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lncRNA ZEB2-AS1 Aggravates Progression of Non-Small Cell Lung Carcinoma via Suppressing PTEN Level

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The aim of this study was to assess the involvement of lncRNA ZEB2-AS1 in the development of NSCLC and to explore the potential mechanism involved.

Material/Methods: ZEB2-AS1 expressions in 48 paired NSCLC tissues and paracancerous tissues were examined by qRT-PCR. ZEB2-AS1 level in NSCLC patients affected by tumor staging and lymphatic metastasis was examined as well. Regulatory effects of ZEB2-AS1 on proliferative, migratory, and invasive properties of NCI-H1650 and HCC827 cells were evaluated. The interaction between ZEB2-AS1 and EZH2 was identified through RIP assay. Subsequently, the binding of EZH2 on PTEN promoter region was tested by ChIP. Finally, rescue experiments were conducted to assess the involvement of PTEN in the development of NSCLC.

Results: ZEB2-AS1 was upregulated in NSCLC tissues and cell lines. Its level was higher in NSCLC patients with T3–T4 or accompanied with lymphatic metastasis relative to those with T1–T2 or without metastatic *loci*. Knockdown of ZEB2-AS1 suppressed proliferative, migratory, and invasive properties of NCI-H1650 and HCC827 cells. PTEN level was elevated after knockdown of ZEB2-AS1 or EZH2 in HCC827 cells. Subsequently, RIP assay proved the interaction between ZEB2-AS1 and EZH2. Knockdown of ZEB2-AS1 markedly reduced the binding of EZH2 on the PTEN promoter region. Notably, knockdown of PTEN reversed the effects of EZB2-AS1 on regulating proliferative, migratory, and invasive properties of NSCLC cells.

Conclusions: lncRNA ZEB2-AS1 is upregulated in NSCLC, which elevates the viability and malignant degree of NSCLC cells by downregulating PTEN, thus aggravating the progression of NSCLC.

MeSH Keywords: Carcinoma, Non-Small-Cell Lung • PTEN Phosphohydrolase • RNA, Long Noncoding

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Background

Lung carcinoma is a common cancer of the respiratory system that endangers human health. The incidence of lung carcinoma is on the rise, and it ranks first in male malignant tumors [1,2]. Non-small cell lung carcinoma (NSCLC) is the major subtype of lung carcinoma, accounting for 85% of all lung carcinoma cases [3,4]. With advances in radiotherapy, chemotherapy and surgical procedures, the survival of NSCLC patients has been markedly prolonged. Nevertheless, the 5-year survival of metastatic NSCLC patients remains poor [5,6]. It is necessary to define the pathogenesis of NSCLC and develop effective therapeutic strategies to improve clinical outcomes.

Long non-coding RNAs (lncRNAs) are non-coding RNAs that are 200 to 100 000 nt long and that regulate gene expressions at transcriptional and post-transcriptional levels [7]. They have been proved to exert important functions in the physiological and pathological processes. Vital functions of lncRNAs in the occurrence and development of tumor diseases have been reported [8,9]. lncRNA ZEB2-AS1 accelerates the proliferative rate of bladder cancer cells by inhibiting miR-27b level [10]. The biological function of ZEB2-AS1 in NSCLC, however, has not been fully investigated.

PTEN (phosphatase and tensin homolog deleted on chromosome ten), is a well-known tumor suppressor located on 10q23.3 [11]. Functional deficiency of PTEN can lead to tumorigenesis or tumor progression [12–14]. Relevant studies have shown the important role of PTEN mutations in the progression of NSCLC [15,16]. The present study assessed the role of ZEB2-AS1 in mediating the malignant development of NSCLC by regulating PTEN levels.

Material and Methods

Subjects and samples

We surgically resected 48 paired tumor tissues and matched adjacent tissues (3 cm away from the tumor edge) from NSCLC patients treated in the First Affiliated Hospital of Bengbu Medical College from February 2007 to December 2018. They did not receive preoperative anti-tumor therapy and were all pathologically diagnosed. Clinical data of enrolled NSCLC patients were collected. This study was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College (BBMC-AECA-170421-001). All subjects volunteered to participate in the trial and signed written informed consent. This study was conducted in accordance with the Declaration of Helsinki.

