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ORIGINAL ARTICLE

TUSC8 enhances cisplatin sensitivity of NSCLC cells through regulating VEGFA

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Summary

Purpose: *We aimed at studying LncRNA TUSC8 expression in non-small cell lung cancer (NSCLC) cells and its sensitivity to cisplatin chemotherapy, and explore its role in the occurrence, development and treatment of NSCLC.*

Methods: *NSCLC tissues and adjacent normal ones were randomly selected from 45 patients in our hospital who were pathologically diagnosed as NSCLC. Then H358 and H1299 cells were treated with cisplatin at different concentrations (0 μM, 2 μM, 4 μM, 8 μM, 16 μM) for 24 hours.*

Results: *Our data showed that long non-coding RNA (LncRNA) TUSC8 mRNA expression in NSCLC tissue specimens was remarkably lower than that in adjacent ones. A great link was found between LncRNA TUSC8 and tumor size, TNM stage and overall survival rates of patients with Lung cancer (LCa). The proliferation of NSCLC cells remarkably reduced after overexpression of LncRNA TUSC8 compared with the control group pcDNA3.1-NC, while cell apoptosis indicated an opposite trend. A binding relationship between LncRNA TUSC8 and its downstream target gene VEGFA was verified by luciferase assay. The proliferation rate of NSCLC cells decreased with the increase of cisplatin concentration, and the inhibition rate of LncRNA TUSC8 overexpression group was higher than that of the control group pcDNA3.1-NC under different concentrations of cisplatin.*

Conclusions: *Lowly expressed LncRNA TUSC8 in NSCLC is related to pathological parameters and prognosis of NSCLC patients. It may negatively regulate VEGFA by targeting its 3'UTR, thereby increasing the sensitivity of NSCLC cell lines to cisplatin, inhibiting the proliferation of NSCLC cells and promoting their apoptosis.*

Key words: *LncRNA TUSC8; VEGFA; NSCLC; cisplatin; malignant progression*

Introduction

Lung cancer (LCa) as one of the common malignant diseases with high morbidity and mortality is the leading cause of cancer deaths in both men and women, according to the data of the American Cancer Society in 2018 [1-3]. Among which, NSCLC is the most common type of LCa, with its average age of diagnosis as 70 years old, and the 5-year survival rate as only 17% [4,5]. Its early diagnosis is still very difficult in spite of its increasing incidence, so most cases have been in the advanced stage, thus missing the best opportunity for surgery [6,7]. Although the clinical application of molecular targeted therapy has improved the prognosis of advanced lung adenocarcinoma to some extent, cisplatin (DDP) containing two drugs combined with chemotherapy is still the main treatment in clinical application [8,9]. However, the efficacy of cisplatin chemotherapy is poor, and the incidence of intrinsic drug resistance and acquisition is high [10]. Therefore, clarifying the

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resistance mechanism of DDP and then adopting targeted treatment is particularly important for improving the current situation of chemotherapy for LCa [10,11].

Genome-wide analysis showed that less than 2% of the protein-coding genes in the human genome and over 90% of the genes are transcribed into non-coding RNA (ncRNA) [12], which can be divided into two types: short and long ncRNAs (LncRNAs) [12,13]. LncRNAs are a class of non-coding RNAs with a length greater than 200 nt [14], which play an important role in the occurrence and development of cancer and are related to the biological processes of various cancers, such as the occurrence, development, invasion and metastasis [15,16]. Although a large number of LncRNAs have been discovered by genomic analysis, only a few have been currently widely studied, of which HOTAIR and MALAT-1 are more prominent. Since the development of LncRNAs, the functions and molecular mechanisms of these two LncRNAs have been widely studied. Cancer clinical research also found that these LncRNAs have the potential to be molecular markers for tumor diagnosis and prognosis, and their expression levels are related to the clinicopathological characteristics and prognosis of various tumors [17,18]. LncRNA TUSC8, a member of the LncRNAs family, has abnormal expression in a variety of solid malignancies and plays a role similar to tumor suppressor genes [19,20].

In present study, given the bioinformatics databases suggest a potential binding relationship between LncRNA TUSC8 and VEGFA, we tested whether lncRNA TUSC8 increases cisplatin sensitivity by targeted down-regulating VEGFA. We characterize a novel mechanism involving LncRNA TUSC8 and its target protein VEGFA in regulation of resistance of NSCLC cells to cisplatin and NSCLC progression, the two of which are expected to become a potential therapeutic target and a new index for detection of cisplatin resistance.

