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*Original Article*

# Influence of LncRNA SDHAP1 on multiplication, migration and invasiveness of non-small cell lung carcinoma cells

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**Abstract:** Objective: To investigate the effects of lncRNA SDHAP1 on the multiplication, migration and invasiveness of NSCLC cells. Methods: From The Cancer Genome Atlas (TCGA) database, the clinical data of NSCLC patients were retrieved to analyze the expression of lncRNA SDHAP1 in LC. In this study, lncRNA SDHAP1 in NSCLC cell lines was regulated, and its expression profiling in non- and cis-platinum (CDDP) resistant NSCLC cell lines was identified by qPCR. The levels of multidrug resistance-related protein 1 (MRP1), p-glycoprotein (P-gp) and glutathione S-transferase-π (GST-π) were measured by Western blotting (WB), the migration and invasion of LC cells were detected by Transwell assay, and the cell multiplication and activity were determined by MTT assays. Results: TCGA database identified upregulated lncRNA SDHAP1 expression in LC. qPCR results revealed that lncRNA SDHAP1 was highly expressed in NSCLC. LncRNA SDHAP1 showed higher expression in patients with stage IV than in those with stage I, II or III, as well as in people aged 21-40 years old. Compared with normal lung epithelial cells, lncRNA SDHAP1 was upregulated in NSCLC cell lines, especially in those resistant to CDDP. LncRNA SDHAP1 downregulation led to a decrease in multiplication, migration and invasiveness of NSCLC cells, and a reduction in activity, migration and invasiveness of CDDP-resistant NSCLC cell lines. In addition, lncRNA SDHAP1 knockdown down-regulated the expression levels of Multidrug resistance-associated proteins MRP1, P-gp and GST-π. Conclusions: LncRNA SDHAP1 is upregulated in NSCLC and is associated with LC staging and age of patients. Silencing lncRNA SDHAP1 can suppress the multiplication, migration, invasiveness and CDDP resistance of cancer cells. Therefore, lncRNA SDHAP1 may serve as a prognostic biomarker and treatment target for NSCLC.

**Keywords:** Non-small cell lung carcinoma, LncRNA SDHAP1, Cis-platinum resistance

## Introduction

Lung carcinoma (LC) has the highest prevalence at present, among which non-small cell lung carcinoma (NSCLC) accounts for approximately 85% of primary LC [1]. The majority of patients with NSCLC are at the advanced stage when they seek medical treatment, which is difficult to be cured by surgery and prone to postoperative relapse [2]. Although many new drugs have been developed for LC in recent years, the 5-year survival rate of advanced LC patients remains as low as 15% [3]. Cisplatinum (CDDP) is the most extensively used platinum-based first-line chemotherapeutic drug, which is mainly to inhibit DNA replication, affect cell transcription and translation, and promote tumor cell apoptosis [4, 5]. CDDP-resistant is an important factor leading to treatment failure and adversely affects the survival and prognosis of patients [6]. Therefore, studying the molecular mechanism of drug-resistance may help us to understand the proliferation and metastasis ability of tumor cells.

Previous studies on the molecular mechanism of tumorigenesis focused on protein coding genes [7]. With the development of high-throughput transcriptome sequencing technology, researchers have found that more than

90% of human genome transcriptome is consisted of non-coding RNAs, and many microRNAs (miRNAs) have been shown to be involved in the malignant behavior of LC [8-10]. In addition to miRNAs, long non-coding RNAs (lncRNAs) have also received close attention, with the functions of modulating chromatin and gene regulation depending on the cell location [11]. LncRNAs act on all aspects of cellular regulation, including transcription regulation, shearing processing, chromatin modification and RNA stability regulation [12]. It has been reported that transcribed at the HOXC site, lncRNA HOTAIR regulates chromatin methylation level of HOXD site by directly binding to PRC2 [13]. Many studies have shown that lncRNAs are closely related to the occurrence and development of various tumors, including LC [14-16]. The correlation between lncRNA SDHAP1 and LC progression has been rarely reported. The purpose of this study was to probe into the impacts of lncRNA SDHAP1 on multiplication, migration and invasiveness of NSCLC cell, so as to understand the molecular pathogenesis and to improve the prognosis of patients with LC.

## Methods

*Data sources and sample collection*

In this study, the RNA-seq and clinical data were retrieved from The Cancer Genome Atlas (TCGA) database for bioinformatics analysis. The R package edgeR was used to analyze the differential expression of lncRNA SDHAP1 in paired samples of NSCLC tissues and adjacent tissues (lung adenocarcinoma, LUAD & lung squamous cell carcinoma, LUSC), as well as in patients with different clinical features.

The clinicopathological data of 46 patients with LUAD who underwent surgical resection in our hospital from January 2017 to March 2018 with preserved pathological tissue specimens and complete clinicopathological data were collected. All patients underwent lung cancer resection, and some fresh tumor tissues and normal lung tissues adjacent to the cancer were collected during the operation and preserved in liquid nitrogen. The lung cancer tissue was confirmed by pathological examination, and the distance between the normal tissue and the lesion was >5 cm. There were 27 males and 19 females with an average age of (59.76±6.93) years old. According to TNM staging, there were 13 cases of stage I, 7 cases of stage II, 21 cases of stage III and 5 cases of stage IV. There were 19 cases with lymph node metastasis and 27 cases without lymph node metastasis. Among the patients, 16 cases were well differentiated, 15 cases were moderately differentiated, and 15 cases were poorly differentiated. Patients and their families signed the informed consent, and all patients were followed up until April 30, 2021 to record their survival.

