Original Article

SNHG9 was upregulated in NSCLC and associated with DDP-resistance and poor prognosis of NSCLC patients

Ruixue Wang1*, Changyu Chen2*, Weibiao Kang3, Guangjun Meng1

1Department of Emergency, The First Affiliated Hospital of Anhui Medical University, Hefei 230031, Anhui Province, People’s Republic of China; 2Department of Gastrointestinal Surgery, The First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, People’s Republic of China; 3Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei 230031, Anhui Province, People’s Republic of China. *Equal contributors.

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Abstract: Lung cancer, a leading cause of cancer-related mortalities worldwide and non-small cell lung cancer (NSCLC) is the main subtype of lung cancer. As a first-line chemotherapeutic drug used for NSCLC, acquired resistance retarded the clinical application of cisplatin (DDP). We herein reported long non-coding RNA SNHG9 was over-expressed in NSCLC tissues and cell lines compared with normal lung tissues and cell line; Increased SNHG9 was also observed in DDP resistant NSCLC tissues and cell lines compared with their DDP sensitive counterparts. Elevated expression of SNHG9 was associated with lower overall survival (OS) rate in NSCLC patients. Besides, silence of SNHG9 suppressed DDP resistance of NSCLC cells. Furthermore, CAPRIN1 was positively regulated by SNHG9 and mediated the promoting role of SNHG9 in DDP resistance of NSCLC cells. SNHG9 could be used as a potential target for DDP resistant NSCLC therapy.

Keywords: SNHG9, CAPRIN1, cisplatin resistance, NSCLC

Introduction

Lung cancer is the third most prevalent cancer and a leading cause of cancer-related mortalities worldwide [1-3]. Lung cancer includes two main subtypes: small cell lung cancer and non-small cell lung cancer (NSCLC) which contains lung squamous cell carcinoma, lung adenocarcinoma and large cell lung carcinoma [1, 3, 4]. NSCLC accounts for more than 80% of all lung cancers [1, 5]. Surgical resection, chemotherapy, radiotherapy and targeted therapy are considered as main treatments for NSCLC currently [1, 6]. However, patients with NSCLC always suffer from recurrence, metastasis and treatment resistance with a 5-year survival rate no more than 20% [7, 8]. Cisplatin (DDP), a first-line chemotherapeutic drug used for NSCLC, could successfully delay the progression of NSCLC [9, 10]. However, acquired drug resistance of DDP in patients with NSCLC retarded the clinical application [9]. Multiple mechanisms have been reported to be involve in DDP resistance of human NSCLC, such as LncRNA MEG3/miR-21-5p/SDX7 pathway [9], LncRNA NNT-AS1/MAPK/Slug pathway [11], LncRNA OR3A4-CDK1 pathway [12], Annexin A2/JNK/p53 pathway [13] etc. The detailed and varied molecular mechanisms of DDP resistance in human NSCLC are desirable for further study.

Long non-coding RNA (LncRNA), commonly more than 200 nucleotides in size without protein-coding capacity, is one of important types of non-coding RNAs which plays pivotal roles in nearly all human physiological processes [14-16]. Recently, increasing literatures unveiled that LncRNAs could act as key tumor promoters or tumor suppressors in human cancers [17, 18]. For example, LncRNA RHPN1-AS1 promoted EMT and progression of human breast cancer [19]; LncRNA CASC19 played important roles in progression of human gastric cancer [20]; LncRNA HOXA-AS2 promoted malignant progression of human NSCLC via regulating microRNA-216a-5p [21] etc. Long non-coding RNAs could directly interact with microRNAs (miRNAs) or proteins and regulate the expression of target genes [22]. As reported previously, LncRNA SNHG9 was low expre-
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Assessed in human pancreatic cancer tissues and was significantly associated with the prognosis of pancreatic cancer patients [23]; SNHG9/miR-199a-5p/Wnt2 axis regulated cell growth and aerobic glycolysis in glioblastoma [24]. However, the role of LncRNA SNHG9 in human NSCLC remains unknown, and the related regulating mechanisms involved in SNHG9 pathway in NSCLC need to be further explored.

