of g-resis-tance genes minimal res dise P-glycoprotein (P-gp) CH tive g s in phosphatidylino 3-kin I3K)/protein kinase B (AKT) p ay.

RESULTS: Co with adjace mal tissues, SNHG7 nig pressed in SCLC tissues. More ver, SNHG ression was signifi-cantly hi in advanced NSCLC patients than th n early-stage. SN level remained signi tly hi in DDP-resistant NSCLC tissu d cel s as well. Knockdown of SNHG7 enha d cisplatin-resistance in NSC s, ma sting as decreased cell lity, i or d invasive rates, DNA syn-th capac promoted apoptosis. Mean-wh SNHG7 ockdown down-regulated the m ls of matrix metalloprotein2 (MMP2), MP9 in vitro. After SNHG7 knock-wn, the expressions of drug-resistant and rel-e genes in the PI3K/AKT pathway were nota-wn-regulated.

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

Key Words:
Non-small c g cancer (C) atin-resistance, SNHG AKT pathway.

Introd on

ung cancer i a common malignancy with highest mor ty and mortality worldwide. A major h logical type, non-small cell lung ar (N LC) accounts for about 85% of all lung cases[1]. Currently, platinum-based ombination chemotherapy is the first-line treat-for NSCLC[2]. However, due to the develop-en 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 ti=26) we collected from NSCLC patien Uygu Autonomous Region Peopl ospita m June 2013 to June 2016. No these ceived pre-operative py. tin (DDP)-resistant nts de d drug resistance after first-l splatin-bas mbination chemotherapy atients deni ther diseases. Collecte tissues immediately placed in RNase cryotubes itrogen, Carlsbad, CA, US nd preserved in l nitrogen within 15 m *ex vi* Signed written informed consen re ob ed from all participants before the st study approved by the Ethics amit Xini Uygur Autonomous Re- eople .

C ture and Transfection

used in this study were provided American type culture collection (ATCC), nassas, VA, USA). All cells were cultured i well 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 ed into 6-well plates (Corning, C ng, NY, USA) at a density of 1×10^5 cell well. Cell transfection was performed at 60 of confluence for 48 h, accordin the tions of Lipofectamine™ 2000 itrogen, C CA, USA). Fresh medi as rep ed 6 h Transfection plasmid re pr d by Gene-Pharma (Shanghai, Ch

Quantitativ al Time-r e Chain Reaction R)

Total R wa acted from tissues using TRIzol reagent (Invi Carlsbad, CA, USA), and ed using Na p 2000 spectrophoto er. RNA samples with 1.8-2.0 of D260/D280 considered ualified. Subsequently, these A samples w reverse transcribed into complementary deo bonucleic acid (cDNA) using Prim eagent (TaKaRa, Otsu, Shiga, Japan). d cDNA was further amplified by eal-time quantitative PCR using SYBR®Premix ™ (TaKaRa, Otsu, Shiga, Japan). Relative xpr on 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 2.0×10^3 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 2.0×10^5/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 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 ×200). 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, 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 paracancerous 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 that 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