*Cell cultivation and treatment*

BEAS-2B, A549 and A549/CDDP, which were human normal lung epithelial cell line, NSCLC cell line and NSCLC CDDP-resistant cell line respectively, were all purchased from ATCC. All the cell lines were cultured in RPMI-1640 medium containing 10% FBS, 100U/mL penicillin and 100 mg/L streptomycin. The logarithmic growth phase cells were gathered for the subsequent experiment. The experiment consisted of transfection group (si-SDHAP1), nonsense sequence negative control group (si-NC) and blank group (control). The prime sequences of small interfering RNAs were as follows: si-SDHAP1: 5'-GCUGGAAUAAAGAGUAACAUU-3', as well as negative control si-NC: 5'-UUCUCCGAACGUGUCACGUTT-3'. The cells were inoculated into a 6-well plate at $2\times10^5$ cells/well 24 h before transfection and then transfected as instructed by the instructions of Lipofectamine RNA imax (Thermo Fisher Scientific) when 50% confluence was confirmed.

*Qpcr*

Total RNA was isolated using the Trizol method and cDNA was synthesized according to the instructions of the reverse transcription kit (Thermo Fisher Scientific). The cDNA of each group was used as a template for PCR reaction on the ABI 7500 fluorescent quantitative PCR instrument. A 20 μL PCR reaction mixture was prepared with 2 μL cDNA, 10 μL SYBR Premix Ex TaqTM II (2×), 0.8 μL Forward Primer (10 μM), 0.8 μL ReversePrimer (10 μM), 0.4 μL ROX Reference Dye (50×) and 6 μL RNase-Free $H_2O$. Primer sequences are detailed in **Table 1** (internal reference: U6). The particularized PCR conditions were: 1) pre-degeneration at

**Table 1.** Primer sequences

| Gene | Forward | Reverse |
|---|---|---|
| SDHAP | 5'-CGACTACAGACGTGTCGGG-3' | 5'-GCCCTCTCGTTCCTTCAACA-3' |
| MRP-1 | 5'-GTACATTAACATGATCTGGTC-3' | 5'-CGTTCATCAGCTTGATCCGAT-3' |
| P-gp | 5'-ATGAAGTTGAATTAGAAAATGCAG-3' | 5'-GGAAACTGGAGGTATACTTTCATC-3' |
| GST-π | 5'-AATGGATCCTCCACCATGCCGCCCTACACCGTGGT-3' | 5'-GACCTCGAGCTACTGTTTCCCGTTGCCAT-3' |
| U6 | 5'-GCTTCGGCAGCACATATACTAAAAT-3' | 5'-CGCTTCACGAATTTGCGTGTCAT-3' |
| β-actin | 5'-CATGTACGTTGCTATCCAGGC-3' | 5'-CTCCTTAATGTCACGCACGAT-3' |

95°C for 10 min; 2) 40 cycles of degeneration at 95°C for 50 s, annealing at 60°C for 50 s and extension at 72°C for 60 s; and 3) final extension at 72°C for 5 min. All reactions were set with three duplicate wells, and quantitative analysis was carried out by the $2^{-\Delta\Delta CT}$ method.

*Cell multiplication and viability by MTT assays*

A549 cells and A549/CDDP cells were collected after conventional culture and transfection, digested by trypsin and inoculated into 96-well plates for conventional culture. The culture was resumed after adding 20 μL MTT (5 g/L) at 0, 24, 48 and 72, respectively. After the removal of the culture solution, 150 μL DMSO was added into each well, and the mixture was shaken at room temperature for 10 min for the final determination of absorbance at 490 nm using a microplate analyzer.

*Cell invasiveness and migration by transwell*

In this experiment, 50 μL diluted Matrigel matrix glue was spread in Transwell chamber for invasiveness test, while Transwell chamber without Matrigel matrix glue was applied for migration test. The rest steps were the same. Cells used in the conventional experiment in each group were suspended in serum-free RPMI1640 medium and starved for 24 h. Then, 100 μL cell suspension ($1\times10^5$/mL) was inoculated into the apical chamber, which was then put into the 24-well plate added with 600 μL RPMI1640 medium (with 20% FBS) for 48 h of conventional incubation in a cell incubator. The Transwell chamber was taken out and gently rinsed with PBS, and following this, the cells attached to the apical chamber were gently wiped off with cotton swabs, immobilized with 95% ethanol, and finally dyed with crystal violet. Under the inverted microscope, 5 fields of vision were randomly selected to observe the number of cells penetrating the chamber, and the average value was calculated. Each experiment group had 3 replicates, and each test was repeated 3 times.

