Low LINC01272 predicts poor prognosis of non-small cell lung cancer and its biological function in tumor cells by inhibiting miR-1303

SUE ZHANG and JIELU ZHOU

Anesthesiology Department, Weifang People’s Hospital, Weifang, Shandong 261041, P.R. China

Received April 1, 2021; Accepted June 24, 2021

DOI: 10.3892/ol.2021.12913

Abstract. Non-small cell lung cancer (NSCLC) is a malignant tumor associated with poor prognosis. The clinical value of long non-coding RNAs (lncRNAs) in the pathomechanism of various types of human malignancy has attracted increasing attention. The present study aimed to investigate the expression of LINC01272 in NSCLC and to determine its prognostic value and biological role. Tumor and adjacent non-tumor tissues from 108 patients with NSCLC and NSCLC cell lines were used in this study. The expression levels of LINC01272 and microRNA (miR)-1303 in tissues of patients and NSCLC cell lines were evaluated by reverse transcription quantitative PCR. The relationship between LINC01272 and the overall survival of patients with NSCLC was analyzed by Kaplan-Meier survival curve and log-rank test. Cox regression analysis confirmed the prognostic value of LINC01272 in patients with NSCLC. Cell Counting Kit-8 assay was used to evaluate the proliferation of NSCLC cells. The migration and invasion of NSCLC cells were determined using Transwell assays. The interaction between LINC01272 and miR-1303 in NSCLC was confirmed by dual-luciferase reporter assay. LINC01272 downregulation in NSCLC tissues was associated with worse overall survival in patients based on bioinformatics analysis. Furthermore, LINC01272 expression, which was decreased in NSCLC tumor tissues and NSCLC cells, was considered as an independent prognostic biomarker in NSCLC. In addition, LINC01272 overexpression inhibited NSCLC cell proliferation, migration and invasion. miR-1303 expression, which was increased in tumor tissues, was sponged by LINC01272 and negatively correlated with LINC01272 expression. miR-1303 expression reversed the inhibitory effects of LINC01272 on NSCLC cell function. In summary, the findings from this study suggested that LINC01272 expression, which was decreased in NSCLC tumor tissues and NSCLC cells, may be used as an independent prognostic biomarker for patients with NSCLC and that its overexpression may suppress NSCLC cell proliferation, migration and invasion by inhibiting miR-1303.

Introduction

According to the International Agency for Research on Cancer, lung cancer was considered as the most common type of cancer and the leading cause of cancer-associated mortality in 2018, accounting for 18.4% of cancer-related deaths worldwide (1). Based on the histological characteristics of tumor cells, lung cancer is mainly divided into two categories, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and >80% of lung cancers belong to the NSCLC category (2). Most cancer patients are diagnosed with advanced cancer at the time of medical treatment, and the five-year survival rate is <18% (3). Studying the pathogenesis of NSCLC and exploring novel therapeutic targets that could be effective for NSCLC treatment is therefore crucial.

Long non-coding RNAs (IncRNAs) are defined as transcripts of >200 nucleotides in length (4). IncRNAs have attracted increasing attention in the recent years due to their important roles in the pathological mechanisms of malignant tumors (5). These functional IncRNAs have clinical significance and biological functions in various types of cancer, such as the role of MVIH in pancreatic ductal adenocarcinomas (6), PCTST in pancreatic cancer (7) and HOTAIR in gastric cancer (8). The expression of LINC01272 has been found to be abnormal in numerous diseases, such as gastric cancer (9), inflammatory bowel diseases (10) and unstable atherosclerotic plaque (11). In addition, LINC01272 was reported to have an important role in promoting gastric cancer progression (9). However, the role of LINC01272 remains unclear in NSCLC. The results from our preliminary bioinformatics analysis using data from The Cancer Genome Atlas (TCGA) database demonstrated that LINC01272 expression is significantly downregulated in NSCLC tumor, and that patients with lung cancer and with low LINC01272 expression have a significantly worse overall survival than patients with high LINC01272 expression. Exploring the clinical significance and function of LINC01272 expression in patients with NSCLC is therefore of great importance to further understand the role of LINC01272 and improve the treatment of NSCLC.