In the current study, we have examined that SNHG9 was over-expressed in human NSCLC tissues compared with normal lung tissues in both TCGA database and the fresh tissues collected from our home hospital. In both NSCLC tissues and cell lines, we observed the increased expression of SNHG9 in DDP resistant NSCLC compared with their DDP sensitive counterparts. High level of SNHG9 was associated with low overall survival (OS) rate in NSCLC patients. Furthermore, knockdown of SNHG9 suppressed cell proliferation and promoted cell apoptosis in DDP resistant NSCLC cells. Depletion of SNHG9 decreased the IC\textsubscript{50} of DDP resistant NSCLC cells for DDP. Moreover, CAPRIN1 was determined to interact with SNHG9 directly and was positively regulated by SNHG9. CAPRIN1 mediated the promoting role of SNHG9 in DDP resistance of NSCLC cells. Therefore, LncRNA SNHG9 was oncogenic and contributed to DDP resistance in human NSCLC. SNHG9 based drugs could be potentially used for adjuvant therapy in DDP resistant NSCLC.

Materials and methods

Tissue samples from NSCLC patients

Fifty pairs of fresh NSCLC tissues and adjacent normal lung tissues were collected from NSCLC patients who underwent surgery in the department of thoracic surgery, the First Affiliated Hospital of Anhui Medical University in 2013-2015. Twenty-six of these NSCLC patients had not received DDP based chemotherapy and they were DDP sensitive. On the other hand, 24 NSCLC patients had received DDP therapy and had got DDP resistance. These patients were followed up for more than 40 months and the OS rates were documented. Local approval from the Institutional Review Boards of Anhui Medical University was got before we performed the work. All of the experiments were carried out according to The Code of Ethics of the World Medical Association (Declaration of Helsinki). Each patient enrolled had signed an informed consent.

Cell lines

Human normal lung cell line BEAS-2B, NSCLC cell lines SK-MES-1, H460, A549 and H1299 were all acquired from ATCC (the American Type Culture Collection, Rockville, MD). DDP resistant cell lines A549/DDP and H1299/DDP were induced in our present laboratory. Briefly, A549 and H1299 cells were treated continuously with DDP until significant DDP resistance was observed by assessing cell viability. All of these cells were cultured in RPMI-1640 medium (Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS; Thermo Fisher Scientific) under 5% CO\textsubscript{2} and 37°C.

RT-qPCR

RT-qPCR (RT-quantitative PCR) was performed to examine RNA levels essentially as described in previous studies [23, 25]. In the present study, RNA levels of SNHG9 and CAPRIN1 were detected. GAPDH was detected as an internal control gene. The primers used were listed in Table 1.

Lentivirus production and stable cell line construction

shRNAs targeting SNHG9 were synthesized and cloned into pLKO.1 vector. The full length of SNHG9 DNA fragment and CDS of CAPRIN1 were cloned and inserted into pSin vector (pSin) according to the manufacturer’s instructions. All primers and shRNA sequences were listed in Table 1. Lentivirus production and transduction were performed as previously described [26, 27]. Forty-eight hours after viral transduction, puromycin was used for selection of stably transduced cells.

Cell functional assays

In this study, MTT assay and cell colony formation assay were performed to evaluate cell proliferation essentially as described in previous studies [9, 11]. Briefly, for MTT assay, 4×10\textsuperscript{4} cells per well were seeded into 96-well cell plates, MTT evaluation was carried out after indicated time. For cell colony formation assay,
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1000 cells per well were seeded into 6-well cell plates, cell colony formation was calculated after about two weeks.

IC\textsubscript{50} analysis was performed to evaluate cell sensitivity to DDP as described in former publications [11]. In brief, cells were treated with different dose of DDP for 48 h, cell viabilities were examined by MTT assay, and the IC\textsubscript{50} value for DDP was analyzed according to the cell growth curves.