*Western blotting*

A549/CDDP cells were gathered after conventional culture and transfection, and lysed by cell lysate for 30 min. The supernatant was extracted by centrifugation at 12,000 r/min at 4°C for 10 min. The protein concentration was determined with the bicinchoninic acid (BCA) kit. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) was performed on 50 μg protein sample. After electrophoresis, the proteins were transferred to a nitrocellulose membrane, sealed with 5% skimmed milk powder for 1 h, and cultured with primary antibodies (multidrug resistance-related protein 1 [MRP1], dilution ratio: 1:1000, Abcam, UK), p-glycoprotein [P-gp], dilution ratio: 1:1000, Abcam, UK), glutathione S-transferase-π [GST-π], dilution ratio: 1:1000, Abcam, UK), β-actin (dilution ratio: 1:1000, Abcam, UK) overnight at 4°C. After TBST rinsing, the membrane was incubated with secondary antibodies for 1 h. ECL luminescence was used for development after membrane washing with TBST. The images of bands were collected utilizing Chem-iDocXRS imaging system (Bio-Rad, USA), and were analyzed using Quantity One 4.6.2 software.

*Statistical processing*

All data were statistically analyzed by SPSS 21.0 (SPSS, Inc, Chicago, IL, USA). The normal distributed measurement data were recorded as mean ± standard deviation; the comparison between groups was made by T test, and that among multiple groups was performed by one-way ANOVA followed with LSD-t post-hoc test. $P<0.05$ indicate that the difference was statis-

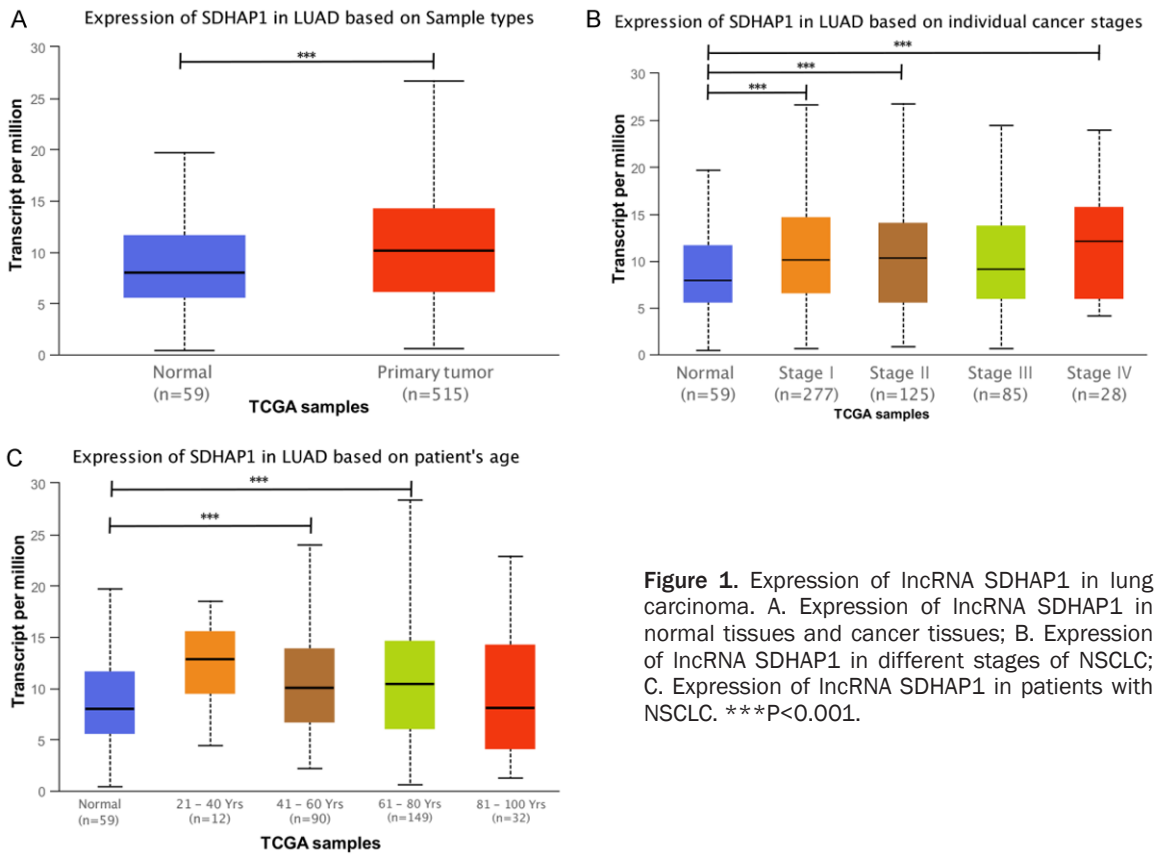



**Figure 1.** Expression of lncRNA SDHAP1 in lung carcinoma. A. Expression of lncRNA SDHAP1 in normal tissues and cancer tissues; B. Expression of lncRNA SDHAP1 in different stages of NSCLC; C. Expression of lncRNA SDHAP1 in patients with NSCLC. ***P<0.001.

tically significant, and the 95% confidence interval (CI) was calculated.