Correspondence to: Dr Jielu Zhou, Anesthesiology Department, Weifang People’s Hospital, 151 Guangwen Street, Weifang, Shandong 261041, P.R. China
E-mail: zhoujielu7105@163.com

Key words: LINC01272, microRNA-1303, prognosis, non-small cell lung cancer, proliferation, migration, invasion
MicroRNAs (miRNAs) are a class of non-coding RNA molecules of ~22 nucleotide in length that promote the degradation of target mRNAs or inhibit mRNA translation by recognizing and binding to the 3'-untranslated regions of target mRNAs (12). Previous studies have demonstrated that microRNAs (miRNAs) play important roles in cancer progression by promoting or inhibiting tumorigenesis (13,14). It has been reported that miR-1303 plays a crucial role in various types of cancer (15,16). For example, it was shown that increased miR-1303 expression in prostate cancer tissues and cell lines could promote the proliferation, migration and invasion of prostate cancer cells (15). Zhang et al (16) reported that miR-1303 expression is decreased in gastric cancer tissues and cell lines, promoting gastric cancer cell proliferation, migration and invasion. Furthermore, a previous study demonstrated that increased expression of miR-1303 in NSCLC tissues and cells could promote NSCLC cell proliferation, migration and invasion and might therefore serve as a potential prognostic biomarker for NSCLC (17). In addition, our preliminary bioinformatics analysis predicted the binding site of LINC01272 to miR-1303. We therefore hypothesized that LINC01272 may have a role in NSCLC by targeting miR-1303.

The present study aimed to analyze the expression level of LINC01272 in patients with NSCLC, evaluate the prognostic value of LINC01272 and analyze the role of the LINC01272/miR-1303 axis in NSCLC.

Materials and methods

Patients and sample collection. The experimental procedures were approved by the Ethics Committee of Weifang People's Hospital (approval no. 011827) and patients provided signed informed consents prior to sampling. Tumor tissue samples and adjacent non-tumor tissue samples (>5 cm from the tumor margin) were collected from 108 patients with NSCLC who underwent curative resection between July 2012 and June 2015 at Weifang People's Hospital. All tissue samples were histopathologically verified and stored in liquid nitrogen. Patients who had received any anti-tumor treatment prior to the surgery were excluded from the study. All patients received a 5-year follow-up with monthly telephone or face-to-face appointment for patient survival. The clinicopathological characteristics of patients are presented in Table I.

Cell culture. The four NSCLC cell lines SK-MES-1 (cat. no. TCHu110), A549 (cat. no. TCHu150), NCI-H460 (cat. no. TCHu205) and NCI-H522 (cat. no. MZ-1314) and the normal lung cell line NHBE-T (cat. no. MZ-2677) were purchased from The Cell Bank of Type Culture Collection of The Chinese Academy of Sciences. All cells were cultured in Dulbecco's modified Eagle medium (DMEM; Invitrogen; Thermo Fisher Scientific, Inc.) supplemented with 10% FBS in Dulbecco's modified Eagle medium (DMEM; Invitrogen; Thermo Fisher Scientific, Inc.) and placed at 37˚C. The cytotoxicity of LINC01272 was generated by subcloning the obtained LINC01272 clones directly into pcDNA3.1 plasmid through digestion and ligation. Then, 30 nM pcDNA3.1 and 30 nM pcDNA3.1-LINC01272 were transfected into A549 and H460 cells, and 50 nM miR-1303 mimic (5'-UUUAGAGAC GGGGCUUUGCUCU-3') and 50 nM mimic NC (5'-UUC UCCGAACUGUCAGCU-3') were transfected into A549 cells using Lipofectamine 3000 (Invitrogen; Thermo Fisher Scientific, Inc.) according to the manufacturers' protocol. Cells were used for subsequent experiments following 48 h transfection at 37˚C.

Bioinformatics analysis. GEPIA 2.0 (http://gepia2. cancer-pku.cn/#index) (18) was used to analyze data from TCGA database (https://cancergenome.nih.gov/) and compare the expression levels of LINC01272 in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) with that of healthy controls. Kaplan-Meier plotter (http://www.kmplot.com/analysis/) (19) was used to analyze the data of the Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo/), the European Genome-Phenome Archive (EGA; https://ega-archive.org/datasets) and TCGA database and evaluate the association between LINC01272 expression and the survival prognosis in patients with lung cancer. The IncBase v.2 of DIANA (http://carolina.imis.athena-innovation.gr/diana_tools/web/index.php?r=Incbasev2/index) was used to predict the binding sites of LINC01272 to potential target miRNAs.