Methods

Patients and NSCLC samples

All fresh tissue specimens (size: 0.8 cm × 0.8 cm × 0.6 cm) were obtained from 45 cases of NSCLC patients in our hospital, placed in cryopreserved tubes within 0.5 h and stored in liquid nitrogen for future use. The normal tissue adjacent to the cancer (3 cm away from the tumor) was used as a control. All patients had not received any radiotherapy or chemotherapy before operation. This study was approved by the Ethics Committee of Lianshui People's Hospital. Patients and their families had been fully informed in this study and signed informed consent.

Cell lines and reagents

NSCLC cell lines A549, H1299, H358 and normal lung epithelial cells (BEAS-2B) provided by the Cell Resource Center, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (Shanghai, China) were cultured in Dulbecco's modified eagle medium (DMEM) (Gibco, Rockville, MD, USA) and William's medium supplemented with 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA) and 100 u/mL penicillin, 100 u/mL streptomycin in an incubator with 5% CO_2 at 37°C.

Transfection

Lipofectamine 3000 reagent (Invitrogen, Carlsbad, CA, USA) was mixed with pcDNA3.1-NC or pcDNA3.1-LncRNA TUSC8 (GenePharma, Shanghai, China) and then transfected into cells when cell density reached 50-70%. 48 hours later, cells were collected for analysis.

Cell Counting Kit-8 (CCK-8)

NSCLC cells were collected 48 h after transfection and seeded into 96-well plates (5000 cells/well). CCK-8 assay (Beyotime Biotechnology, Shanghai, China) was conducted based on instructions.

Colony formation assay

Cell suspension was repeatedly blown with a pipette tip, and the viable cells were counted using cell counting plates after trypan blue staining. 100 cells were seeded into a six-well plate filled with 2 mL of complete medium. After cultured for 7 days, the colony formation rate was calculated.

Flow cytometry analysis of the cell apoptosis

The combination of Annexin V-FITC (Merck, USA) and PI was used for flow cytometry analysis. Cell density was adjusted to 1×10^6/mL, and cell apoptosis was detected by flow cytometry (BD Company, Franklin Lakes, NJ, USA) after 15 min of staining by Annexin V and PI.

Quantitative real-time PCR (qPCR)

1 mL of TRIzol (Invitrogen, Carlsbad, CA, USA) was used to lyse the tissues and cells to extract total RNA.

Table 1. Primers used in the qPCR reaction

Gene Name	*Primer sequences (5'-3')*
LncRNA TUSC8	forward: 5'-TGTGAAGAGGAGAACATAAAAGG-3 '
	reverse: 5'-AAGCAAGATAATACAGTGGCGA-3 '
VEGFA	forward: 5'-TGAAGGAGAAGGTGTCTGCGGGA-3 '
	reverse: 5'-AGGACGGTGCGGTGAGAGTG-3 '
GAPDH	forward: 5'-CTCCTCCTGTTCGACAGTCAGC-3 ',
	reverse: 5'-CCCAATACGACCAAATCCGTT-3 '.

Real-time PCR was performed according to the instructions of SYBR® Premix Ex Taq™ kit (TaKaRa, Tokyo, Japan) on StepOne Plus Real-time PCR System, with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as internal reference. The sequences of primers used are shown in Table 1.

Western blot

Transfected cells were collected, and proteins were extracted for quantitative detection. Cells were lysed using cell lysis buffer, shaken on ice for 30 minutes, and centrifuged at 14,000 × g for 15 minutes at 4°C. Total protein concentration was calculated by bicinchoninic acid (BCA) method (Beyotime, Shanghai, China) protein assay. Western blot was carried out using primary antibodies against VEGFA and then the horseradish peroxidase-labeled secondary antibody. The intensity of protein image was determined using alpha SP image analysis software.

Dual-luciferase Reporter Assay

HEK293T cells were plated in 24-well plates and co-transfected with VEGF / NC and pMIR luciferase reporter plasmids. The plasmid was then introduced into the cells using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). 48 hours later, luciferase activity of reporter was normalized to the control using luciferase reporter assay system (Promega, Madison, WI, USA).

Statistics

Numerical variables were presented as mean ± standard deviation (SD), and differences between two groups were analyzed using the Student's t-test. Percentage (%) was used to express the categorical variables, and chi-square test or the exact probability Fisher test was used for data analysis. Kaplan-Meier curves were produced and compared between patients with low expression of LncRNA TUSC8 and those with high expression by the log-rank test. Statistical analysis was performed using SPSS 22. 0 software (IBM, Armonk, NY, USA), and p less than 0.05 was considered as statistically significant.