Table 1. Primer sequences used in the study.

Gene	Primer sequences
EZH2	F: 5'-TGCACATCCTGACTTCTGTG-3'
	R: 5'-AAGGGCATTCACCAACTCC-3'
PTEN	F: 5'-CCAGTCAGAGGCGCTATGTG -3'
	R: 5'-ACTTGTCTTCCCGTCGTGTG -3'
ZEB2-AS1	F: 5'-CCTGGAAAGGGAAATCCTG-3'
	R: 5'-AGGATGAATATAGACAGGCCA-3'
GAPDH	F: 5'-CGGAGTCAACGGATTTGGTCGT-3'
	R: 5'-GGGAAGGATCTGTCTCTGACC-3'

Cell culture

Lung carcinoma cell lines (A549, NCI-H1650, and HCC827) were provided by Cell Bank (Shanghai, China). Cells were cultured in Dulbecco's modified Eagle's medium (DMEM, Thermo Fisher Scientific, Waltham, MA, USA) containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA), 100 µg/mL penicillin, and 0.1 mg/mL streptomycin in a 37°C, 5% CO_2 incubator.

Cell transfection

Cells were cultured until 60% confluence and then subjected to transfection using Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Complete medium was replaced 6 hours later. Cells transfected for 24–48 h were harvested for *in vitro* experiments.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Cellular RNAs were extracted by TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Reversely transcribed complementary deoxyribose nucleic acid (cDNA) was used for PCR using the SYBR Green method. Primer sequences are listed in Table 1.

Cell Counting Kit (CCK-8)

Cells were inoculated in a 96-well plate and cultured overnight. At the appointed time points, CCK-8 solution (Dojindo Laboratories, Kumamoto, Japan) was added, and 450 nm absorbance (A) was recorded for depicting the viability curves.

Transwell

Transwell chambers were coated by diluted Matrigel and 50 µl of FN (100 µg/mL) overnight at 4°C. We added 500 µL of medium containing 10% FBS and 200 µL of serum-free suspension (1×10^6/mL) in the basolateral and apical chamber,

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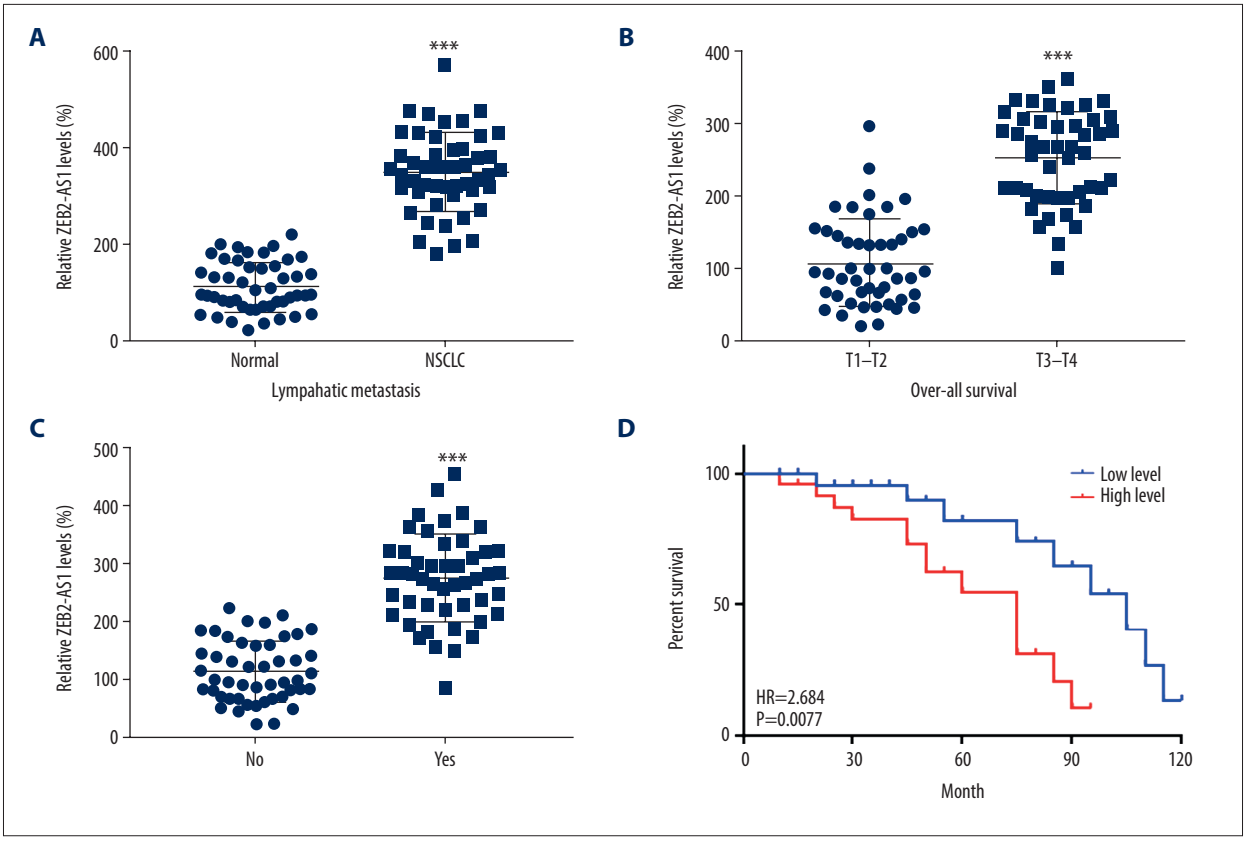

