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Original Article

Long noncoding RNA LINC01296 induces non-small cell lung cancer growth and progression through sponging miR-5095

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Abstract: Long noncoding RNAs (lncRNAs) played in authentic biological cell roles such as cell apoptosis, cycle, differentiation, development, migration and invasion. However, the expression pattern and function of a new lncRNA LINC01296 in non-small cell lung cancer (NSCLC) are unknown and need to be studied. In our study, we indicate that the expression of LINC01296 was overexpressed in NSCLC samples compared to adjacent non-tumor tissues. Ectopic expression of LINC01296 promoted NSCLC cell proliferation and migration. Moreover, we demonstrated that LINC01296 has a potential binding site for miR-5095 by using online program tool StarBase. Overexpression of LINC01296 inhibited the expression of miR-5095 in the A549 cell. Furthermore, the miR-5095 expression was downregulated in the NSCLC tissues than in the adjacent non-tumor tissues. In addition, we found that there is a negative correlation between miR-5095 expression and LINC01296 level in the NSCLC tissues. Overexpression of miR-5095 suppressed NSCLC cell proliferation and migration. Finally, we demonstrate that ectopic expression of LINC01296 promoted cell proliferation and migration via inhibiting miR-5095 expression. These results suggested that LINC01296 might act a role as an oncogene in the tumorigenesis and development of NSCLC.

Keywords: Non-small cell lung cancer, lncRNA, LINC01296, miR-5095

Introduction

Lung cancer is primary cause of the mortality in both women and men and accounted for majority of tumor deaths worldwide [1-5]. Non-small cell lung cancer (NSCLC) is the most frequently type of lung tumor and accounts for about 85% of primary lung cancer [6-9]. Characteristically, cells of NSCLC could migrate to local samples and spread to distant tissues in the later stage [10-12]. Despite progression in chemotherapeutic and surgical interventions, the five-year survival of NSCLC cases remains discontent and recurrence rate of NSCLC patient is high, due to tumor metastasis [6, 13-16]. Thus, it is urgent to study the molecular mechanisms underlying initiation and development of NSCLC and find new therapeutic strategies for treatment of NSCLC.

Long noncoding RNAs (lncRNAs) are arbitrarily regarded as longer than about 200 nucleotides (nts) with no or limited protein coding capacity [17-20]. Recently, some lncRNAs were revealed to be played in authentic biological cell roles such as cell apoptosis, cycle, differentiation, development, migration and invasion [21-24]. A number of lncRNAs were deregulated in diverse tumors including colorectal cancer, hepatocellular carcinoma, osteosarcoma, gastric cancer, ovarian carcinoma and also NSCLC [25-30]. More recently, a new LINC01296 was shown to be involved in several tumors development such as prostate cancer, colorectal cancer, bladder cancer, gastric cancer, esophageal squamous cell carcinoma (ESCC), cholangiocarcinoma and osteosarcoma [31-37]. For instance, Qiu et al. [33]. Found that LINC01296 was upregulated and the higher expression of LINC01296 was an independent predictor for colorectal cancer patients' prognosis. Seitz and colleagues used the lncRNA profiling to found that LINC01296 was a candidate oncogene in the bladder cancer [34]. Qin et al. [37] indicat-

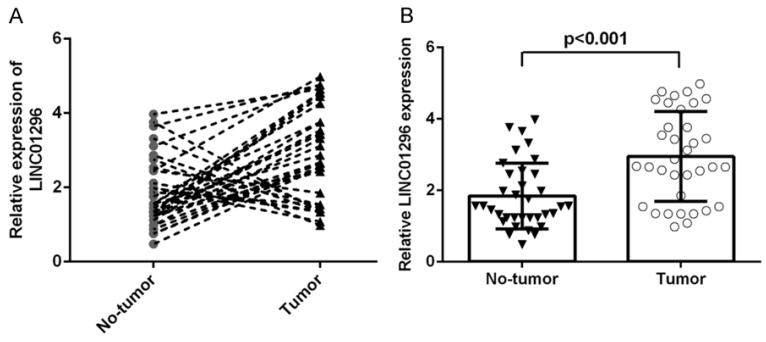

Figure 1. LINC01296 was overexpressed in NSCLC samples. A. The expression of LINC01296 was upregulated in 25 cases (25/35; 71.4%) compared to adjacent non-tumor tissues. The LINC01296 expression was determined by qRT-PCR. B. The LINC01296 expression was higher in the NSCLC tissues than in the adjacent non-tumor tissues.