## Results

*Expression of lncRNA SDHAP1 in NSCLC*

In this study, the clinical data of LC were retrieved from TCGA database to compare the expression of lncRNA SDHAP1 in malignant tumors (n=515) and normal tissues (n=59). The results showed that 1) LncRNA SDHAP1 was up-regulated in LC (P=1.90E-05, **Figure 1A**); 2) LncRNA SDHAP1 presented higher expression in patients with stage IV than in those with stage I, II or III (P<0.05, **Figure 1B**); 3) The expression of lncRNA SDHAP1 was higher in people aged 21-40 years old, but the expression in patients aged 41-60 years old and 61-80 years old was also significantly higher than that in healthy people (**Figure 1C**). The above results indicate that the aberrant expression of lncRNA SDHAP1 may be closely related to the progression of NSCLC. Therefore, this study will focus on the role of lncRNA SDHAP1 in NSCLC.

*Expression of lncRNA SDHAP1 in NSCLC cells*

lncRNA SDHAP1 expression in NSCLC wild-type and CDDP-resistant cell lines was investigated. qPCR analysis revealed that lncRNA SDHAP1 was up-regulated in NSCLC compared with normal lung epithelial cells, and was elevated in CDDP-resistant lines as compared to wild-type lines (**Figure 2A**). In addition, SDHAP1 siRNA was used to regulate the expression of lncRNA SDHAP1 in cell lines. It was found that lncRNA SDHAP1 was evidently downregulated in both A549 cells and A549/CDDP cells transfected with SDHAP1 siRNA (P<0.05, **Figure 2B** and **2C**).

*Impacts of knocking down lncRNA SDHAP1 on viability of A549 and A549/CDDP cells*

SDHAP1 siRNA was used to down-regulate the expression of lncRNA SDHAP1 in NSCLC wild-type and CDDP-resistant cell lines. Further, the cancer cells were intervened by CDDP to observe the alterations of cell activity by MTT assay. Compared with si-NC group, the multiplication of si-SDHAP1 transfected A549 cells

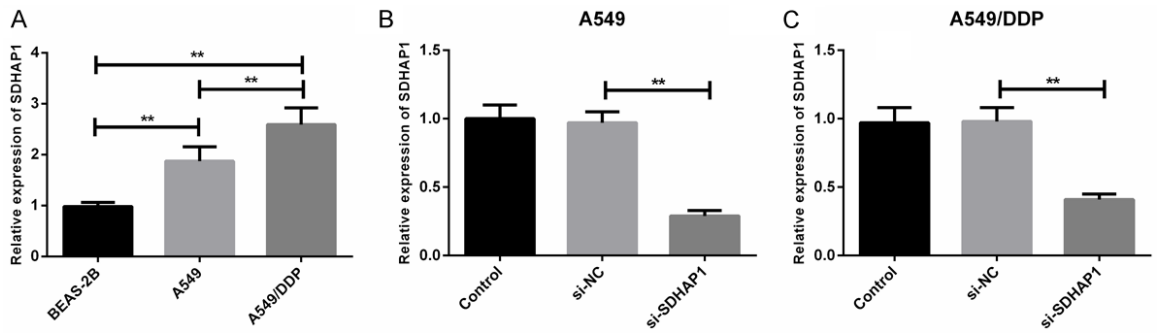



**Figure 2.** Expression of lncRNA SDHAP1 in NSCLC cells. A. Expression of lncRNA SDHAP1 in normal lung epithelial cells and NSCLC cells; B. Expression of lncRNA SDHAP1 in transfected A549 cells; C. Expression of lncRNA SDHAP1 in transfected A549/CDDP cells; **P<0.01.

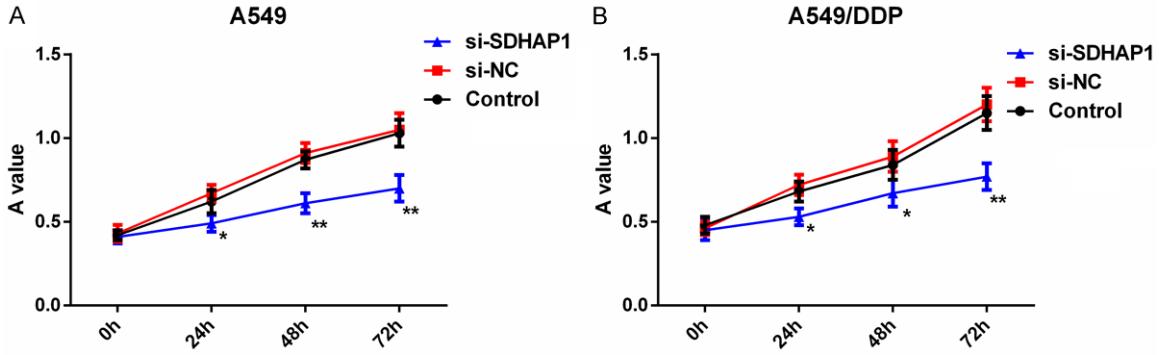



**Figure 3.** Effect of knocking down lncRNA SDHAP1 on the viability of A549 cells and A549/CDDP cells. A. A549 cell viability; B. A549/CDDP cell viability; *P<0.05, **P<0.01 *vs.* si-NC group.

was inhibited (P<0.05, **Figure 3A**), as of the viability of si-SDHAP1 transfected A549/CDDP cells (P<0.05, **Figure 3B**). It indicates that lncRNA SDHAP1 knock-down reduces the multiplication capacity of NSCLC cells and inhibits the CDDP tolerance.