Results

LncRNA TUSC8 was lowly expressed in NSCLC and closely related to the pathological stage and tumor size of NSCLC patients

QPCR results indicated a significant reduced LncRNA TUSC8 mRNA expression in NSCLC tissues compared to adjacent ones (Figure 1A). We divided the 45 NSCLC tissue samples into LncRNA TUSC8 high-expression and low-expression groups, and further explored the association between LncRNA TUSC8 MSC-AS1 and clinicopathological parameters as well as prognosis of NSCLC patients. Table 2 indicates that lowly expressed LncRNA TUSC8 showed a positive correlation with pathological T stage and tumor size of NSCLC patients, but not with age, gender, and distant metastasis (Figure 1B). Additionally, Kaplan-Meier analysis suggested that the overall survival of NSCLC patients with low expression of LncRNA TUSC8 was worse than those with high expression. Thus, the above results demonstrate that LncRNA TUSC8 may serve as a new biological marker to predict the malignant progress of NSCLC. Meanwhile, qPCR results also showed a reduced LncRNA TUSC8 level in LCa cell lines compared with the normal lung epithelial cells BEAS-2B (Figure 1C).

LncRNA TUSC8 inhibited proliferation and promoted apoptosis of NSCLC cells

According to LncRNA TUSC8 gene expression, we constructed LncRNA TUSC8 overexpression vector in H358 and H1299 cell lines and verified the overexpression efficiency by qPCR (Figure 2A). Subsequently, CCK-8 and colony formation assay suggested that the prolifera-

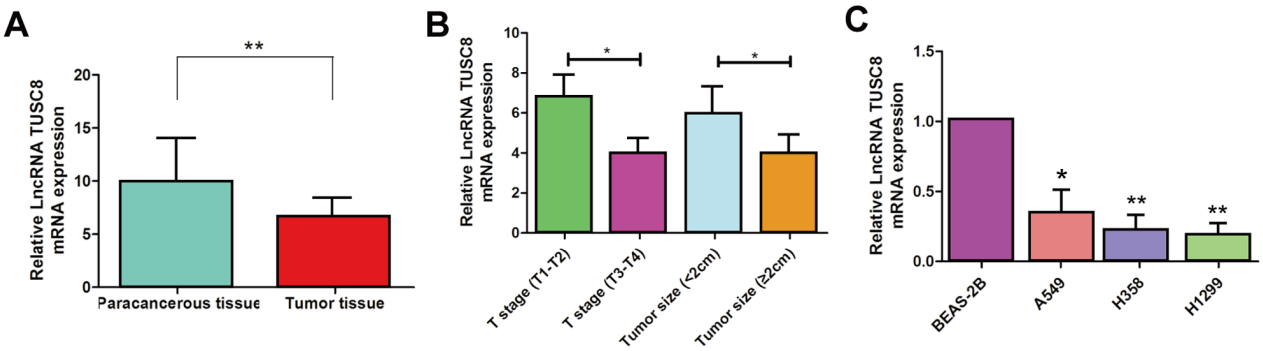

Figure 1. LncRNA TUSC8 was lowly expressed in non-small cell lung cancer tissues and cell lines. **A:** qRT-PCR was used to detect the difference in the expression of LncRNA TUSC8 in tumor tissues and adjacent tissues of non-small cell lung cancer; **B:** qRT-PCR was used to detect the expression difference of LncRNA TUSC8 in non-small cell lung cancer tissues with different pathological T stages and tumor sizes; **C:** qRT-PCR was used to detect the expression level of LncRNA TUSC8 in non-small cell lung cancer cell lines; Data are shown as mean ± SD, *p <0.05, **p <0.01.