To evaluate cell apoptosis, caspase-3 activity assay and DNA fragmentation assay were carried out as described earlier [9, 28, 29]. For caspase-3 activity assay, the Caspase-3 Colorimetric Assay kit from Promega Corporation was used; for DNA fragmentation assay, cytoplasmic histone-associated DNA fragments were evaluated by a Nucleosome ELISA kit.

**Biotin RNA pulldown assay**

Biotin RNA pulldown assay was performed as previously described [30], to examine the interaction between CAPRIN1 protein and SNHG9. Briefly, sense or antisense biotin-labeled DNA oligomers targeting SNHG9 were incubated with lysates from A549/DDP and H1299/DDP cells. Streptavidin-coupled agarose beads (Invitrogen) were used to enrich the SNHG9 complex one hour after incubation. All steps were performed in RNase-free environment. The protein level of CAPRIN1 in the protein-RNA complex was next detected by western blot.

### Table 1. Oligomers used in this study

<table>
<thead>
<tr>
<th>Name</th>
<th>Application</th>
<th>Sequence</th>
</tr>
</thead>
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<td>qRT-SNHG9-F</td>
<td>qRT-PCR</td>
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<td>qRT-SNHG9-R</td>
<td>qRT-PCR</td>
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</tr>
<tr>
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<td>qRT-PCR</td>
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</tr>
<tr>
<td>qRT-GAPDH-F</td>
<td>qRT-PCR</td>
<td>TAGTGTATCAAGAGGGGAGT</td>
</tr>
<tr>
<td>qRT-GAPDH-R</td>
<td>qRT-PCR</td>
<td>TGTATCCAACACTTATGC ATAC</td>
</tr>
<tr>
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</tr>
<tr>
<td>SNHG9-shRNA1-R</td>
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<td>SNHG9-shRNA2-F</td>
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<tr>
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<td>SNHG9-clone-F</td>
<td>plasmid construction</td>
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<td>lncRNA pull down</td>
<td>(biotin)-CCGCGGTCTGCGCGAGGTCGAGTCAGCGG</td>
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**RNA immunoprecipitation (IP) assay**

RNA immunoprecipitation (IP) assay was conducted to examine the interaction between CAPRIN1 protein and SNHG9 essentially as described in former studies [31]. The CAPRIN1 protein-SNHG9 RNA complex was captured by anti-CAPRIN1 antibody (Proteintech Group, Inc., Chicago, USA), and the captured SNHG9 RNA was examined by RT-qPCR. The anti-IgG antibody (Proteintech Group, Inc., Chicago, USA) was used as control.

**Western blot**

Protein levels of CAPRIN1 were detected by western blot, which was carried out according to former publications [25]. CAPRIN1 Rabbit Polyclonal antibody (1:1000, 15112-1-AP, Proteintech Group, Inc., Chicago, USA) and Actin
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Mouse Monoclonal antibody (1:10000, 66009-1-Ig, Proteintech Group, Inc., Chicago, USA) were used. Actin was detected as an internal control.

Statistical analyses

In this study, each experiment was repeated for 3 times at least, and the figures represented the average. For RT-qPCR and cell functional assays, we used unpaired two-tailed t test to perform statistical analyzing. Kaplan-Meier curves were made to analyze the OS difference in NSCLC patients and log-rank test was used to calculate statistical significance. It was statistically significant when $P<0.05$.

Results

SNHG9 was upregulated in NSCLC and associated with DDP-resistance and poor prognosis of NSCLC patients

To explore the expression pattern of SNHG9 in NSCLC. Firstly, the expression level of SNHG9 in 553 NSCLC tissues and 59 normal lung tissues was analyzed from The Cancer Genome Atlas (TCGA) database. As shown in Figure 1A, the expression level of SNHG9 was significantly higher in NSCLC tissues compared with normal lung tissues. Similarly, the expression level of SNHG9 was much higher in 50 local NSCLC tissues compared with adjacent normal lung tissues. C. The expression level of SNHG9 in DDP sensitive (CS) were much lower than that in DDP resistant (CT) NSCLC tissues. D. Kaplan-Meier curves showed the different OS rates in high SNHG9 group and low SNHG9 group NSCLC patients. E. RT-qPCR showed the expression level of SNHG9 in BEAS-2B, SK-MES-1, H460, A549, A549/DDP, H1299 and H1299/DDP cells. GAPDH was detected as control for RT-qPCR. *$P<0.05$; **$P<0.01$.