ed that the LINC01296 expression was overexpressed in gastric cancer tissues and knockdown expression of LINC01296 inhibited gastric cancer cell migration, invasion and proliferation and induced cell apoptosis via regulating miR-122 expression. Zhang and colleagues showed that LINC01296 expression was overexpressed in cholangiocarcinoma and the LINC01296 expression was positively correlated with clinical stage and tumor severity [32]. LINC01296 knockdown inhibited cell migration, invasion and viability. They also demonstrated that LINC01296 induced cholangiocarcinoma growth and progression through inhibiting miR-5095. However, its expression pattern and function in NSCLC are unknown and need to be studied.

In this research, we indicate that the expression of LINC01296 was overexpressed in NSCLC samples compared to adjacent non-tumor tissues. Ectopic expression of LINC01296 promoted NSCLC cell proliferation and migration.

Materials and methods

NSCLC tissues, cell lines cultured and plasmid DNA Transfection

Human NSCLC tissues samples and matched non-tumor samples were collected from Thoracic department of Shanghai Pulmonary Hospital, Tongji University (Shanghai, China). These samples were speedy frozen in the liquid nitrogen until use. Human NSCLC cell lines (H1299, SPC-A1, A549 and H23) and one normal bronchial epithelial cell line (16HBE) were purchased from the ATCC (American Type Culture Collection, Manassas, USA). These cells were kelpt in RPMI-1640 complete medium. miR-5095 mimic and scramble, pcDNA-LINC01296 and control plasmid were collected from Invitrogen (Carlsbad, California). Lipofectamine 2000 transfection kit (Invitrogen, USA) was utilized for transfection.

RNA isolation and qRT-PCR

Total RNA from samples or tissues was extracted with TRIzol (Bio Basic, Inc., Toronto, Canada). Quantitative PCR (qRT-PCR) was conducted to measure the expression of lncRNA, miRNA and mRNA on the 7900HT Real-Time PCR System (Applied Biosystems) with SYBR Kit (Takara Bio Inc). GAPDH and U6 were taken as the internal control for mRNA or miRNA respectively. The 2^{-DDCt} was done to detect RNAs. The primer sequences which were used in the study were shown as following: miR-5095, 5'-TACAGG CGTGAACCACC-3'; LINC01296 forward sequences, 5'-GAGAAGCAGTGGTGGGTTCC-3' and reverse sequences, 5'-GAGCAACACAGATGAACCGC-3'; GAPDH forward sequences, 5'-TCCTCTGACTTCAACAGCGACAC-3' and reverse sequences, 5'-CAC CCTGTTGCTGTAGCCAAATTC-3'.

Dual luciferase reporter assay

A mixture containing pMIR-LINC01296 Mut or pMIR-LINC01296 WT plasmid, pRL-TK Renilla Plasmid, miR-5095 mimic or scramble were co-transfected into A540 cell by uisng Lipofectamine 2000 (Invitrogen). Renilla and Firefly luciferase activities were determined at 2 days post-transfection with Dual Luciferase Reporter (Promega). The Renilla luciferase activity was used as the control.