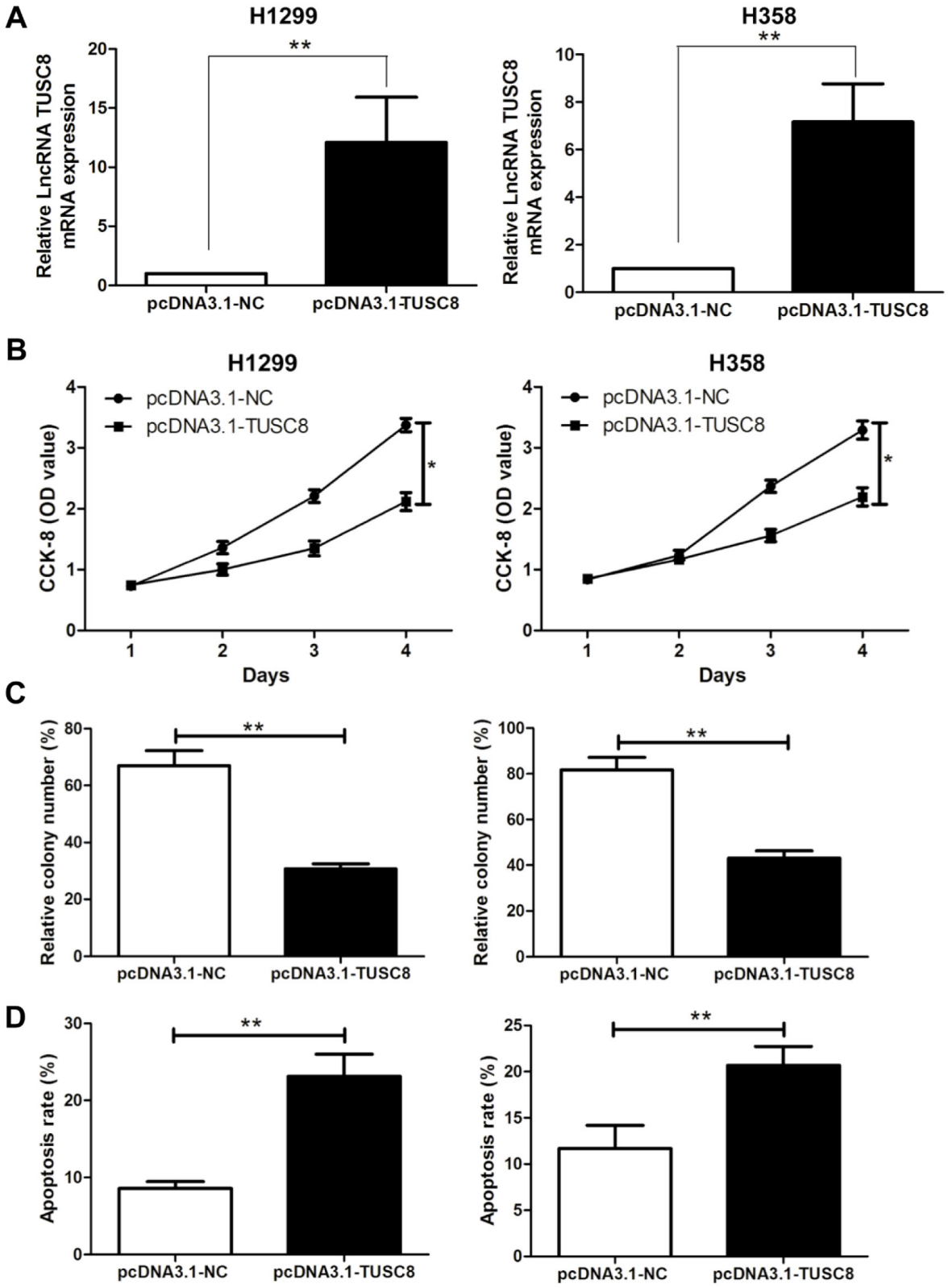

Figure 2. LncRNA TUSC8 inhibits the proliferation of non-small cell lung cancer cells and increases its apoptosis. **A:** qRT-PCR verified the transfection efficiency of LncRNA TUSC8 after transfection of pcDNA3.1-NC and pcDNA3.1-LncRNA TUSC8 in non-small cell lung cancer cell lines H358 and H1299, respectively; **B:** The CCK-8 experiment was used to detect the effect of cell proliferation after transfection of pcDNA3.1-NC and pcDNA3.1-LncRNA TUSC8 in non-small cell lung cancer cell lines H358 and H1299 respectively; **C:** The plate cloning experiment was used to detect the clonal formation ability of pcDNA3.1-NC and pcDNA3.1-LncRNA TUSC8 transfected in non-small cell lung cancer cell lines H358 and H1299, respectively; **D:** Flow cytometry experiment was used to detect the apoptosis ability of non-small cell lung cancer cell lines H358 and H1299 after transfection with pcDNA3.1-NC and pcDNA3.1-LncRNA TUSC8, respectively. Data are mean ± SD, *p <0.05, **p <0.01.

tive ability of NSCLC cells was markedly reduced after overexpression of LncRNA TUSC8 compared with the control group pcDNA3.1-NC (Figure 2B & 2C); on the contrary, flow cytometry assay revealed an increased cell apoptosis induced by LncRNA TUSC8 overexpression (Figure 2D).