Figure 1. SNHG9 was upregulated in NSCLC and associated with DDP-resistance and poor prognosis of NSCLC patients. A. TCGA data analysis showed the expression level of SNHG9 was higher in 553 human NSCLC tissues compared with 59 normal lung tissues. B. RT-qPCR showed the expression level of SNHG9 was higher in 50 local NSCLC tissues compared with adjacent normal lung tissues. C. The expression level of SNHG9 in DDP sensitive (CS) were much lower than that in DDP resistant (CT) NSCLC tissues. D. Kaplan-Meier curves showed the different OS rates in high SNHG9 group and low SNHG9 group NSCLC patients. E. RT-qPCR showed the expression level of SNHG9 in BEAS-2B, SK-MES-1, H460, A549, A549/DDP, H1299 and H1299/DDP cells. GAPDH was detected as control for RT-qPCR. *$P<0.05$; **$P<0.01$. 
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A549, H1299 and DDP resistant NSCLC cell lines A549/DDP, H1299/DDP was also examined by RT-qPCR. Concordant with the tissue result, the expression level of SNHG9 was much higher in NSCLC cell lines compared with normal lung cell line BEAS-2B and was dramatically higher in DDP resistant NSCLC cell lines compared with DDP sensitive NSCLC cell lines (Figure 1E). Therefore, high level of SNHG9 was positively associated with DDP resistance and poor survival rates.

SNHG9 knockdown enhanced DDP sensitivity in DDP-resistant NSCLC

To figure out the specific functions of SNHG9 in DDP resistance of NSCLC. Firstly, two shRNAs (sh-SNHG9#1 and sh-SNHG9#2) against SNHG9 were stably transfected into DDP resistant cell lines A549/DDP and H1299/DDP to knockdown the endogenous SNHG9 (Figure 2A). Then functional assays were verified, as examined by MTT assay, cell viabilities of both A549/DDP and H1299/DDP cells dramatically decreased after transfected with sh-SNHG9#1 or sh-SNHG9#2 compared with sh-Ctrl over a period of 4 days with DDP treatment (Figure 2B, 2C). Concordantly, SNHG9 knockdown significantly decreased cell colony formation of A549/DDP and H1299/DDP cells with DDP treatment (Figure 2D). Moreover, in A549/DDP and H1299/DDP cells, inhibition of SNHG9 by sh-SNHG9#1 or sh-SNHG9#2 also dramatically decreased the IC50 for DDP (Figure 2E); increased cell apoptosis of A549/DDP and H1299/DDP cells after DDP treatment was...
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also determined by caspase-3 activity (Figure 2F) and DNA fragmentation (Figure 2G). Taken together, knockdown of SNHG9 promoted DDP sensitivity in DDP-resistant NSCLC cells.

**SNHG9 upregulated CAPRIN1 through direct interaction**

For further study, potential targets that might be directly interacted with SNHG9 were searched for by using starBase v2.0 (http://starbase.sysu.edu.cn/). Several candidate proteins (including HuR, eIF4AII, DGCR8, FMRP, CAPRIN1 etc.) were predicted to be direct targets of SNHG9 (Figure 3A). Among these potential targets, CAPRIN1 was examined to be directly interacted with SNHG9 as CAPRIN1 could be pulled down by SNHG9-DNA-antisense biotin probe in both A549/DDP and H1299/DDP cells, which was determined by biotin RNA pull-down assay (Figure 3B-D). To confirm this result, RNA immunoprecipitation assay was carried out and SNHG9 could be enriched by CAPRIN1 antibody in both A549/DDP and
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H1299/DDP cells (Figure 3E-G). Moreover, the protein level of CAPRIN1 significantly decreased in both A549/DDP and H1299/DDP cells stably transfected with sh-SNGH9#1 or sh-SNGH9#2 compared with sh-Ctrl, as determined by western blot (Figure 3H). In addition, SNGH9 overexpression dramatically enhanced the protein level of CAPRIN1 as shown in Figure 3I. Therefore, SNGH9 directly interacted with CAPRIN1 protein and positively regulated the expression of CAPRIN1.