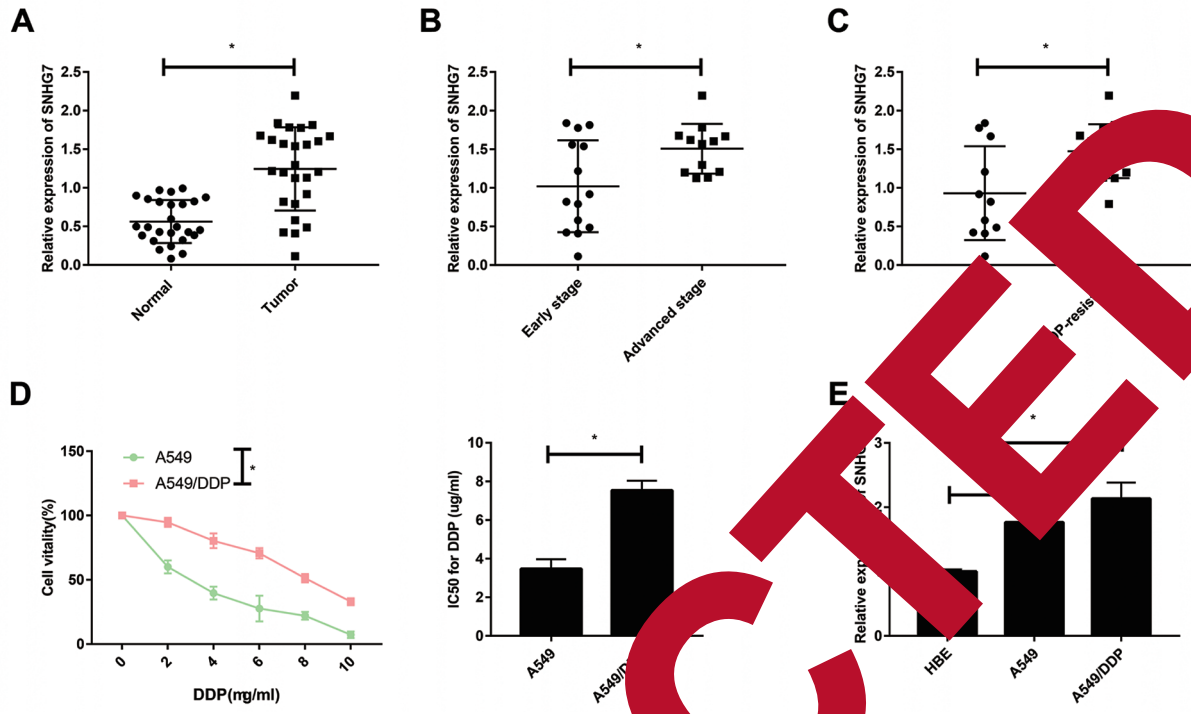


Figure 1. SNHG7 was highly expressed in cisplatin-resistant NSC[illegible]ients. ***A,*** [illegible]G7 was highly expressed in NSCLC tissues compared with adjacent normal tissues (n=26). ***B,*** SNHG7 ex[illegible]nced-stage NSCLC was significantly higher than those in early-stage. ***C,*** SNHG7 expressi[illegible] significantly hi[illegible]DDP-resistant patients than DDP-sensitive patients. ***D,*** A549/DDP cells showed remarkably h[illegible]latin than parental cells. ***E,*** SNHG7 expression was higher in A549/DDP cells than that of A549 cells.

various components such as ty[illegible]ollagen [illegible] ECM, which are pronounced[illegible]gressio[illegible] of malignant tumors[12]. M[illegible] induc[illegible]nvasive cell growth by breaking[illegible]gh th[illegible] of basement membra[illegible] a[illegible]llular [illegible]-trix[13,14]. In this stu[illegible]RT-PC[illegible]lts revealed that the levels [illegible]MP2, MM[illegible]d MMP9 were significa[illegible]regulated i[illegible]49/DDP cells transfecte[illegible]with s[illegible]HG7 (Figure 2G). The above ex[illegible]ental result[illegible]gested that cisplatin-sen[illegible]ty increased sig[illegible]antly in A549/DDP[illegible]s with[illegible]HG7 knockdown.

Over[illegible]ion of[illegible]HG7 Decreased [illegible]platin[illegible]ista[illegible]in NSCLC Cells

[illegible]verse[illegible]G7 expression was significan[illegible]up-regu[illegible]d after transfection of p-comp[illegible] deoxyribonucleic acid (pcDNA)-SN-[illegible] (Figure 3A). Cell viability and IC50 for [illegible]splatin were markedly higher in A549/DDP [illegible] over-expressing SNHG7 (Figure 3B). The pe[illegible]tage 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).