*Impacts of knocking down lncRNA SDHAP1 on invasiveness and migration of A549 cells*

For the purpose of studying the impacts of lncRNA SDHAP1 on NSCLC cell invasiveness and migration, we used SDHAP1 siRNA to down-regulate the expression of lncRNA SDHAP1 in NSCLC wild-type and CDDP-resistant cell lines, and continued to verify the influence of lncRNA SDHAP1 knockdown on invasiveness and migration of A549 cells *in vitro* by Transwell experiment. Compared with siRNA NC group, knocking down lncRNA SDHAP1 in NSCLC wild-type cells noticeably lowered the invasiveness of A549 cells *in vitro*, and resulted in a decrease in migration number of A549 cells (**Figure 4A**, **4B**). The above results demonstrate that knocking down lncRNA SDHAP1 leads to the reduction of migratory and invasive capacity of NSCLC.

*Impacts of knocking down lncRNA SDHAP1 on invasiveness and migration of A549/CDDP cells*

SDHAP1 siRNA was used to down-regulate the expression of lncRNA SDHAP1 in A549/CDDP cells, and the cells were further intervened by CDDP for Transwell analysis. Knocking down lncRNA SDHAP1 resulted in a lower number of invaded A549/CDDP cells *in vitro* compared with siRNA NC group (**Figure 5A**). Meanwhile, lncRNA SDHAP1 knockdown remarkably reduced the number of migrated A549/CDDP cells *in vitro* compared with siRNA NC group (**Figure 5B**). It suggests that knocking down lncRNA SDHAP1 leads to the reduction of migratory and invasive capacity of CDDP-resistant NSCLC cell lines.