Cell growth assays and migration assay

For cell growth, cells were cultured in the 96-well plate. Cell Counting Kit-8 (CCK-8, Dojindo, Kumamoto, Japan) was done to measure the cell proliferation. Proliferation rate was determined at 0, 1, 2 and 3 day after treated. The absorbance at the 450 nm was determined by using Spectrophotometer (BioTek, Winooski, VT). For cell migration, wound healing assay

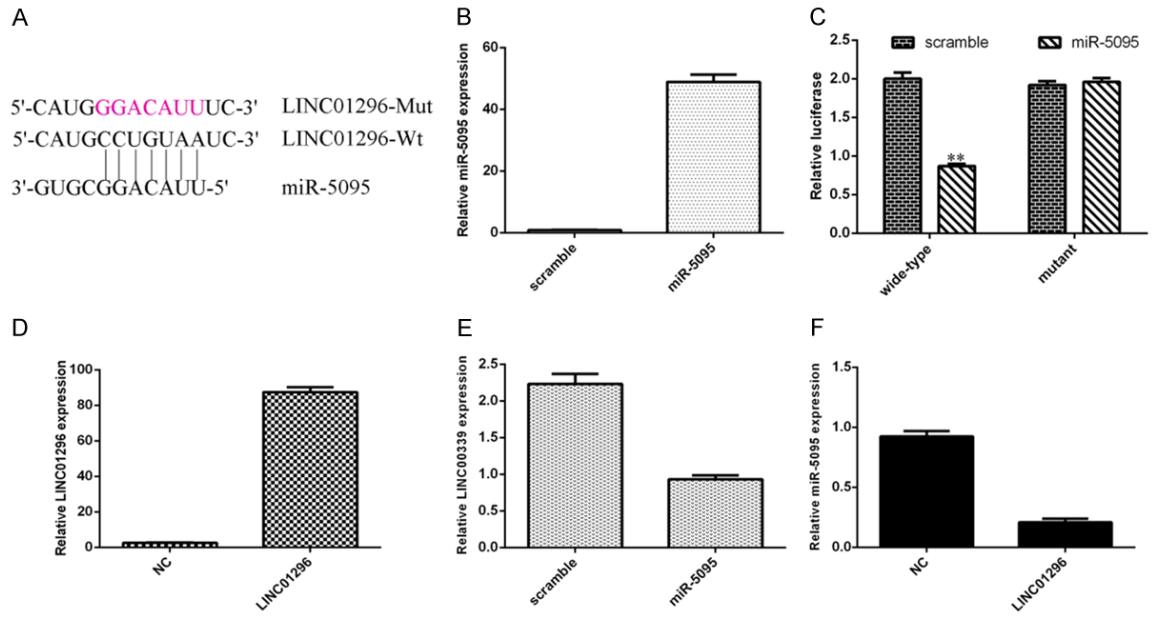

Figure 2. LINC01296 sponges miR-5095 in NSCLC cells. A. LINC01296 has a potential binding site for miR-5095 by using online program tool StarBase v3.0 (http://starbase.sysu.edu.cn/). B. The expression of miR-5095 was measured by qRT-PCR in the A549 cell. C. Ectopic expression of miR-5095 reduced the luciferase reporter activity carrying the 3'-UTR of LINC01296 but not the mutant of 3'-UTR of LINC01296. D. The expression of LINC01296 was upregulated in the A549 cell after treated with pcDNA-LINC01296 by qRT-PCR. E. Ectopic expression of miR-5095 suppressed the LINC01296 expression in the A549 cell. F. Overexpression of LINC01296 inhibited the expression of miR-5095 in the A549 cell. **P < 0.01.

was performed. When the cell was reached confluence, the cell wound was created by pipette tip. Figures were taken subsequent to scratching and at 48 hours subsequent to scratching.

Statistical analyses

Numerical data were shown as mean ± standard deviation (SD). The difference among the treatment groups was analyzed by Student's t test. P at < 0.05 was considered to be statistically significant. The SPSS 8.0 (SPSS, Inc.) was used in this study.

Results

LINC01296 was overexpressed in NSCLC samples

To study the role of lncRNA LINC01296 in NSCLC, we firstly measured LINC01296 expression in 35 NSCLC samples and adjacent non-tumor samples through performing qRT-PCR. As indicated in the **Figure 1A**, the expression of LINC01296 was upregulated in 25 cases (25/35; 71.4%) compared to adjacent non-tumor tissues. Furthermore, the LINC01296 expression was higher in the NSCLC tissues than in the adjacent non-tumor tissues (**Figure 1B**).