LncRNA TUSC8 specifically binds VEGFA

Ongoing attempts were performed to further determine the ways by which LncRNA TUSC8 inhibits the malignant progression of NSCLC. Bioinformatics analysis revealed that LncRNA TUSC8 may specifically bind to VEGFA. Lucif-

Table 2. Association of LncRNA TUSC8 expression with clinicopathologic characteristics of non-small cell lung cancer

Indexes	*Cases (N)*	*TUSC8 expression*		*p value*
		High group (n=23)	*Low group (n=22)*	
Age (years)				0.641
<60	20	11	9	
≥60	25	12	13	
Gender				0.295
Male	23	10	13	
Female	22	13	9	
T stage				0.004
T1-T2	26	18	8	
T3-T4	19	5	14	
Tumor size (cm)				0.023
<2	28	18	10	
≥2	17	5	12	
Distant metastasis				0.102
No	26	16	10	
Yes	19	7	12	

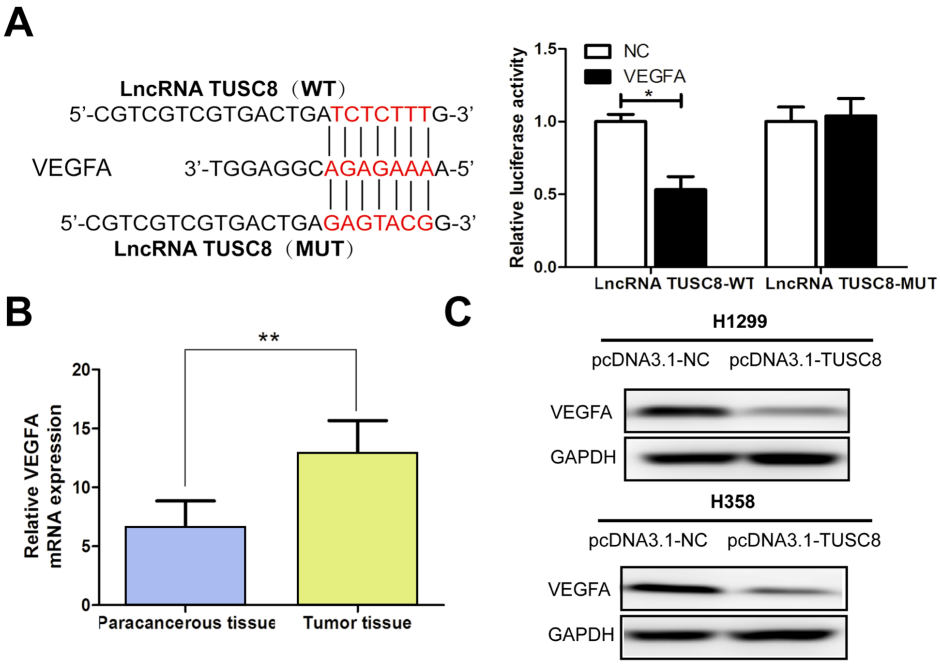

Figure 3. Interaction of LncRNA TUSC8 and VEGFA. **A:** Luciferase reporter gene experiments suggest that LncRNA TUSC8 can specifically bind to VEGFA; **B:** qRT-PCR was used to detect the difference of VEGFA expression in non-small cell lung cancer tumor tissues and adjacent tissues; **C:** Western blot verified the expression level of VEGFA protein in non-small cell lung cancer cell lines H358 and H1299 after transfection with pcDNA3.1-NC and pcDNA3.1-LncRNA TUSC8, respectively. Data are mean ± SD, *p <0.05, **p <0.01.

erase assay suggested that overexpression of VEGFA attenuated the luciferase activity of cells in the LncRNA TUSC8-wt group (Figure 3A). It was found that VEGFA mRNA level was increased remarkably in NSCLC tissues (Figure 3B), which was negatively correlated with the expression of LncRNA TUSC8. Meanwhile, Western blot results showed that VEGFA protein level was markedly reduced after overexpression of LncRNA TUSC8 (Figure 3C).

LncRNA TUSC8 increases sensitivity of cisplatin to NSCLC cell lines

The CCK-8 results demonstrated that the drug resistance concentration of two NSCLC cell lines to cisplatin was less than 50 μM, and 16 μM was observed as the best (Figure 4A). Subsequently, the sensitivity of cells transfected with pcDNA3.1-LncRNA TUSC8 to cisplatin was also observed by CCK8 test; as a result, NSCLC cells were sensitive to 8 μM cisplatin after overexpression of LncRNA