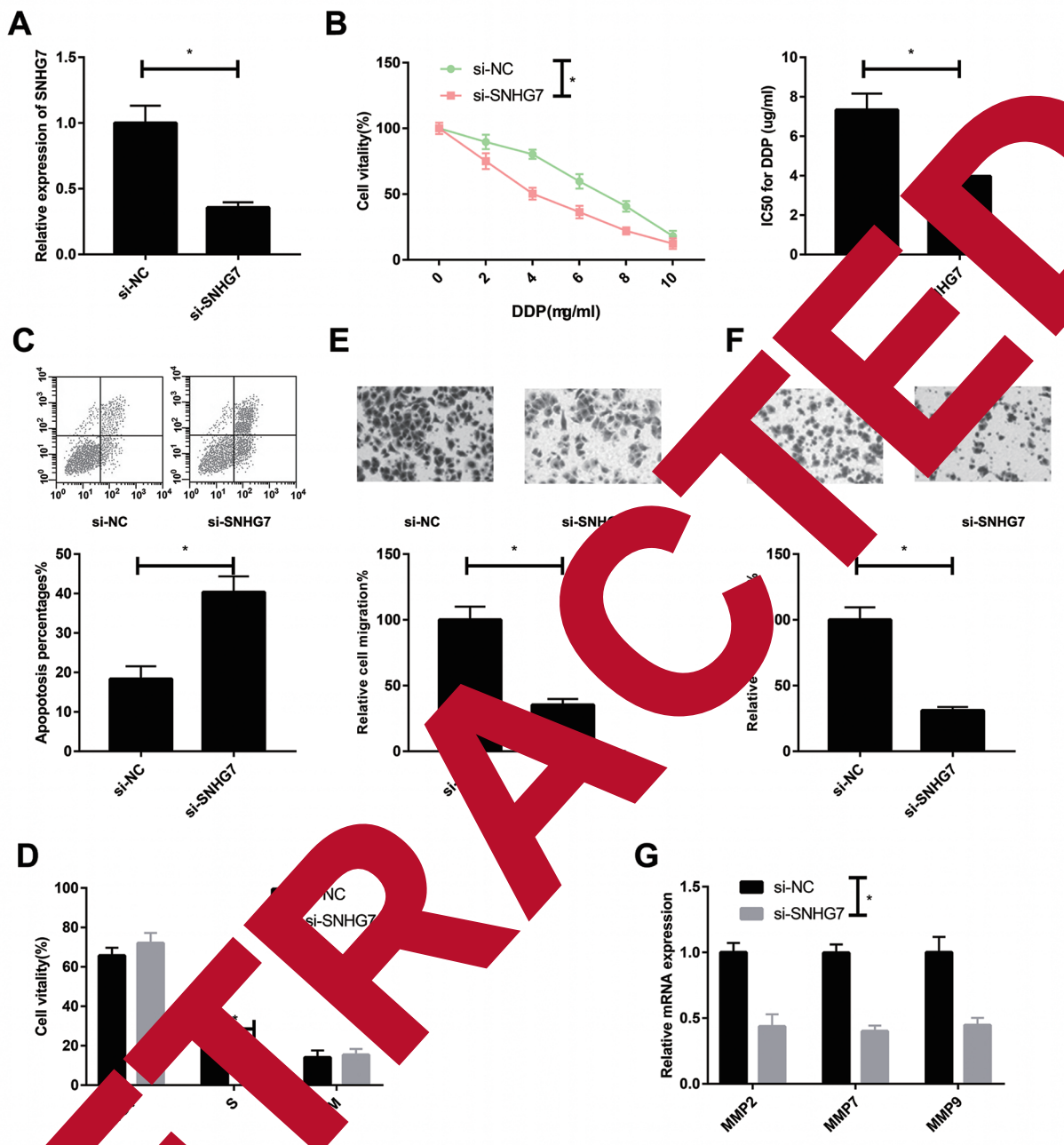
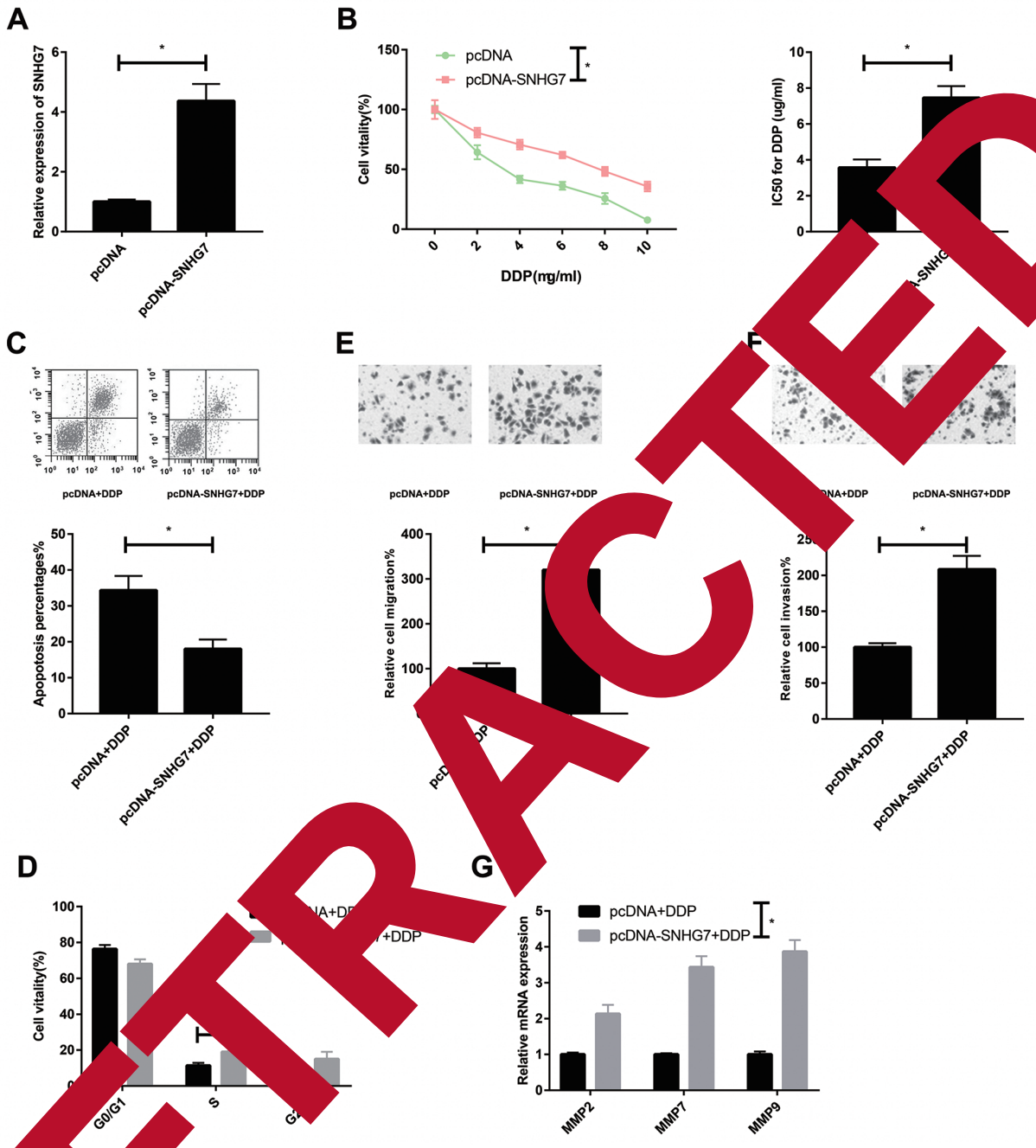