Figure 1. ZEB2-AS1 was upregulated in NSCLC and was negatively correlated with disease prognosis. (**A**) ZEB2-AS1 level in NSCLC tissues and paracancerous tissues. (**B**) ZEB2-AS1 level in NSCLC patients with T1–T2 and T3–T4. (**C**) ZEB2-AS1 level in NSCLC patients either with lymphatic metastasis or not. (**D**) Kaplan-Meier curves introduced for assessing the overall survival in NSCLC patients with high level or low level of ZEB2-AS1. * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

respectively, of the 24-well plate. After 24-h culture, 30-min methanol fixation and 30-min 0.1% crystal violet staining were performed. Invasive cells were imaged using an inverted microscope. Migration assay procedures were the same except for pre-coating with Matrigel and FN.

Western blot analysis

Radioimmunoprecipitation assay (RIPA) (Beyotime, Shanghai, China) was performed to extract cellular protein, which was quantified by bicinchoninic acid (BCA) method (Beyotime, Shanghai, China). Protein samples were loaded for electrophoresis and transferred onto polyvinylidene fluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Membranes were blocked in 5% skim milk for 2 h and incubated with PTEN (Cell Signaling Technology, Danvers, MA, USA, Cat#: 9188, GAPDH (Cell Signaling Technology, Danvers, MA, USA, Cat#: 5174), and secondary antibodies. Band exposure was achieved by electrochemiluminescence (ECL) (Pierce, Rockford, IL, USA) and analyzed using Image J software.

RNA immunoprecipitation (RIP)

Millipore Magna RIPTM RNA-Binding Protein Immunoprecipitation Kits (Millipore, Billerica, MA, USA) were used for RIP. Cell lysate was incubated with anti-EZH2 or anti-IgG at 4°C for 6 h. RNA was extracted from protein-RNA complexes using 0.5 mg/ml proteinase K containing 0.1% sodium dodecyl sulphate (SDS). Non-specific absorption in magnetic beads was removed by RIP washing buffer. Finally, the relative level of the extracted RNA was tested by qRT-PCR.

Chromatin immunoprecipitation (ChIP)

Cells were subjected to 10-min cross-link with 1% formaldehyde at room temperature. Subsequently, cells were lysed using lysis buffer and sonicated for 30 min. Finally, the sonicated lysate was immuno-precipitated with anti-EZH2, anti-H3K27me3, or anti-IgG.