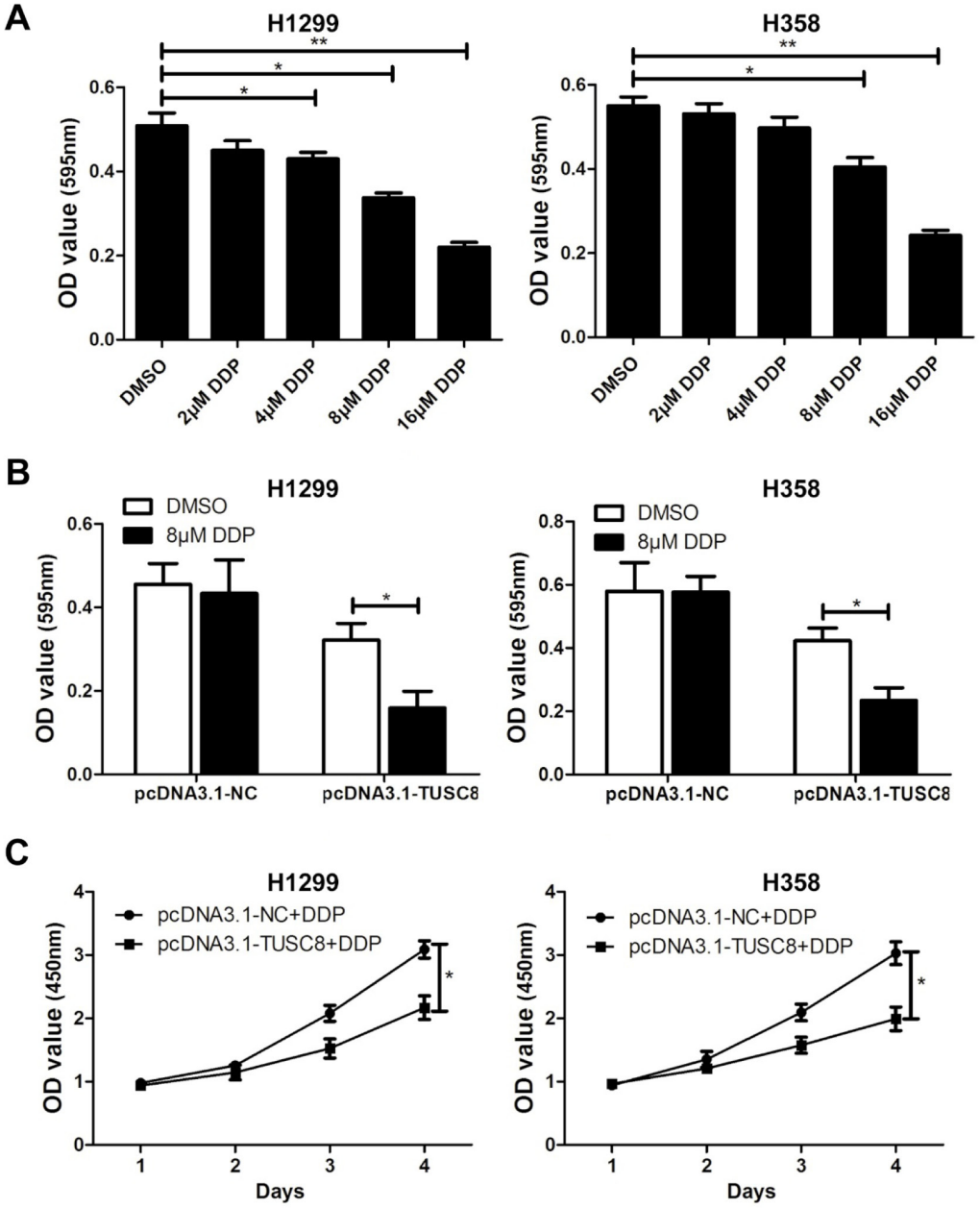

Figure 4. LncRNA TUSC8 increases the sensitivity of cisplatin to NSCLC cell lines. **A:** The sensitivity of non-small cell lung cancer cell lines H358 and H1299 to 2 μM, 4 μM, 8 μM, 16 μM cisplatin (DTX) was evaluated; **B:** CCK-8 was used to detect the cytotoxicity of cisplatin after transfection of LncRNA TUSC8 overexpression vector in non-small cell lung cancer cell lines H358 and H1299; **C:** CCK-8 was used to detect the proliferation of H358 and H1299 cells transfected with LncRNA TUSC8 overexpression vector at a concentration of 8 μM cisplatin. Data are mean ± SD, *p<0.05.