LINC01296 sponges miR-5095 in NSCLC cells

The online program tool StarBase v3.0 (http://starbase.sysu.edu.cn/) was performed to predict miRNA-lncRNA interactions; we demonstrated that LINC01296 has a potential binding site for miR-5095 (**Figure 2A**). We then showed that the expression of miR-5095 was upregulated in the A549 cell after treated with miR-5095 mimic by qRT-PCR (**Figure 2B**). Next, dual luciferase reporter was done to validate the binding between LINC01296 and miR-5095. We demonstrated that ectopic expression of miR-5095 reduced the luciferase reporter activity carrying the 3'-UTR of LINC01296 but not the mutant of 3'-UTR of LINC01296 (**Figure 2C**). In addition, we indicated that the expression of LINC01296 was upregulated in the A549 cell after treated with pcDNA-LINC01296 by qRT-PCR (**Figure 2D**). Ectopic expression of miR-5095 suppressed the LINC01296 expression in the A549 cell (**Figure 2E**). Overexpression of LINC01296 inhibited the expression of miR-5095 in the A549 cell (**Figure 2F**).

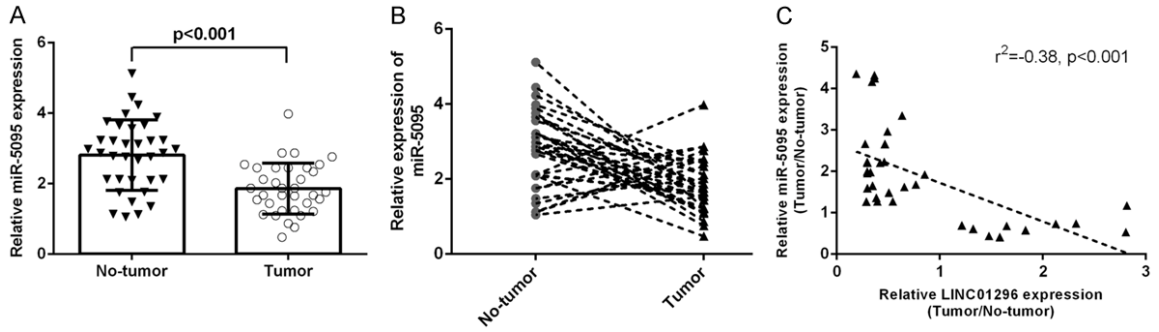

Figure 3. miR-5095 was downregulated in NSCLC samples. A. The expression of miR-5095 was downregulated in 26 cases (26/35; 74.3%) compared to adjacent non-tumor tissues. The miR-5095 expression was determined by qRT-PCR. B. The miR-5095 expression was lower in the NSCLC tissues than in the adjacent non-tumor tissues. C. There is a negative correlation between miR-5095 expression and LINC01296 level in the NSCLC tissues.