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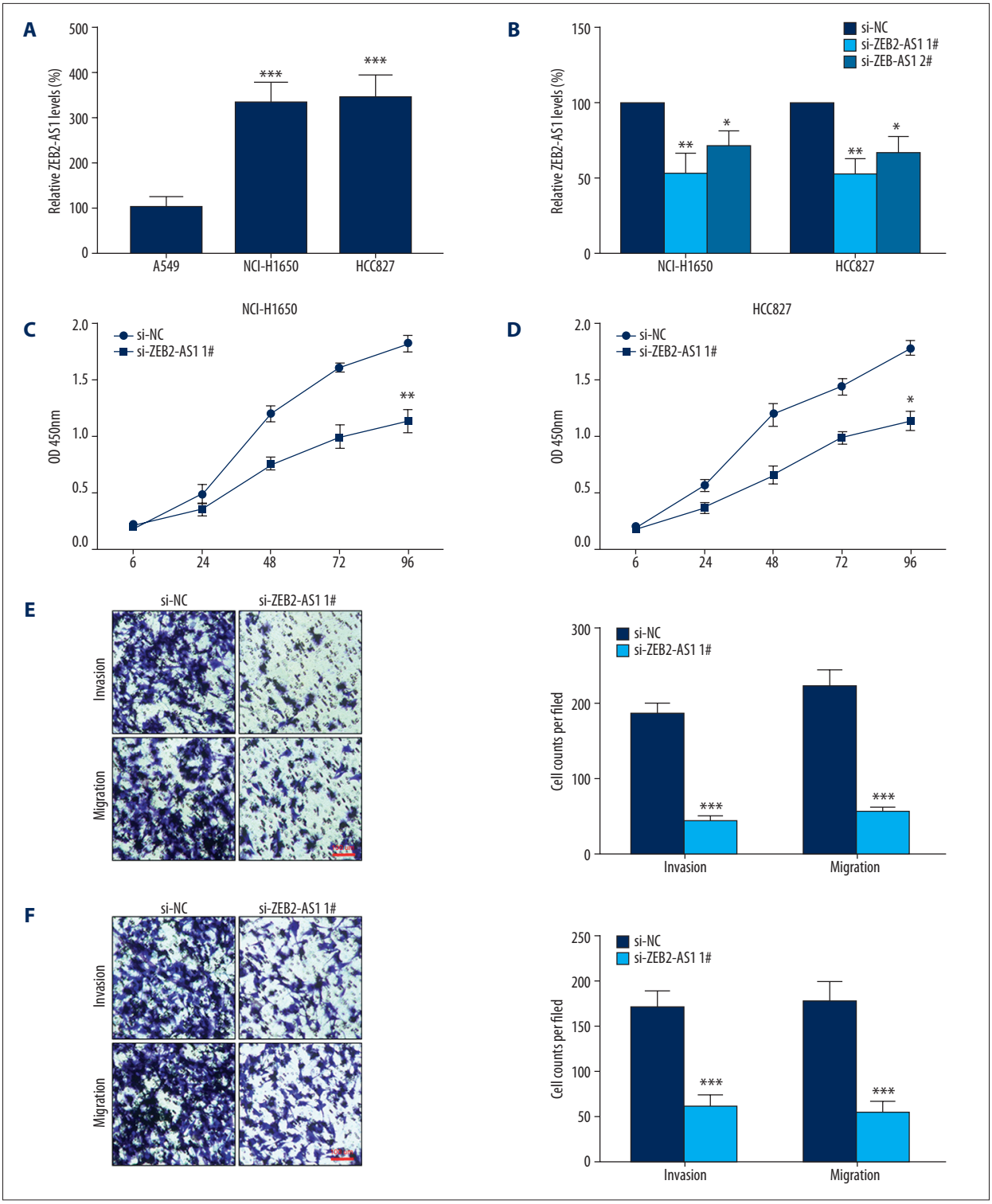