Fig Kn wn of SNHG7 enhanced cisplatin-resistance in NSCLC cells. ***A,*** Transfection efficacy of si-SNHG7 in A549/ **B,** Decre cell viability and lower IC_{50} for cisplatin were observed in A549/DDP cells transfected with si-SNHG ow cyto y showed that apoptosis was markedly induced in drug-resistant cells with SNHG7 knockdown. nsfect si G7 in A549/DDP cells decreased the number of cells in S phase. ***E,*** Transfection of si-SNHG7 in /DDP c eased the migratory rate. ***F,*** Transfection of si-SNHG7 in A549/DDP cells decreased invasive rate (ma cation: 40 ***G,*** RT-PCR results showed significantly down-regulated levels of MMP2, MMP7 and MMP9 in A549/DD nsfected 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



Figu ...xpressio... SNHG7 decreased cisplatin-resistance in NSCLC cells. ***A,*** Transfection efficacy of pcD-NA-SNH... A549/DD... ls. ***B,*** Increased cell viability and higher IC_{50} for cisplatin were observed in A549/DDP cells ...fected ...cDN... NHG7. ***C,*** Flow cytometry showed that apoptosis was markedly inhibited in drug-resistant cells w... HG7 o... ion. ***D,*** Transfection of pcDNA-SNHG7 in A549/DDP cells increased the number of cells in S phase. ***E,*** ...fection o... NA-SNHG7 in A549/DDP cells increased the migratory rate. ***F,*** Transfection of pcDNA-SNHG7 in A5... DP cells increased invasive rate (magnification: 40×). ***G,*** RT-PCR results showed significantly up-regulated levels of ... MMP9 in A549/DDP cells transfected with pcDNA-SNHG7.