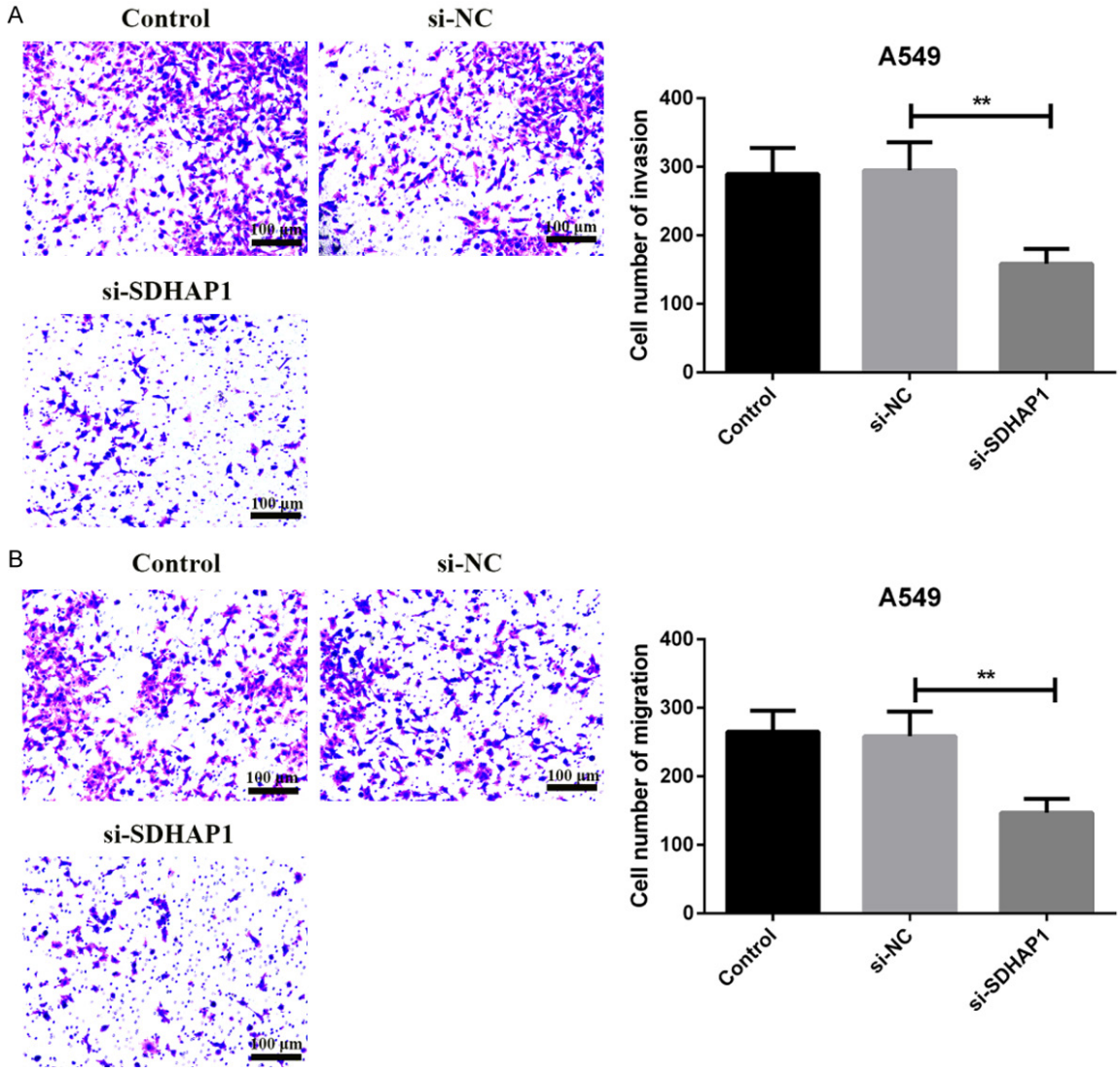



**Figure 4.** Effect of knocking down lncRNA SDHAP1 on invasiveness and migration of A549 cells. A. Number of invaded A549 cells; B. Number of migrated A549 cells; **P<0.01.

*Knocking down lncRNA SDHAP1 down-regulated drug-resistant proteins associated with A549/CDDP cells*

The impacts of lncRNA SDHAP1 on multidrug resistance-related proteins in NSCLC cell lines were explored at the molecular level. qPCR and western blotting results showed that compared with si-NC group, MRP1, P-gp and GST-π in si-SDHAP1 transfected A549/CDDP cells were all notably downregulated (P<0.05, **Figure 6**).

*Relationship between lncRNA SDHAP1 expression and prognosis in patients with LUAD*

PCR results showed that lncRNA SDHAP1 expression was significantly upregulated in LUAD tissues compared with adjacent tissues (P<0.05). ROC curve results revealed an area under the curve (AUC) of 0.8070, indicating that lncRNA SDHAP1 had a good diagnostic value for LUAD. The results of KM curve showed that the 3-year survival of patients with high SDHAP1 expression was significantly worse than that of patients with low SDHAP1 expression (P<0.05, **Figure 7**).

## Discussion

Clinically, chemotherapy is the means to prolong the life of patients with advanced NSCLC, in which CDDP has been widely used. However, CDDP resistance of cancer cells during treatment limits the efficacy of CDDP, which leads to