Figure 2. Knockdown of ZEB2-AS1 suppressed proliferative, migratory, and invasive properties of NSCLC. (**A**) Relative level of ZEB2-AS1 in NSCLC cell lines. (**B**) Transfection efficacy of si-ZEB2-AS1 1# and si-ZEB2-AS1 2# in NCI-H1650 and HCC827 cells. (**C**) CCK-8 assay showed the viability in NCI-H1650 cells transfected with si-NC or si-ZEB2-AS1 1#. (**D**) CCK-8 assay showed the viability in HCC827 cells transfected with si-NC or si-ZEB2-AS1 1#. (**E**) Transwell assay showed the invasion and migration in NCI-H1650 cells transfected with si-NC or si-ZEB2-AS1 1#. (**F**) Transwell assay showed the invasion and migration in HCC827 cells transfected with si-NC or si-ZEB2-AS1 1#, * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

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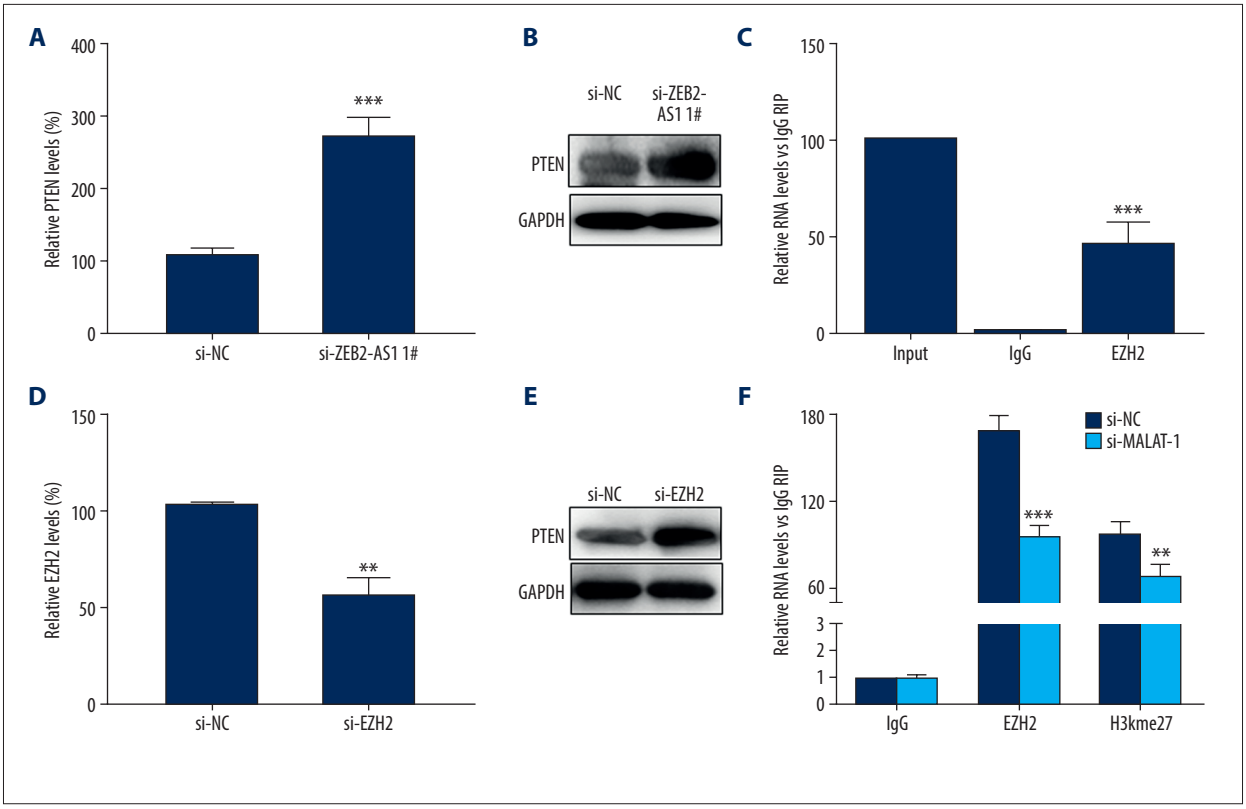