RNA extraction and reverse transcription quantitative (RT-q) PCR. TRIzol reagent (Invitrogen; Thermo Fisher Scientific, Inc.) was used to extract total RNA from tissue samples and NSCLC cells. The purity and concentration of the extracted RNA were evaluated by NanoDrop 2000 (Thermo Fisher Scientific, Inc.). Then, cDNA was synthesized using the Revert Aid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Inc.) according to the manufacturers' instructions. The levels of LINC01272 and miR-1303 were measured using RT-qPCR, which was carried out using a SYBR Green PCR kit (Bio-Rad Laboratories, Inc.) and the Applied Biosystems 7900 Real-Time PCR system (Applied Biosystems; Thermo Fisher Scientific, Inc.). LINC01272 and miR-1303 expression were normalized to GAPDH and U6, respectively. The PCR reaction conditions were as follows: 95˚C for 10 min, followed by 39 cycles at 95˚C for 10 sec and 60˚C for 30 sec. The sequences of the primers were as follows: LINC01272, forward 5'-TGTTCATGTCGTACACCCA-3', reverse 5'-TGT GAGAGGGGATTTTCTGG-3'; GAPDH, forward 5'-TGT TCCTCAATGGTTGAAC-3', reverse 5'-ATGGGATGGC GGGTGTCAT-3'; miR-1303, forward 5'-GCCGAAGTTAGA GACGGGTT-3', reverse 5'-CTCAACTGGTGTCGGGA-3'; and U6, forward 5'-CTCGGTTGCGACGAGCR-3' and reverse 5'-AACGTTACAGAATTCGG-3'. The relative expression levels were calculated using the 2^ΔΔCt method (20).

Cell proliferation assay. The proliferation of A549 and H460 cells was evaluated using a Cell Counting Kit-8 (CCK-8) assay.
ONCOLOGY LETTERS 22: 652, 2021

Table I. Association between LINC01272 expression and the clinicopathological characteristics of patients with non-small cell lung cancer.

| Variable                  | Low (n=58) | High (n=50) | P-values |
|---------------------------|------------|-------------|----------|
| Age, years                | 0.704      |             |          |
| ≤60                       | 39         | 20          | 19       |
| >60                       | 69         | 38          | 31       |
| Sex                       | 0.971      |             |          |
| Female                    | 43         | 23          | 20       |
| Male                       | 65         | 35          | 30       |
| Smoking                   | 0.982      |             |          |
| No                        | 39         | 21          | 18       |
| Yes                       | 69         | 37          | 32       |
| Tumor size, cm            | 0.021      |             |          |
| ≤3                        | 54         | 23          | 31       |
| >3                        | 54         | 35          | 19       |
| Lymph node metastasis     | 0.037      |             |          |
| No                        | 51         | 22          | 29       |
| Yes                       | 57         | 36          | 21       |
| Differentiation           | 0.101      |             |          |
| Well and moderate         | 60         | 28          | 32       |
| Poor                      | 48         | 30          | 18       |
| TNM stage                 | 0.009      |             |          |
| I-II                      | 46         | 18          | 28       |
| III                       | 62         | 40          | 22       |

TNM, Tumor-Node-Metastasis.

Figure 1. LINC01272 expression and its relationship with overall survival based on bioinformatics analysis. (A) LINC01272 expression in non-small cell lung cancer tumor tissues and normal tissues was determined using TCGA database. *P<0.05 vs. normal. (B) Relationship between LINC01272 expression and overall survival in patients with lung cancer was determined using Gene Expression Omnibus, the European Genome-Phenome Archive and TCGA database (log-rank P=0.041). LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; T, tumor; N, normal; TCGA, The Cancer Genome Atlas.