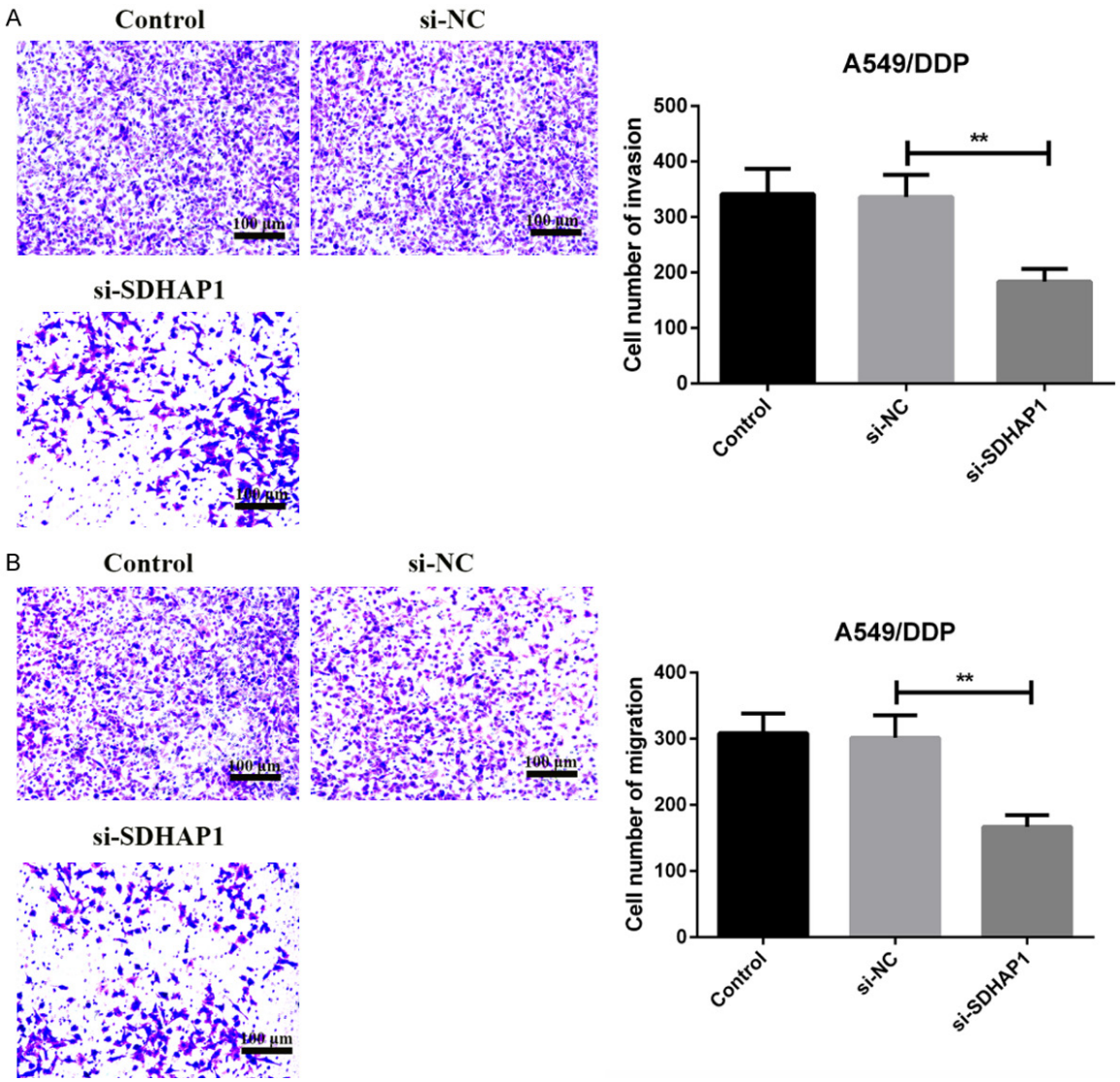



**Figure 5.** Effect of knocking down lncRNA SDHAP1 on invasiveness and migration of A549/CDDP cells. A. Number of invaded A549/CDDP cells; B. Number of migrated A549/CDDP cells; **P<0.01.

disease recurrence and metastasis [17]. CDDP is a metal complex of platinum, which acts on the inner and inter-strand cross-links of DNA, forming DDP-DNA complex and interfering with DNA replication [18]. Therefore, it is urgent to understand the molecular mechanism of CDDP resistance [19]. LncRNA SDHAP1, located on chromosome 3 with a length of 2591 nucleotides, has been associated with chemotherapy resistance of ovarian cancer [20]. Whereas, its mechanism in NSCLC has not been reported.

In our research, the clinical data of NSCLC were retrieved from TCGA database for bioinformatics analysis, which identified up-regulated lncRNA SDHAP1 in NSCLC. Moreover, lncRNA SDHAP1 presented higher expression in patients with stage IV compared with those with stage I, II or III, and was higher in people aged 21-40 years. Then, A549 cells and A549/CDDP cells were gathered after culture for qPCR analysis, the results of which showed that lncRNA SDHAP1 was upregulated in both cell lines. Subsequently, the expression of lncRNA SDHAP1 was inhibited by siRNA transfection to observe the changes in biological behaviors of cells. The results identified that knocking down lncRNA SDHAP1 decreased the multiplication, migration and invasiveness of

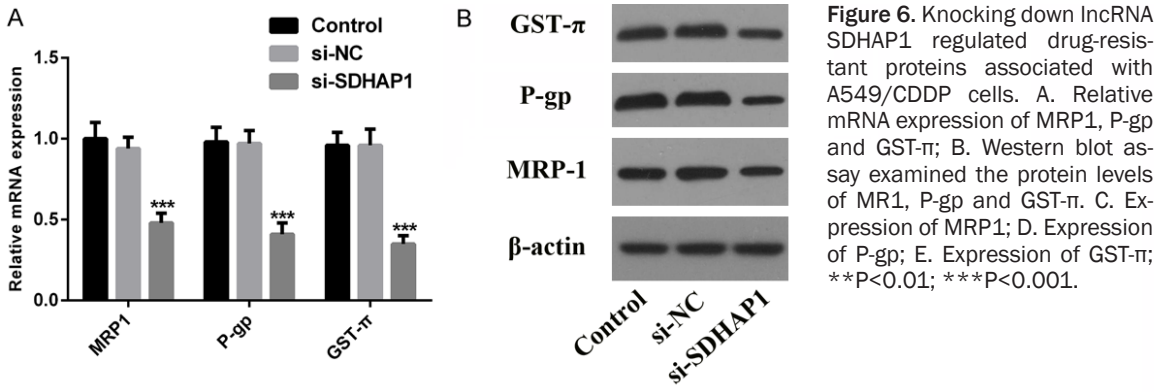
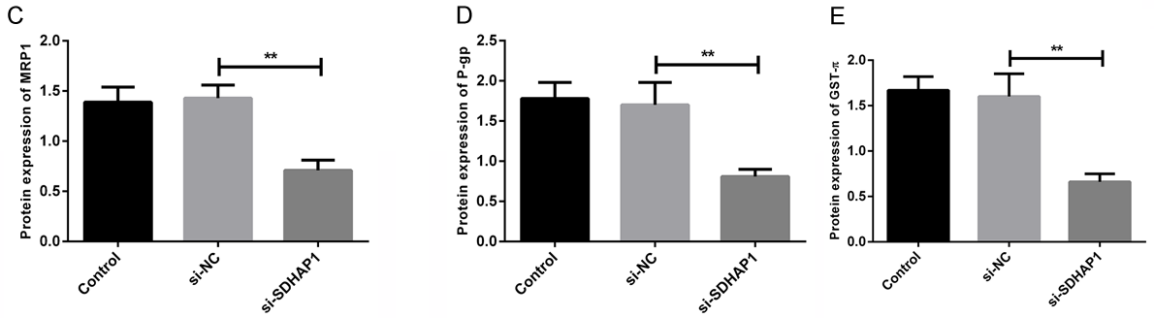



**Figure 6.** Knocking down lncRNA SDHAP1 regulated drug-resistant proteins associated with A549/CDDP cells. A. Relative mRNA expression of MRP1, P-gp and GST-π; B. Western blot assay examined the protein levels of MR1, P-gp and GST-π. C. Expression of MRP1; D. Expression of P-gp; E. Expression of GST-π; **P<0.01; ***P<0.001.