Figure 3. ZEB2-AS1 mediated PTEN level via interacting with EZH2. (**A**) PTEN level in HCC827 cells transfected with si-NC or si-ZEB2-AS1 1#. (**B**) Protein level of PTEN in HCC827 cells transfected with si-NC or si-ZEB2-AS1 1#. (**C**) RIP assay showed the enrichment of ZEB2-AS1 in anti-IgG and anti-EZH2. (**D**) Relative level of EZH2 in HCC827 cells transfected with si-NC or si-EZH2. (**E**) Protein level of PTEN in HCC827 cells transfected with si-NC or si-EZH2. (**F**) ChIP assay showed the immunoprecipitants of IgG, EZH2, and H3K27me3 in HCC827 cells transfected with si-NC or si-ZEB2-AS1 1#, * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

Statistical analysis

Statistical Product and Service Solutions (SPSS) 16.0 (SPSS IBM, Armonk, NY USA) software was used for data analyses. Data are expressed as mean±standard deviation. Differences between 2 groups were analyzed by the *t* test. Survival analysis was conducted using Kaplan-Meier method, followed by log-rank test for comparing differences. $P<0.05$ was considered statistically significant.

Results

ZEB2-AS1 was upregulated in NSCLC and was negatively correlated to disease prognosis

QRT-PCR data revealed the higher abundance of ZEB2-AS1 in NSCLC tissues relative to normal ones (Figure 1A). Moreover, ZEB2-AS1 level was higher in NSCLC patients with T3–T4 than in those with T1–T2 (Figure 1B). Compared with non-metastatic NSCLC patients, those accompanied with lymphatic metastasis presented higher levels of ZEB2-AS1 (Figure 1C). Kaplan-Meier curves were used for assessing the prognostic potential of ZEB2-AS1 in NSCLC. Worse prognosis was identified in NSCLC patients with high expression of ZEB2-AS1 relative to those with low expression (Figure 1D).

Knockdown of ZEB2-AS1 suppressed proliferative, migratory, and invasive properties of NSCLC cells

The *in vitro* level of ZEB2-AS1 was high in NSCLC cell lines (Figure 2A). To further investigate the biological function of ZEB2-AS1, we constructed 2 ZEB2-AS1 siRNAs. Both si-ZEB2-AS1 1# and si-ZEB2-AS1 2# showed high transfection efficacies in NCI-H1650 and HCC827 cells, which was more pronounced in the former (Figure 2B). In the following *in vitro* experiments, si-ZEB2-AS1 1# was selected for silencing ZEB2-AS1. Transfection of si-ZEB2-AS1 1# markedly decreased viability in NCI-H1650 and HCC827 cells, as shown by CCK-8 assay (Figure 2C, 2D). Furthermore, Transwell assay showed the decreased invasive and migratory rates after silencing of ZEB2-AS1 in NSCLC cells (Figure 2E, 2F). These results