CAPRIN1 inhibition enhanced DDP sensitivity in DDP-resistant NSCLC

We next examined the role of CAPRIN1 in DDP resistance of NSCLC cells. As shown in Figure 4A and 4B, si-CAPRIN1#1 and si-CAPRIN1#2 dramatically decreased both RNA and protein levels of CAPRIN1 in A549/DDP and H1299/DDP cells. Cell viabilities of A549/DDP and H1299/DDP cells were significantly decreased after depletion of CAPRIN1 over a period of 4 days with DDP treatment (Figure 4C, 4D). Meanwhile, cell colony formation of A549/DDP and H1299/DDP cells with DDP treatment was significantly suppressed by si-CAPRIN1#1 or si-CAPRIN1#2 as shown in Figure 4E and 4F. The IC_{50} of A549/DDP and H1299/DDP cells for DDP was also decreased after transfection with si-CAPRIN1#1 or si-CAPRIN1#2 compared with control (Figure 4G). Concordantly, depletion of CAPRIN1 dramatically promoted cell apoptosis of A549/DDP and H1299/DDP cells after DDP treatment as determined by caspase-3 activity assay and DNA fragmentation assay (Figure 4).
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As a result, CAPRIN1 inhibition enhanced DDP sensitivity in DDP-resistant NSCLC cells.

CAPRIN1 rescued the deceased DDP-resistance due to SNHG9 knockdown in DDP-resistant NSCLC

To examine whether CAPRIN1 played a pivotal role in SNHG9-mediated decreased DDP resistance of NSCLC cells, A549/DDP cells was co-transfected with sh-SNHG9#1/sh-Ctrl and CAPRIN1-oe/Vector. (A) Protein level of CAPRIN1 was examined by western blot. Actin was detected as control. (B) Cell colony formation assay, (C) MTT assay, (D) IC_{50} analysis, (E) Caspase-3 activity assay and (F) DNA fragmentation assay showed SNHG9 knockdown decreased cell viabilities, cell colony formation, IC_{50} for DDP, increased cell apoptosis respectively, and forced expression of CAPRIN1 abolished these changes. *P<0.05; **P<0.01.

Discussion

In this study, we have documented that LncRNA SNHG9 was high expressed in human NSCLC tissues compared with normal lung tissues (including TCGA data and fresh tissues); expression level of SNHG9 increased significantly in DDP resistant NSCLC tissues compared with DDP sensitive NSCLC tissues; similar result was also found in induced DDP resistant cell lines A549/DDP and H1299/DDP compared with their respective parental cell lines. Moreover, SNHG9 was determined to be negatively correlated with OS rate in patients with NSCLC. shRNA mediated depletion of SNHG9 dramatically decreased cell viability, cell colony formation, IC_{50} for DDP, increased cell apoptosis in DDP resistant cells. In addition, SNHG9 was examined to directly interact with CAPRIN1 protein as determined by Biotin RNA pulldown assay (Figure 4H, 4I). As a result, CAPRIN1 inhibition enhanced DDP sensitivity in DDP-resistant NSCLC cells.