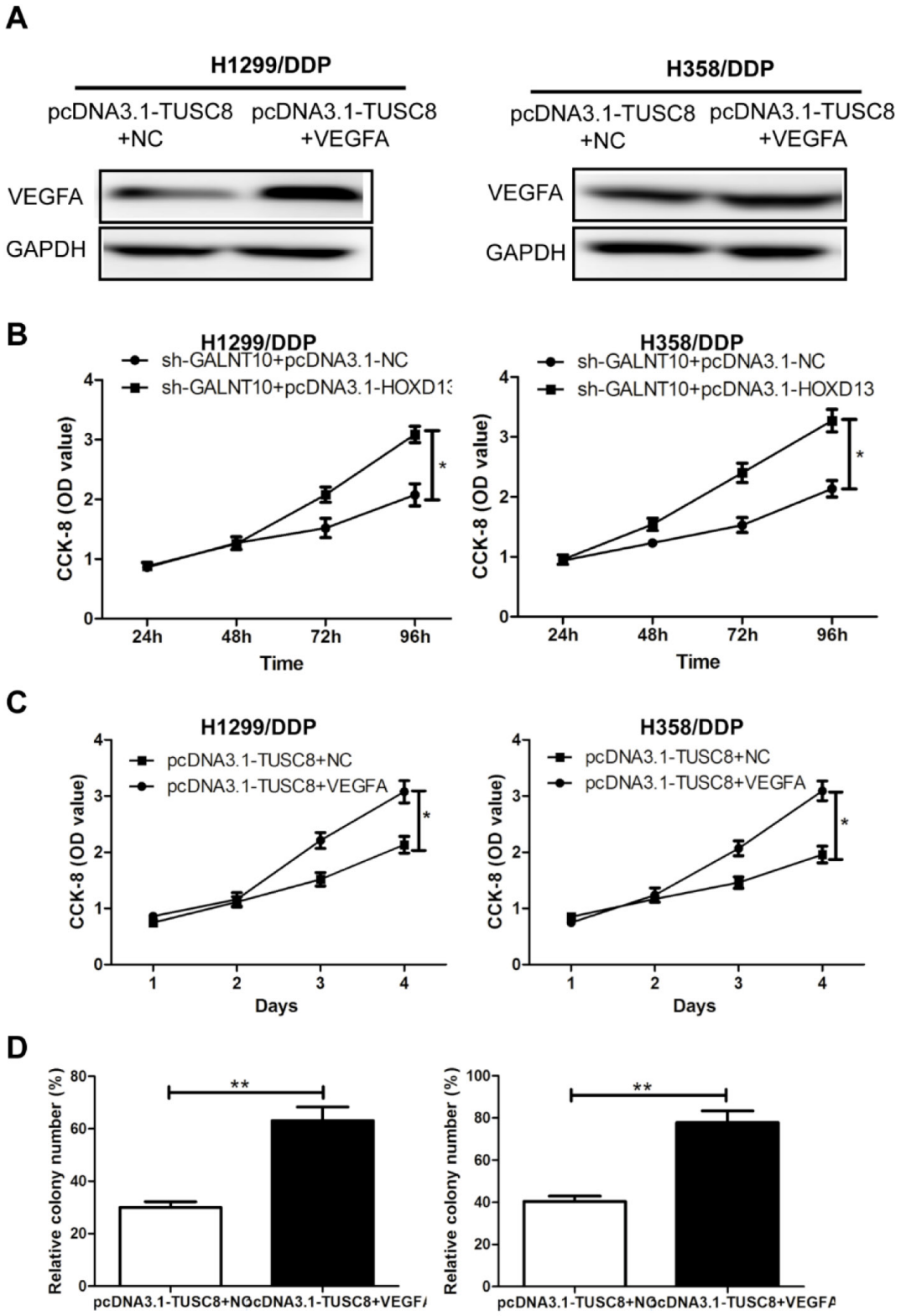

Figure 5. Overexpression of VEGFA can reverse the biological function and cisplatin sensitivity of LncRNA TUSC8 of non-small cell lung cancer cells. **A:** Western blot was used to detect the expression level of VEGFA after co-transfection of LncRNA TUSC8 and VEGFA overexpression vectors in cisplatin-resistant non-small cell lung cancer cell lines H358 and H1299; **B:** s CCK-8 was used to detect the cytotoxicity of cisplatin after co-transfection of LncRNA TUSC8 and VEGFA overexpression vector in cisplatin-resistant non-small cell lung cancer cell lines H358 and H1299; **C:** CCK-8 was used to detect the cell proliferation ability after co-transfection of LncRNA TUSC8 and VEGFA overexpression vectors in cisplatin-resistant non-small cell lung cancer cell lines H358 and H1299; **D:** The plate cloning experiment was performed to test the ability of cell clone formation after co-transfection of LncRNA TUSC8 and VEGFA overexpression vectors in cisplatin-resistant non-small cell lung cancer cell lines H358 and H1299. Data are mean ± SD, *p<0.05, **p<0.01.

TUSC8 (Figure 4B). In addition, the effects of 8 μM cisplatin combined with pcDNA3.1-LncRNA TUSC8 transfection and cisplatin alone were compared and the results indicated a markedly reduced proliferative ability in the former (Figure 4C).