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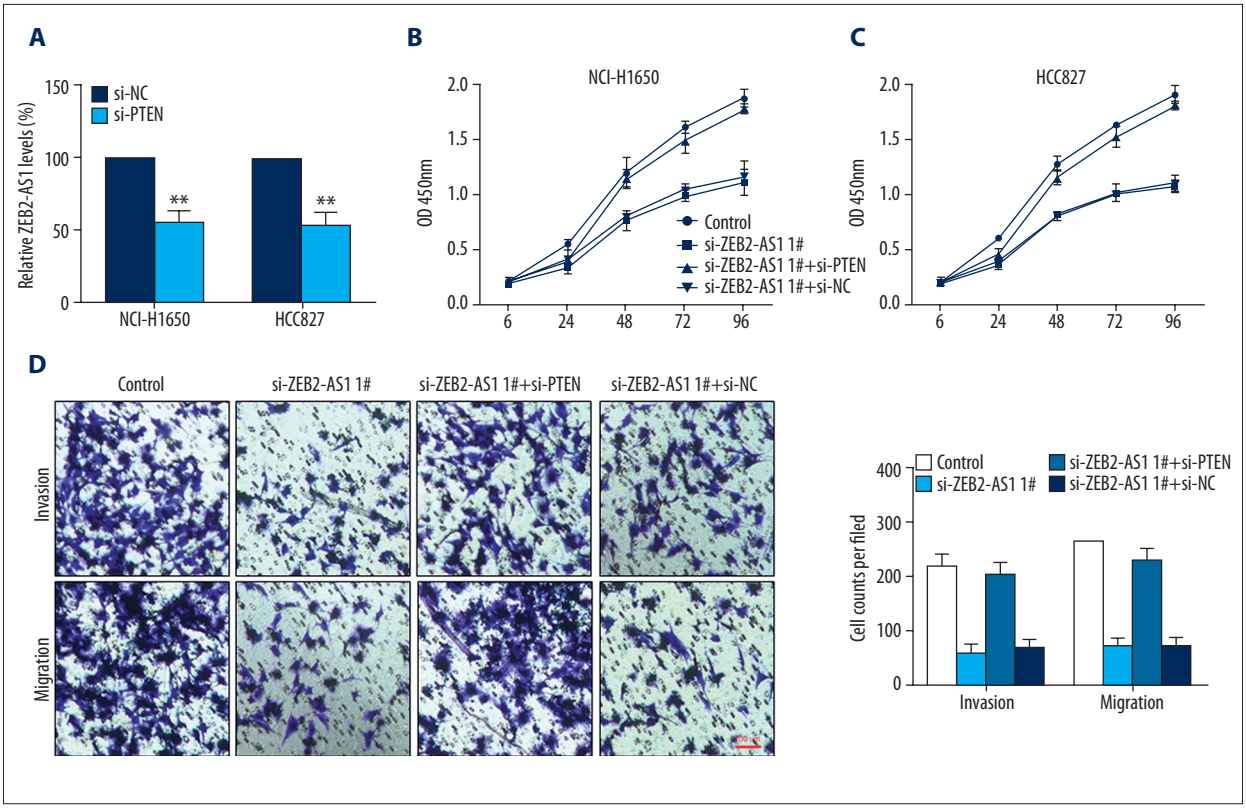

Figure 4. ZEB2-AS1 aggravated malignant phenotypes of NSCLC by suppressing PTEN level. (**A**) Relative level of ZEB2-AS1 in NCI-H1650 and HCC827 cells transfected with si-NC or si-PTEN. (**B**) CCK-8 assay showed the viability in NCI-H1650 cells transfected with si-NC, si-ZEB2-AS1 1#, si-ZEB2-AS1 1#+si-PTEN, or si-ZEB2-AS1 1#+si-NC. (**C**) CCK-8 assay showed the viability in HCC827 cells transfected with si-NC, si-ZEB2-AS1 1#, si-ZEB2-AS1 1#+si-PTEN, or si-ZEB2-AS1 1#+si-NC. (**D**) Transwell assay showed the invasion and migration in HCC827 cells transfected with si-NC, si-ZEB2-AS1 1#, si-ZEB2-AS1 1#+si-PTEN, or si-ZEB2-AS1 1#+si-NC, * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

suggest that ZEB2-AS1 increased the viability and malignance of NSCLC cells.

ZEB2-AS1 mediated PTEN level by interacting with EZH2

Both mRNA and protein levels of PTEN were upregulated after transfection of si-ZEB2-AS1 1# in HCC827 cells (Figure 3A, 3B). Subsequent RIP assay demonstrated the higher enrichment of ZEB2-AS1 in anti-EZH2 than that of anti-IgG, indicating the interaction between ZEB2-AS1 and EZH2 (Figure 3C). We found that transfection of si-EZH2 markedly downregulated EZH2 level in HCC827 cells, showing high transfection efficacy (Figure 3D). In addition, transfection of si-EZH2 upregulated protein levels of PTEN (Figure 3E). ChIP assay showed decreased immunoprecipitants of EZH2 and H3K27me3 in HCC827 cells transfected with si-ZEB2-AS1 1# compared with those transfected with si-NC (Figure 3F). These results suggest that silencing of ZEB2-AS1 reduced the binding of EZH2 to the PTEN promoter region, and ZEB2-AS1 negatively regulated PTEN levels by recruiting EZH2.