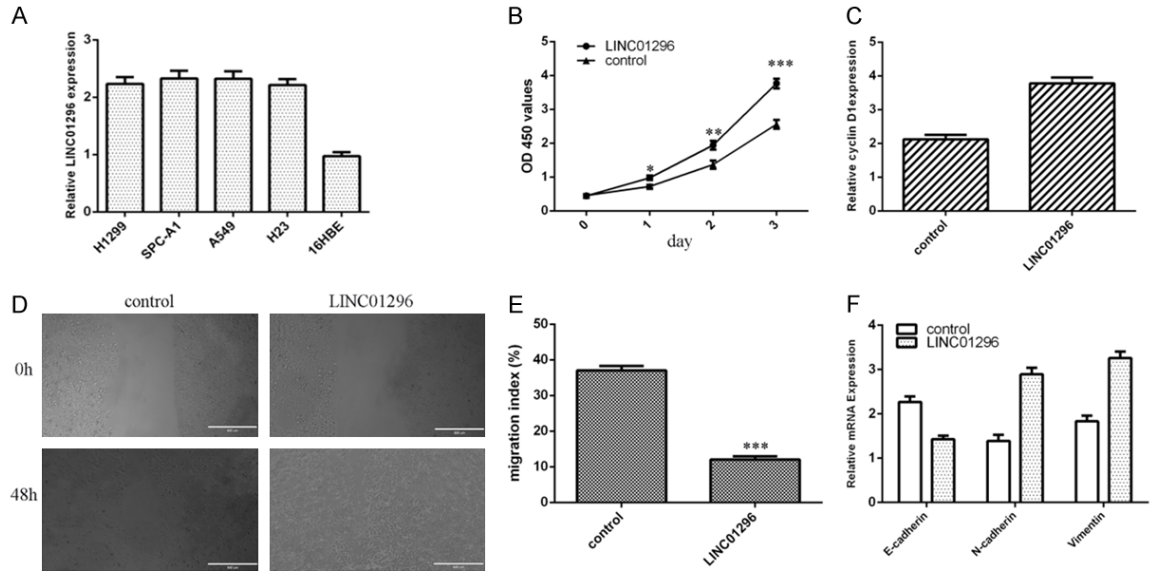

Figure 4. Ectopic expression of LINC01296 promoted cell proliferation and migration. (A) The expression of LINC01296 in the four NSCLC cell lines (H1299, SPC-A1, A549 and H23) and one normal bronchial epithelial cell line (16HBE) was detected by qRT-PCR. (B) Ectopic expression of LINC01296 induced the A549 cell proliferation by CCK-8 analysis. (C) Elevated expression of LINC01296 increased the cyclin D1 expression in the A549 cell. (D) Overexpression of LINC01296 promoted the A549 cell migration. (E) The relative migration index was shown (F) LINC01296 overexpression suppressed the expression of E-cadherin and induced the expression of N-cadherin and Vimentin in the A549 cell. *P < 0.05, **P < 0.01 and ***P < 0.001.

miR-5095 was downregulated in NSCLC samples

To study the role of miR-5095 in NSCLC, we then detected miR-5095 expression in 35 NSCLC samples and adjacent non-tumor samples through performing qRT-PCR. As shown in the **Figure 3A**, the expression of miR-5095 was downregulated in 26 cases (26/35; 74.3%) compared to adjacent non-tumor tissues. Furthermore, the miR-5095 expression was lower in the NSCLC tissues than in the adjacent non-tumor tissues (**Figure 3B**). In addition, there is a negative correlation between miR-5095 expression and LINC01296 level in the NSCLC tissues (**Figure 3C**).

Ectopic expression of LINC01296 promoted cell proliferation and migration

We then found that the expression of LINC01296 was upregulated in the four NSCLC cell lines (H1299, SPC-A1, A549 and H23) compared to one normal bronchial epithelial cell line (16HBE) (**Figure 4A**). Ectopic expression of LINC01296 induced the A549 cell proliferation