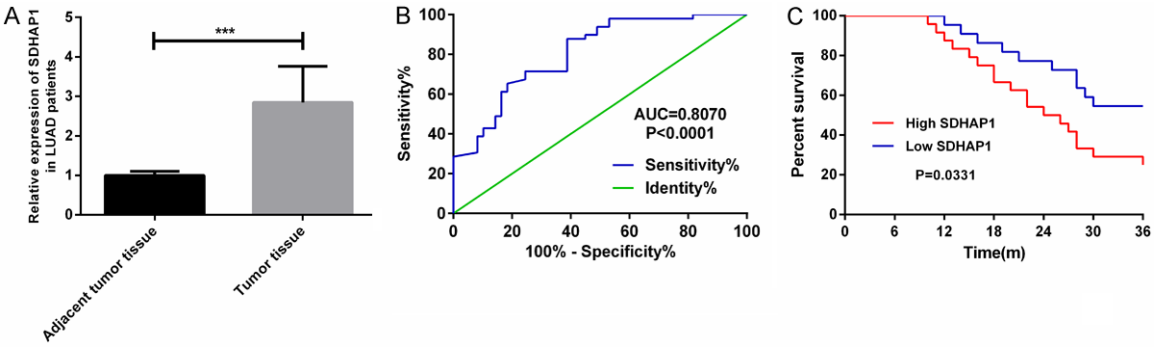




**Figure 7.** Expression of lncRNA SDHAP1 in lung adenocarcinoma and its value in diagnosis and prognosis. A. Expression of lncRNA SDHAP1 in the tumor tissues and adjacent normal tissues of patients with lung adenocarcinoma; B. Diagnostic significance of lncRNA SDHAP1 in patients with lung adenocarcinoma; C. Effect of lncRNA SDHAP1 on the prognosis of patients with lung adenocarcinoma; ***P<0.001.

A549 cells. Different from general multidrug resistance, the mechanism of CDDP resistance in tumors is very complex with multiple triggers, which mainly include the signal axis for maintaining cell growth, the regulatory pathway of apoptosis, and DNA repair system, covering almost every link of cell growth and development [21, 22]. Studies have pointed out [23] that lncRNA MEG3 can enhance the mitochondrial apoptosis pathway induced by chemotherapeutic drugs in human LUAD via activation of P53 and Bcl-x genes. In this research, we found that lncRNA SDHAP1 down-regulation reduced A549/CDDP cell activity and mitigated its migratory and invasive capacity. Recurrence and metastasis bear major responsibility for death in cancer patients [24]. The findings of this research indicate that reducing the expression of lncRNA SDHAP1 can reverse the resistance of A549/CDDP cells to CDDP. In addition, lncRNA SDHAP1 down-regulation were found to reduce the levels of MRP1, P-gp and GST-π. The development of CDDP resistance involves a wide spectrum of mechanisms, among which drug efflux received by membrane transporters is one of the important mechanisms leading to CDDP resistance. For example, overexpression of P-gp and MRP1

can reduce the toxicity of drugs on LC cells [25, 26]. In other related studies [27], miR-21 knockdown was found to suppress A549/CDDP cell vitality and induce apoptosis, and inhibit the expression of drug resistance related proteins P-gp and GST-π. The results of this study are consistent with the above conclusions. Subsequently, we collected the clinical data of a certain number of patients with LUAD to observe the expression of lncRNA SDHAP1 in clinical patients and its diagnostic value. The results showed that the expression of lncRNA SDHAP1 in cancer tissues was significantly upregulated compared with that in paracancerous tissues. In addition, ROC curve and KM curve analyses showed that lncRNA SDHAP1 had a certain diagnostic value for LUAD and the high expression of lncRNA SDHAP1 was associated with poor prognosis of patients. Studies have shown that [28] lncRNAs can participate in the biological regulation of tumors and are of great value in the diagnosis, treatment and prognosis of tumors. At the same time, more and more evidence suggest that lncRNA is involved in the occurrence and development of NSCLC. For example, lncRNA MALAT1 has been shown as an independent prognostic indicator for patients with early LUAD [29]. High expression of LncRNA HOTAIR in NSCLC samples is related to the poor prognosis of patients [30]. In this study, we also found that lncRNA SDHAP1 had a certain value in the diagnosis and prognosis of patients with LUAD. Of course, this study still has some limitations. TWe qualitatively analyzed the impacts of lncRNA SDHAP1 on malignant behaviors and CDDP resistance of NSCLC but failed to discuss its downstream regulatory targets. In future studies, we will further discuss the correlation between lncRNA SDHAP1 and the clinicopathology of NSCLC.

To sum up, lncRNA SDHAP1 is upregulated and correlated with LC staging and age in NSCLC. Silencing lncRNA SDHAP1 can suppress the multiplication, migration, invasiveness and CDDP resistance of cancer cells, indicating the role of lncRNA SDHAP1 as a potential prognostic and therapeutic target in NSCLC.

## Disclosure of conflict of interest

None.

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