(Beyotime Institute of Biotechnology). NSCLC cells were seeded into 96 well plates at the density of 3×10^5 cells/well and cultured in a humidified incubator at 37°C. At 0, 24, 48 and 72 h, CCK-8 (10 µl) reagent was added to each well and cells were further incubated for 2 h at 37°C. The optical density was evaluated at 450 nm using a microplate analyzer (Bio-Rad Laboratories, Inc.).
Cell migration and invasion assays. The migratory and invasive abilities of A549 and H460 cells were determined using Transwell chambers (Corning, Inc.). Chambers precoated with Matrigel (Corning, Inc.) were used for invasion assay, whereas chambers not precoated with Matrigel were used for migration assay. A549 and H460 cells (3x10^4 cells/well) were seeded into the upper chamber with serum-free DMEM medium, and the lower chamber was filled with DMEM medium supplemented with 10% FBS. After incubation at 37˚C for 48 h, cells in the lower chambers were stained with 0.1% crystal violet for 20 min at room temperature. The number of migrated or invaded cells in five randomly selected fields was counted under an inverted light microscope (Olympus Corporation; magnification, x200).

Dual-luciferase reporter assay. The binding sequence of LINC01272 to miR-1303 was obtained using DIANA (http://starbase.sysu.edu.cn/) platform. The wild type (WT) LINC01272 sequence containing the miR-1303-binding sequence and the mutant (MUT) LINC01272 sequence were cloned into the pmirGLO dual luciferase miRNA target expression vector (Promega Corporation). Then, LINC01272 (WT) and LINC01272 (MUT) were co-transfected with miR-1303 mimic or mimic NC, respectively, into A549 cells using Lipofectamine 3000 reagent (Invitrogen; Thermo Fisher Scientific, Inc.). After 48 h transfection, the relative luciferase activity was measured using the dual-luciferase reporter assay system (Promega Corporation). Firefly luciferase activity was normalized to Renilla luciferase activity. All procedures followed the manufacturers' instructions.

Results

LINC01272 expression and its relationship with patient overall survival based on bioinformatics analysis. According to bioinformatics analysis, the results from TCGA database analysis revealed that the expression of LINC01272 was downregulated in NSCLC tumors compared with normal tissues (Fig. 1A), and the results from GEO, EGA and TCGA database analyses showed that low LINC01272 expression was associated with worse overall survival in patients with lung cancer (Fig. 1B).

LINC01272 is downregulated in NSCLC tissues and cell lines. The expression level of LINC01272 in NSCLC tissues and cell lines was evaluated using RT-qPCR. As presented in Fig. 2A, LINC01272 expression was significantly decreased in NSCLC tissues compared with adjacent non-tumor tissues (P<0.001). In addition, LINC01272 expression was significantly decreased in NSCLC cells compared with NHBE cells (all P<0.01; Fig. 2B). Furthermore, because A549 and H460 cells expressed the lowest levels of LINC01272, these cells lines were used for subsequent experiments.

Relationship between LINC01272 expression and the clinicopathological characteristics of patients with NSCLC. Analysis...
the relationship between LINC01272 expression and the clinicopathological characteristics of patients with NSCLC suggested that LINC01272 might be involved in the development of NSCLC. The median expression value of miR-1303 (0.50) was used as the cutoff value to divide the patients into low and high miR-1303 expression groups. As presented in Table I, LINC01272 expression was associated with tumor size (P=0.021), lymph node metastasis (P=0.037) and Tumor-Node-Metastasis (TNM) stage (P=0.009). However, there were no association between LINC01272 expression and the other variables, including age, sex, smoking and differentiation (all P>0.05).

Association between LINC01272 expression and the overall survival of patients with NSCLC. The prognostic value of LINC01272 expression in patients with NSCLC was evaluated by Kaplan-Meier survival curves and Cox regression analyses. Patients with NSCLC with high LINC01272 expression had

Table II. Cox regression analysis results for patients with non-small cell lung cancer.

| Variables               | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | HR  | 95% CI          | P-value | HR  | 95% CI          | P-value |
| Age                     | 1.365 | 0.815-2.241     | 0.267   | -   | -               | -       |
| Sex                     | 1.226 | 0.761-1.960     | 0.403   | -   | -               | -       |
| Smoking                 | 1.872 | 0.758-2.955     | 0.181   | -   | -               | -       |
| Tumor size              | 1.376 | 0.862-2.103     | 0.159   | -   | -               | -       |
| Lymph node metastasis   | 1.599 | 1.022-2.389     | 0.038   | 1.423 | 0.927-2.138     | 0.091  |
| Differentiation         | 1.285 | 1.018-2.654     | 0.042   | 1.253 | 0.906-1.966     | 0.128  |
| TNM stage               | 1.941 | 1.385-3.159     | 0.012   | 1.596 | 1.107-2.506     | 0.027  |
| LINC01272               | 2.085 | 1.523-3.503     | 0.005   | 1.988 | 1.290-3.078     | 0.009  |

P<0.05 and *P<0.01. TNM, Tumor-Node-Metastasis; CI, confidence interval; HR, hazard ratio.