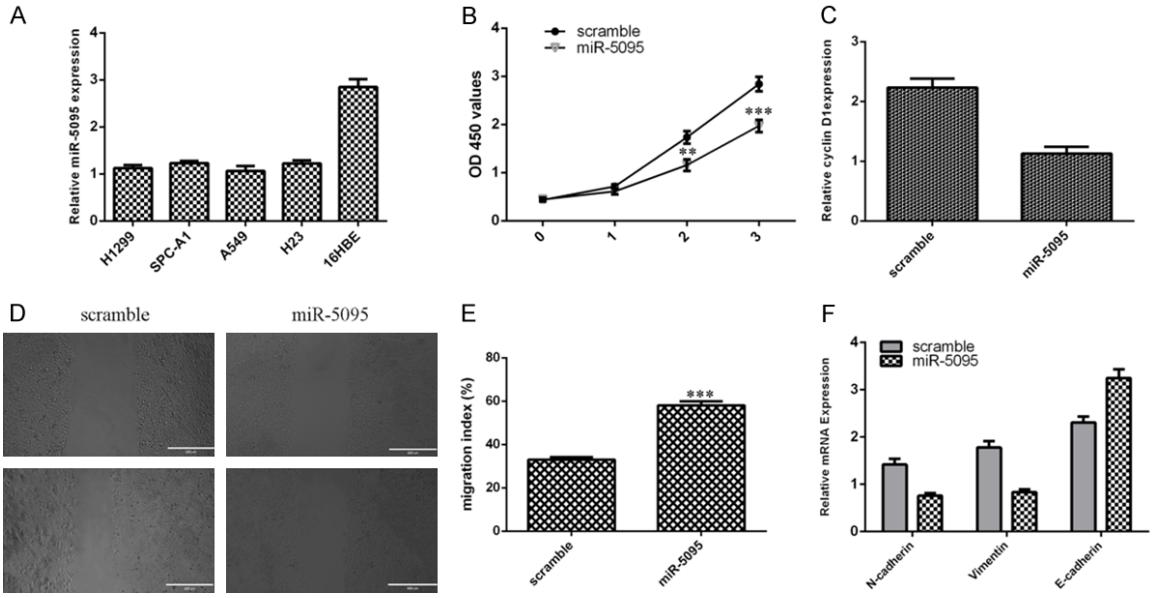

Figure 5. Overexpression of miR-5095 suppressed cell proliferation and migration. A. The expression of miR-5095 in the four NSCLC cell lines (H1299, SPC-A1, A549 and H23) and one normal bronchial epithelial cell line (16HBE) was detected by qRT-PCR. B. Ectopic expression of miR-5095 suppressed the A549 cell proliferation via CCK-8 analysis. C. Elevated expression of miR-5095 suppressed the cyclin D1 expression in the A549 cell. D. Overexpression of miR-5095 decreased the A549 cell migration. E. The relative migration index was shown. F. The mRNA expression of E-cadherin, N-cadherin and Vimentin in the A549 cell was detected by qRT-PCR. **P < 0.01 and ***P < 0.001.

by CCK-8 analysis (**Figure 4B**). Moreover, elevated expression of LINC01296 increased the cyclin D1 expression in the A549 (**Figure 4C**). Furthermore, overexpression of LINC01296 promoted the A549 cell migration (**Figure 4D** and **4E**). LINC01296 overexpression suppressed the expression of E-cadherin and induced the expression of N-cadherin and Vimentin in the A549 cell (**Figure 4F**).

Overexpression of miR-5095 suppressed cell proliferation and migration

Then, we demonstrated that the expression of miR-5095 was downregulated in the four NSCLC cell lines (H1299, SPC-A1, A549 and H23) compared to one normal bronchial epithelial cell line (16HBE) (**Figure 5A**). Ectopic expression of miR-5095 suppressed the A549 cell proliferation via CCK-8 analysis (**Figure 5B**). Moreover, elevated expression of miR-5095 suppressed the cyclin D1 expression in the A549 (**Figure 5C**). Furthermore, overexpression of miR-5095 decreased the A549 cell migration (**Figure 5D** and **5E**). miR-5095 overexpression enhanced the expression of E-cadherin and inhibited the expression of N-cadherin and Vimentin in the A549 cell (**Figure 5F**).

miR-5095 reversed the promoting effects of LINC01296 on NSCLC cells

To investigate the important role of miR-5095 binding in LINC01296-induing NSCLC progression, we transfected miR-5095 mimic in LINC01296 overexpressing A549 cell. We indicated that elevated expression of miR-5095 attenuated the inducing effect on cell proliferation of A549 cell via CCK-8 assay (**Figure 6A**). In addition, our data suggested that overexpression of miR-5095 suppressed the cyclin D1 expression in the LINC01296-overexpressing A549 cell (**Figure 6B**). Ectopic expression of miR-5095 enhanced the expression of E-cadherin and inhibited the expression of N-cadherin and Vimentin in the LINC01296-overexpressing A549 cell (**Figure 6C**). Elevated expression of miR-5095 attenuated the promoting effect on cell migration of A549 cell (**Figure 6D** and **6E**).