ZEB2-AS1 aggravated malignant phenotypes of NSCLC by suppressing PTEN level

It is speculated that PTEN may be involved in the malignant progression of NSCLC influenced by ZEB2-AS1. First of all, transfection of si-PTEN markedly upregulated ZEB2-AS1 level in NCI-H1650 and HCC827 cells (Figure 4A). Transfection of si-ZEB2-AS1 1# in NCI-H1650 and HCC827 cells reduced the viability, which was partially reversed after co-transfection of si-PTEN (Figure 4B, 4C). Similarly, the inhibited invasive and migratory abilities in NSCLC cells with ZEB2-AS1 knockdown were partially reversed after PTEN knockdown (Figure 4D). It is generally considered that ZEB2-AS1 accelerates the proliferative, migratory, and invasive properties of NSCLC by negatively regulating PTEN level (Figure 5).

Discussion

NSCLC is a common malignant tumor, ranking first in morbidity and mortality [17]. Improvement of diagnostic efficacy and

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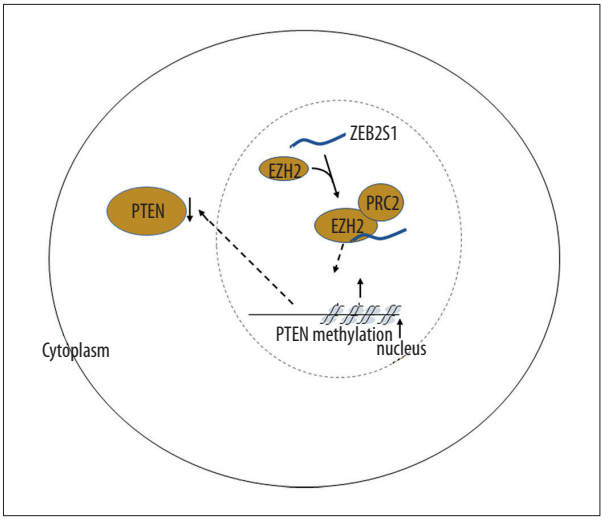

Figure 5. In non-small cell lung cancer, ZEB2-AS1 promoted cell proliferation, migration, and invasion through recruiting EZH2 to downregulate PTEN.

overall survival of NSCLC patients is a challenge in clinical practice [18]. In the present study, lncRNA ZEB2-AS1 was upregulated in NSCLC tissues, especially those with T3–T4. Survival analysis demonstrated that ZEB2-AS1 reduced the overall survival of NSCLC, suggesting that ZEB2-AS1 serves as an oncogene in the development of NSCLC.

Relevant studies have illustrated the close relationship between lncRNAs and survival of NSCLC [19,20]. Certain lncRNAs may be utilized as prognostic hallmarks for NSCLC. Accumulating evidence shows that ZEB2-AS1 exerts a vital role in tumors through accelerating proliferation and metastasis, as well as by inhibiting apoptosis of tumor cells [10,21,22]. The present study showed that knockdown of ZEB2-AS1 attenuated viability, migratory, and invasive abilities of NCI-H1650 and HCC827 cells. Moreover, our results confirmed that ZEB2-AS1 aggravated the malignant degree of NSCLC by suppressing PTEN levels.

EZH2 is an important component of the catalytic complex of PRC2, which catalyzes trimethylation of lysine 27 on histone H3 protein subunit and silences target genes [23–25]. It is reported that HOXA11-AS can simultaneously bind to several RNA-binding proteins (e.g., PRC2, LSD1, and DNMT1) to promote the proliferative and invasive capacities of gastric cancer [26]. Our experiments showed that PTEN level was upregulated by knockdown of EZH2 in NSCLC cells. Moreover, ZEB2-AS1 recruited EZH2 to bind to the PTEN promoter region to silence PTEN expression. In summary, ZEB2-AS1 silenced PTEN expression by recruiting EZH2, thus aggravating the malignant progression of NSCLC.

Conclusions

lncRNA ZEB2-AS1 is upregulated in NSCLC, which increases the viability and malignant degree of NSCLC cells by downregulating PTEN, thus aggravating the progression of NSCLC. lncRNA ZEB2-AS1 may be utilized as a drug target for NSCLC treatment.

Conflict of interest

None.

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