Figure 4. Inhibitory effects of LINC01272 overexpression on non-small cell lung cancer cell proliferation, migration and invasion. (A) Relative expression of LINC01272 was significantly increased after transfection with pcDNA3.1-LINC01272 in A549 cells and H460 cells. Proliferation of (B) A549 cells and (C) H460 cells was significantly inhibited by LINC01272 overexpression. In A549 cells and H460 cells, LINC01272 overexpression decreased the (D) migratory and (E) invasive abilities. ***P<0.01 and ****P<0.001 vs. control. OD, optical density.
higher overall survival than those with low LINC01272 expression (log-rank P=0.020; Fig. 3). In addition, the results from Cox regression analysis (Table II) indicated that LINC01272 expression, lymph node metastasis, differentiation and TNM stage were associated with the overall survival of patients with NSCLC, and that LINC01272 expression and TNM stage could be used as two independent prognostic factors [LINC01272, hazard ratio (HR)=1.988, 95% confidence interval (CI)=1.290-3.078; P=0.009; TNM stage: HR=1.596, 95% CI=1.107-2.506; P=0.027].

Inhibitory effects of LINC01272 overexpression on NSCLC cell proliferation, migration and invasion. Following transfection with pcDNA3.1 or pcDNA3.1-LINC01272, the expression level of LINC01272 was significantly increased by pcDNA3.1-LINC01272 in A549 cells and H460 cells (Fig. 4A; P<0.001). Furthermore, the proliferation of A549 cells (Fig. 4B; P<0.01) and H460 cells (Fig. 4C; P<0.01) was significantly inhibited following LINC01272 overexpression. In A549 cells and H460 cells, the migratory (Fig. 4D; P<0.01) and invasive (Fig. 4E; P<0.001) abilities were significantly inhibited by LINC01272 overexpression.

Negative relationship between LINC01272 and miR-1303 in NSCLC. The complementary binding sequences between LINC01272 and miR-1303 were seen in Fig. 5A. As presented in Fig. 5B, miR-1303 was significantly upregulated following transfection with miR-1303 mimic but downregulated after LINC01272 overexpression in A549 cells (P<0.001). Furthermore, a dual-luciferase reporter assay was conducted to confirm the interaction between LINC01272 and miR-1303 in NSCLC cells. The results demonstrated that overexpression of miR-1303 inhibited the relative luciferase activity of LINC01272 (WT) group (P<0.01), whereas no changes were observed in the luciferase activity of LINC01272 (MUT) group (P>0.05; Fig. 5C). As presented in Fig. 5D, miR-1303 expression was significantly increased in tumor tissues compared with adjacent non-tumor tissues (P<0.001). In addition, a negative correlation was observed between miR-1303 expression and LINC01272 expression in NSCLC tissues (Fig. 5E; r=-0.598, P<0.001).
miR-1303 overexpression reverses the function of LINC01272 in NSCLC cells. As presented in Fig. 6A, miR-1303 expression was significantly decreased after transfection with pcDNA3.1-LINC01272, whereas it was significantly increased by miR-1303 mimic in A549 cells (all P<0.001). In addition, miR-1303 mimic reversed the suppressive effect of LINC01272 overexpression on NSCLC (B) cell proliferation, (C) migration and (D) invasion. **P<0.01 and ***P<0.001 vs. controls. *P<0.05, **P<0.01 and ***P<0.001 vs. pcDNA3.1-LINC01272. OD, optical density; miR, microRNA; NSCLC, non-small cell lung cancer.

Furthermore, miR-1303 overexpression reversed the inhibitory effects of LINC01272 overexpression on the function of A549 cells (Fig. 6B-D; P<0.05).