Discussion

In our study, we indicate that the expression of LINC01296 was overexpressed in NSCLC samples compared to adjacent non-tumor tissues. Ectopic expression of LINC01296 promoted NSCLC cell proliferation and migration.

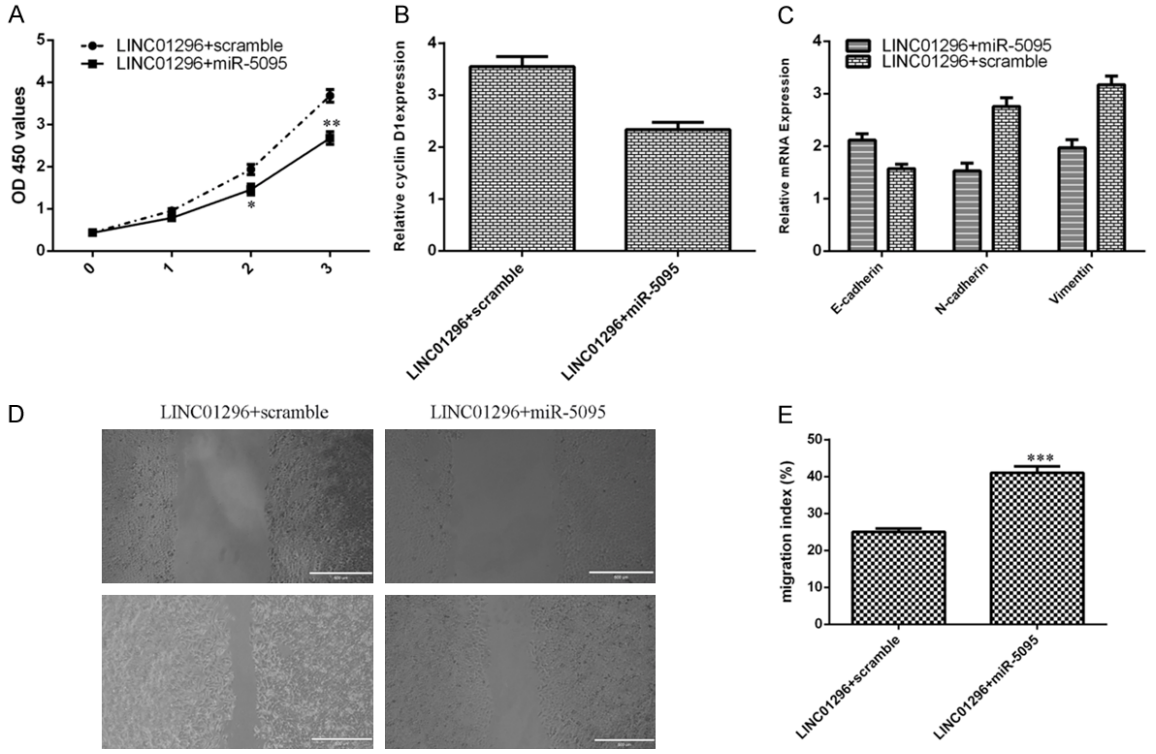

Figure 6. miR-5095 reversed the promoting effects of LINC01296 on NSCLC cells. A. Elevated expression of miR-5095 attenuated the inducing effect on cell proliferation of A549 cell via CCK-8 assay. B. The mRNA expression of cyclin D1 was detected by qRT-PCR. C. The mRNA expression of E-cadherin, N-cadherin and Vimentin in the A549 cell was detected by qRT-PCR. D. Elevated expression of miR-5095 attenuated the promoting effect on cell migration of A549 cell. E. The relative migration index was shown. *P < 0.05, **P < 0.01 and ***P < 0.001.