be...d 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 propos it was showed that the drug pumping effec transmembrane transporters reduced intrac ar concentration of anti-tumor drugs. Furtherm the presence of cell membrane glycoprotein (P with 170 kDa was confirmed DR cell known as MDR1[20]. Drugs tr orte 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 f with a molecular weight of approximat It is the first MDR-associated transp found i breast cancer cells[16]. BCRP main mps intracellular drug by hydrolyzing AT ion, reduces intracellular drug con tratio leads to drug resistance[22]. Nak n and Ros shown that BCRP funct as a d transp in a dimer manner. I expe nt, we fou that SNHG7 knock low the ex ions of MRD1 and BC thus ng cis n-sensitivity in NS

Recent st e elucidate crucial role of the P AK hway in the occurrence and development of s. It mainly influences ene abolism, gr proliferation, invasi and apoptosis of tu or cells[24]. The main mbers in this thway, including PI3K, AKT, R, and p70s have been utilized as targets f eloping a umor drugs. Meanwhile, they hav ted ising aspects in clinical treatment[2 AKT pathway is also important in isplatin-resistant tumor cells. Over-expression of leads to cisplatin-resistance in lung can- Conversely, AKT1 knockdown reverses cisplatin-resistance in A549/DDP cells through mTOR-P70S6K1 pathway[17]. Our study found that SNHG7 knockdown significantly down-regulated

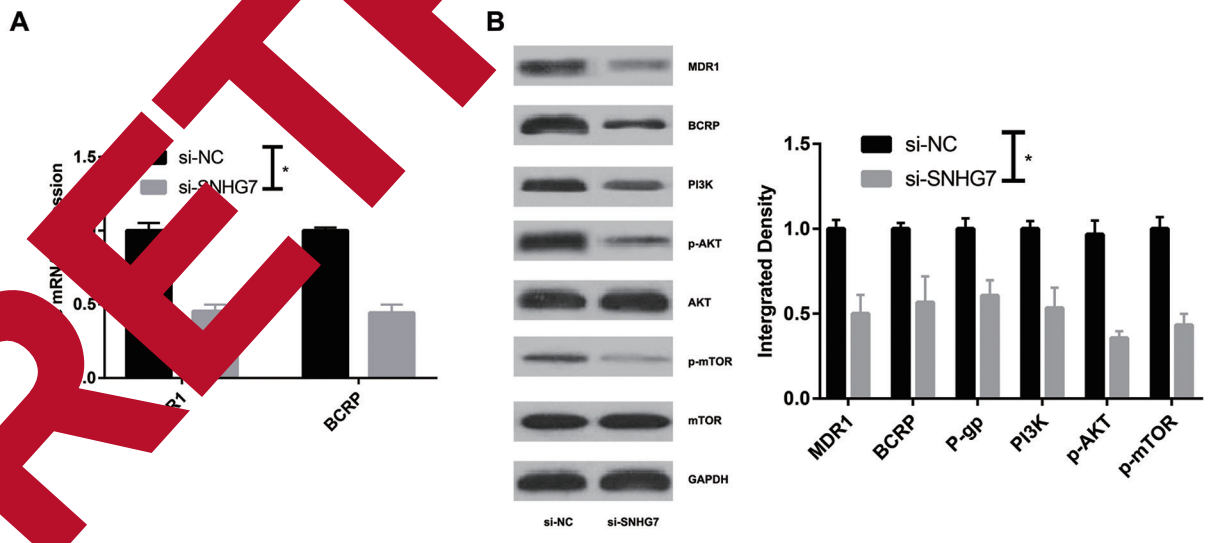


Figure 4. Knockdown of SNHG7 inhibited PI3K/AKT pathway. ***A,*** Transfection of si-SNHG7 in A549/DDP cells significantly down-regulated the mRNA levels of MRD1 and BCRP. ***B,*** Transfection of si-SNHG7 in A549/DDP cells significantly down-regulated the protein levels of MRD1, BCRP and relative genes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