SNHG9#1+Vector), and this decrease was rescued by CAPRIN1 overexpression (sh-SNHG9#1+CAPRIN1-oe) in A549/DDP cells. Concordant with former results, depletion of SNHG9 by sh-SNHG9#1 dramatically decreased cell viability (determined by MTT assay) (Figure 5B), cell colony formation (Figure 5C), IC_{50} for DDP (Figure 5D) in A549/DDP cells with the treatment of DDP. However, these decreases were abrogated by co-transfection with CAPRIN1-oe (Figure 5B-D). Moreover, knockdown of SNHG9 significantly enhanced cell apoptosis as determined by caspase-3 activity assay and DNA fragmentation assay in A549/DDP cells after the treatment of DDP; these changes were all abolished by co-transfection with CAPRIN1-oe (Figure 5E, 5F). Therefore, CAPRIN1 rescued the deceased DDP-resistance due to SNHG9 knockdown in DDP-resistant NSCLC cells and the role of SNHG9 in DDP resistance of NSCLC cells was mediated by CAPRIN1.
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assay and RNA-IP assay; the expression of CAPRIN1 was positively regulated by SNHG9. Furthermore, CAPRIN1 knockdown by siRNA concordantly decreased cell viability, cell colony formation, IC_{50} for DDP, increased cell apoptosis in DDP resistant cells A549/DDP and H1299/DDP. Rescue experiments showed forced expression of CAPRIN1 abolished the decreased cell proliferation, resistance to DDP and increased cell apoptosis induced by depletion of SNHG9 in A549/DDP cells. As reported in former studies, high level of SNHG9 was demonstrated to be associated with better prognosis in human pancreatic cancer patients [23]; SNHG9 promoted cell growth and aerobic glycolysis via miR-199a-5p/Wnt2 axis in glioblastoma [24]. We herein firstly reported the DDP resistance promoting role of SNHG9 in human NSCLC. The functions of SNHG9 were different among human pancreatic cancer, glioblastoma and NSCLC, which showed tissue specificity in different kinds of human cancers.

CAPRIN1 was examined to be the direct target of SNHG9 and SNHG9 positively regulated the expression of CAPRIN1. CAPRIN1 also acted as a promoting role in DDP resistance in DDP resistant NSCLC cells. As reported in previous studies, CAPRIN1 was an oncogene and promoted tumor growth and metastasis in human osteosarcoma [32], CAPRIN1 was a novel target of miRNA-223 and promoted cell proliferation and invasion in human breast cancer cells [33]. In human hepatocellular carcinoma, CAPRIN1 was negatively regulated by miRNA-621 and promoted cell proliferation of hepatocellular carcinoma cells; abnormal high expression of CAPRIN1 was associated with poor prognosis in hepatocellular carcinoma patients [25, 34]. Therefore, CAPRIN1 was a wide tumor promoter in various kinds of human cancers including NSCLC, and we herein firstly demonstrated the promoting role of CAPRIN1 in DDP resistance of human cancer.

In this present study, we determined that SNHG9 directly interacted with CAPRIN1 protein. As known widely, LncRNAs could bind and sponge miRNAs, and the target genes of these miRNAs were in line indirectly regulated by LncRNAs [22, 35]. As reported previously, CAPRIN1 was a direct target of miRNA-223 and miRNA-621, which negatively regulated the expression of CAPRIN1 [25, 33]. In this article, we did not examine the interaction between LncRNA SNHG9 and miRNA-223 or miRNA-621. Moreover, there might be some other miRNAs that directly targeted CAPRIN1. As a result, besides direct interaction between SNHG9 and CAPRIN1, there might be some other indirect pathways involved in SNHG9/CAPRIN1 regulation. We will perform this exploration in future.

In summary, LncRNA SNHG9 promoted DDP resistance of human NSCLC cells. CAPRIN1 was positively regulated by SNHG9 and mediated the promoting role of SNHG9 in DDP resistance of NSCLC. The expression level of SNHG9 was negatively associated with OS rate in NSCLC patients. SNHG9 could be used as a potential target for DDP resistant NSCLC therapy.

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Disclosure of conflict of interest

None.

Address correspondence to: Guangjun Meng, Department of Emergency, The First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Hefei 230031, Anhui Province, People’s Republic of China. E-mail: ayfyjzk@163.com

References

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