Moreover, we demonstrated that LINC01296 has a potential binding site for miR-5095 by using online program tool StarBase. Overexpression of LINC01296 inhibited the expression of miR-5095 in the A549 cell. Furthermore, the miR-5095 expression was downregulated in the NSCLC tissues than in the adjacent non-tumor tissues. In addition, we found that there is a negative correlation between miR-5095 expression and LINC01296 level in the NSCLC tissues. Overexpression of miR-5095 suppressed NSCLC cell proliferation and migration. Finally, we demonstrate that ectopic expression of LINC01296 promoted cell proliferation and migration via inhibiting miR-5095 expression. These results suggested that LINC01296 might act a role as an oncogene in the tumorigenesis and development of NSCLC.

LINC01296 was shown to be involved in several tumors development such as colorectal cancer, bladder cancer, prostate cancer, gastric cancer, cholangiocarcinoma, esophageal squamous cell carcinoma (ESCC) and osteosarcoma [31-37]. For instance, Qiu et al. [33]. Found that LINC01296 was overexpressed and the higher expression of LINC01296 was an independent predictor for colorectal cancer patients' prognosis. Seitz and colleagues performed the lncRNA profiling to found that LINC00958 was a candidate oncogene in the bladder cancer [34]. Qin et al. [37]. Showed that the LINC01296 expression was overexpressed in gastric cancer tissues and knockdown expression of LINC01296 inhibited gastric cancer cell migration, invasion and proliferation and induced cell apoptosis via regulating miR-122 expression. Zhang and colleagues found that LINC01296 expression was overexpressed in cholangiocarcinoma and the LINC01296 expression was positively correlated with clinical stage and tumor severity [32]. LINC01296 knockdown inhibited cell migration, invasion and viability. Yu et al. [36]. showed that LINC01296 expression was upregulated in osteosarcoma and the higher expression of LINC01296 was associated with poor survival. Overexpression of LINC01296 promoted osteosarcoma cell invasion, migration and proliferation. However, the expression pattern and functional role of LIN-

C01296 remains unclear. In this research, we firstly measured the LINC01296 expression in 35 NSCLC samples and adjacent non-tumor samples through performing qRT-PCR. We found that the expression of LINC01296 was upregulated in NSCLC tissues compared to adjacent non-tumor tissues. Ectopic expression of LINC01296 promoted NSCLC cell proliferation and migration. Furthermore, we demonstrated that elevated expression of LINC01296 induced the cyclin D1 expression in the A549 cell. Furthermore, LINC01296 overexpression suppressed the expression of E-cadherin and induced the expression of N-cadherin and Vimentin in the A549 cell.

Binding relationship between miR-5095 and LINC01296 was confirmed by our research, which helps us to further comprehend LINC-01296's promoting of lung NSCLC progression via interacting with miR-5095. Previous studies also found that lncRNA act as sponges for miRNA [38, 39]. For example, Chi et al. [40] demonstrated that LncRNA RP11-79H23.3 acts as a ceRNA to modulate PTEN expression via sponging miR-107 expression in the bladder Cancer development. Li et al. [41]. Showed that lncRNA LINC00978 induced NSCLC cell invasion and proliferation through inhibiting miR-6754-5p. Moreover, Zhang et al. [32]. demonstrated that LINC01296 induced cholangiocarcinoma growth and progression through sponging miR-5095. We furtherly demonstrated that ectopic expression of miR-5095 reduced the luciferase reporter activity carrying the 3'-UTR of LINC01296 but not the mutant of 3'-UTR of LINC01296 In addition, ectopic expression of LINC01296 inhibited miR-5095 expression in the A549 cell. The miR-5095 expression was lower in the NSCLC tissues than in the adjacent non-tumor tissues. There is a negative correlation between miR-5095 expression and LINC01296 level in the NSCLC tissues. Overexpression of miR-5095 suppressed cell proliferation and migration. Finally, we demonstrate that ectopic expression of LINC01296 promoted cell proliferation and migration via inhibiting miR-5095 expression.

In summary, we found that the expression of LINC01296 was overexpressed in NSCLC samples compared to adjacent non-tumor tissues. Ectopic expression of LINC01296 promoted NSCLC cell proliferation and migration partly via inhibiting miR-5095 expression.

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Disclosure of conflict of interest

None.

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