Discussion

It has been demonstrated that lncRNAs aberrant expression is closely related to the progression of numerous types of cancer (6,7,21), suggesting that lncRNAs might be involved in the progression of cancer. In addition, numerous lncRNAs,
including PTAR (22), NBR2 (23) and DLEU2 (24), have been reported to be abnormally expressed in NSCLC. According to bioinformatics analysis of data from TCGA database, LINC01272 expression level was found to be significantly downregulated in NSCLC. The findings from the present study confirmed the downregulation of LINC01272 in NSCLC tumor tissues and cells. Furthermore, LINC01272 expression was significantly correlated with tumor size, lymph node metastasis and TNM stage in patients with NSCLC. In addition, LINC01272 has been found to serve as an important regulator in other diseases. For example, LINC01272 is upregulated in gastric cancer and its expression is associated with tumor stage and lymph node metastasis (9). Wang et al (10) reported an increased expression of LINC01272 in tissues and plasma samples of patients with inflammatory bowel disease compared with healthy volunteers. The present study hypothesized therefore that LINC01272 may be involved in the progression of NSCLC.

Increasing evidence has demonstrated that certain IncRNAs can function as potential biomarkers for NSCLC prognosis (25), such as SLC16A1-AS1 (26), XIST (27) and LINC-PINT (28). Our preliminary bioinformatics analysis using GEO, EGA and TCGA database data reported that patients with lung cancer and with low LINC01272 expression had a significantly worse overall survival than patients with high LINC01272 expression. Furthermore, in the present study, decreased expression of LINC01272 was found in NSCLC tissues. The present study analyzed the prognostic significance of LINC01272 in NSCLC. It has been reported that SLC16A1-AS1 (HR=3.351, 95% CI=2.027-5.541, P<0.001) (26), XIST (HR=2.645, 95% CI=1.672-7.393, P=0.029) (27) and LINC-PINT (HR=2.628, 95% CI=1.589-4.348, P<0.001) (28) can be used as prognostic biomarkers in patients with NSCLC. The prognostic value of LINC01272 was evaluated according to the 5-year survival information of patients with NSCLC in the present study. The overall survival of patients with low LINC01272 expression was worse compared with that of patients with high LINC01272 expression. In addition, LINC01272 was independently related to overall survival, suggesting that LINC01272 may be considered as a potential prognostic biomarker for NSCLC. Since the HR of LINC01272 is lower than the HRs of SLC16A1-AS1, XIST and LINC-PINT, the overall mortality risk of patients with NSCLC and with low LINC01272 expression was relatively low.

Increasing evidence indicates that IncRNAs can regulate NSCLC tumor biological functions (29-31). For example, LINC00673 can regulate the proliferation, migration and invasion of NSCLC cells by sponging miR-150-5p (29). Furthermore, PCAT7 can promote the proliferation, migration and invasion, and inhibit the apoptosis of NSCLC cells by inhibiting miR-134-5p (30). A study by An et al (31) reported that LINC00668 downregulation inhibits NSCLC cell proliferation, migration and invasion, and stimulates NSCLC cell apoptosis. The results from the present study demonstrated that LINC01272 overexpression could inhibit NSCLC cell proliferation, migration and invasion. In addition, LINC01272 knockdown has been found to inhibit the biological function of gastric cancer cells (9). LINC01272 may therefore serve an anticancer role in NSCLC.

Previous studies have demonstrated that miRNA- IncRNA interactions play important roles in the occurrence and development of cancer (32-34). According to bioinformatics prediction, miR-1303 was identified as a target gene of LINC01272 in the present study, and this interaction was confirmed through a luciferase reporter assay. miR-1303 is a key molecule involved in various cancers, such as prostate cancer (15) and gastric cancer (16). The present study reported a higher miR-1303 expression in tumor tissues compared with non-tumor tissues, which was in accordance with a study from Chen et al (35). Furthermore, miR-1303 expression was negatively correlated with LINC01272 expression in tumor tissues of patients with NSCLC. In addition, overexpression of LINC01272 inhibited miR-1303 expression in NSCLC cells, and miR-1303 overexpression reversed the effects of LINC01272 on NSCLC cell proliferation, migration and invasion, suggesting that LINC01272 may inhibit NSCLC cell function by targeting miR-1303. Certain IncRNAs have been found to exert their biological functions by regulating miR-1303 in several diseases. For example, BCRT1 was reported to contribute to breast cancer cell proliferation, migration and invasion by targeting miR-1303/PTBP3 axis (36). In addition, LINC0143 upregulation can promote cell proliferation and migration by sponging miR-1301 in esophageal squamous cell carcinoma (37).