VEGFA reverses the biological function and cisplatin sensitivity of LncRNA TUSC8 to NSCLC cells

To further determine the mutual regulation of LncRNA TUSC8 and VEGFA in NSCLC cells, we performed co-transfection of LncRNA TUSC8 and VEGFA overexpression vectors in cisplatin-resistant NSCLC cells, and examined the transfection efficiency of VEGFA by Western blot experiments. It was found that co-transfection remarkably elevated VEGFA expression compared to single overexpression of LncRNA TUSC8 (Figure 5A). Meanwhile, the CCK-8 proliferation assay investigated that simultaneous overexpression of above two genes reversed the sensitivity of NSCLC cells to 8 μM cisplatin in single overexpression of LncRNA TUSC8 group (Figure 5B). In addition, colony formation assay demonstrated that overexpression of VEGFA counteracted the inhibitory effect of overexpression of LncRNA TUSC8 on the proliferation ability of cisplatin-resistant NSCLC cells (Figure 5C and 5D).

Discussion

According to the latest statistics, lung cancer accounts for 13% of new tumor patients (1.6 million) and 23% of death patients (1.4 million) [1-3] among which NSCLC accounts for 80-85% of all LCa cases, becoming a major cause leading to deaths [4,5]. The high mortality rate of LCa has not been on a downward trend, mainly due to the lack of early diagnosis and effective treatment [6]. Surgery is the main method for the treatment of NSCLC, but most NSCLC patients have been in an advanced stage, thus losing the surgery opportunity, so early diagnosis of NSCLC is a key to reduce the mortality [7,8]. At present, the main reason for the poor prognosis of LCa is the high incidence of invasion and metastasis of tumor cells; however, the specific mechanism remains unclear [8]. With the deepening of research, it has been found that LncRNAs, originally considered as transcriptional by-products, play an important role in the occurrence and development of tumors, and their mechanism of participating in the regulation of tumors is similar to that of miRNAs or may be more complex. However, only a few functional characteristics of LncRNAs have been confirmed in oncology studies so far [12-15]. The present data show that LncRNA TUSC8 level, remarkably lower in NSCLC tissues than in the corresponding paracancer tissues, was closely associated with the pathological classification and tumor size of NSCLC, suggesting that LncRNA TUSC8 may be a specific marker for NSCLC prediction. Subsequently, we demonstrated that upregulation of LncRNA TUSC8 was able to suppress the proliferation and promote the apoptosis of NSCLC cells.

To further determine the biological function of LncRNA TUSC8, we further searched for its target genes. Bioinformatics analysis indicates that LncRNA TUSC8 may exert its effects by acting on VEGFA. Overexpression of LncRNA TUSC8 in NSCLC cells downregulated VEGFA protein expression, thus inhibiting the development of NSCLC. We also found an increased expression of VEGFA in tumor tissues comparison to matched paracancereous ones, suggesting a relation of VEGFA level to NSCLC. Thus, it is suggested that LncRNA TUSC8 and VEGFA have the potential to serve as new markers for prediction of NSCLC prognosis.

Due to the insidious malignant changes of NSCLC, early diagnosis of LCa is particularly important in the treatment of LCa and the improvement of its survival rate [5-7]. Although second-line chemotherapy containing platinum drugs has become the main treatment method for advanced NSCLC patients, drug resistance is the main reason for the failure of chemotherapy. Therefore, early detection and diagnosis of LCa is the key to improve the effective rate of LCa treatment, while gene therapy for advanced cancer patients has become a hotspot in tumor treatment research in recent years [8-11]. In our experiments, human NSCLC cell lines H358 and H1299 cells were treated with cisplatin at different concentrations, and the cell proliferation was found to be inhibited to different degrees, suggesting that cisplatin intervention might inhibit the activity of H358 and H1299 cells by upregulation of LncRNA TUSC8 expression. In addition, we found that overexpression of VEGFA could counteract the biological function of overexpression of LncRNA TUSC8 in NSCLC cells, indicating that LncRNA TUSC8 may inhibit the malignant progression of NSCLC through down-regulating VEGFA and increasing cisplatin sensitivity of NSCLC cells. Therefore, it was confirmed that LncRNA TUSC8 may play an inhibitory role in the occurrence and development of NSCLC, which is conducive to the early diagnosis of NSCLC and may be a sensitizer for tumor chemotherapy drugs.

Conclusions

In summary, these studies suggested that the low expression of LncRNA TUSC8 was remarkably correlated with the pathological stage and tumor size of NSCLC. In addition, LncRNA TUSC8 inhibits the malignant progression of NSCLC by down-regulating VEGFA to increase the cisplatin sensitivity of NSCLC cells.

Conflict of interests

The authors declare no conflict of interests.

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