A study by Liu et al (15) reported that miR-1303 can enhance the cell proliferation, migration and invasion via targeting DKK3 in prostate cancer. Cheng et al (38) demonstrated that miR-1303-p can regulate the cell proliferation and apoptosis of clear cell renal cell carcinoma by targeting STARD9. Therefore, we speculated that miR-1303 may regulate NSCLC cell function by targeting DKK3 or STARD. However, whether DKK3 and STARD9 are targets of miR-1303 in NSCLC remains unclear. Thus, the lack of miR-1303 target is a major limitation of the present study, and further investigation is therefore required to validate the results. In addition, the sample size was small, which is also a limitation of this study, and future study including a large research cohort is needed.

In conclusion, the present study demonstrated that LINC01272 expression was decreased in NSCLC tumor tissues and NSCLC cells compared with normal tissues and cells, suggesting that LINC01272 may serve as an independent prognostic biomarker for patients with NSCLC. In addition, LINC01272 overexpression could inhibit NSCLC cell proliferation, migration and invasion by inhibiting miR-1303 in NSCLC. The novel LINC01272 /miR-1303 axis may therefore be considered as a new biomarker and therapeutic target for NSCLC treatment.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Authors' contributions

SZ and IZ designed the study, performed clinical studies and analyzed data. JZ performed the cell experiments. SZ and JZ wrote and revised the manuscript. SZ and IZ confirmed the authenticity of all raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

A signed written informed consent was obtained from each patient and the experimental procedures were all in accordance with the guideline of the Ethics Committee of Weifang People's Hospital (approval no. 011827).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394–424, 2018.
2. Goebel C, Louden CL, McKenna R Jr, Onugha O, Wachtel A and Long T: Diagnosis of non-small cell lung cancer for early stage asymptomatic patients. Cancer Genomics Proteomics 16: 229-244, 2019.
3. Yang Q, Tang Y, Tang C, Cong H, Wang X, Shen X and Ju S: Diminished LINC00173 expression induced miR-182-5p accumulation promotes cell proliferation, migration and apoptosis inhibition via AGER/NF-kB pathway in non-small-cell lung cancer. Am J Transl Res 11: 4248-4262, 2019.
4. Wang J, Su Z, Lu S, Fu W, Liu Z, Ji X and Tai S: LncRNA HOTAIR-AS2 and its molecular mechanisms in human cancer. Chin Clin Acta 485: 229-233, 2018.
5. Chi Y, Wang D, Wang J, Yu W and Yang J: Long non-coding RNA in the pathogenesis of cancer. Cells 8: 1015, 2019.
6. Hu S, Zheng Q, Xiong J, Wu H, Wang W and Zhou W: Long non-coding RNA MVH promotes cell proliferation, migration, invasion through regulating multiple cancer-related pathways, and correlates with worse prognosis in pancreatic ductal adenocarcinomas. Am J Transl Res 12: 2118-2135, 2020.
7. Wang Y, Ding X, Hu H, He Y, Lu Z, Wu P, Tian L, Xia T, Yin J, Yuan H, et al: Long non-coding RNA Inc-PCTST predicts prognosis through inhibiting progression of pancreatic cancer by downregulation of TACC-3. Int J Cancer 143: 3143-3154, 2018.
8. Liu SX, Sun M, Nie FQ, Ge YB, Zhang EB, Yin DD, Kong R, Xia R, Lu KH, Li JH, et al: Lnc RNA HOTAIR functions as a competing endogenous RNA to regulate HER2 expression by sponging miR-331-3p in gastric cancer. Mol Cancer 13: 92, 2014.
9. Leng X, Liu G, Wang S, Song J, Zhang W, Xiang L, Ma Y and Song F: LINC01272 promotes migration and invasion of gastric cancer cells via EMT. Onco Targets Ther 13: 3401-3410, 2020.
10. Wang S, Hou Y, Chen W, Wang J, Xie W, Zhang X and Zeng L: KIF9-AS1, LINC01272 and DIO3OS lncRNAs as novel biomarkers for inflammatory bowel disease. Mol Med Rep 17: 2195-2202, 2018.
11. Huang J, Scanlon JP, Mahmoud AD, Rodor J, Ballantyne M, Fontaine MAC, Temmerman L, Kaczynski J, Connor KL, Bhushan R, et al: Novel plaque enriched long noncoding RNA in atherosclerotic macrophage regulation (PELATON). Arterioscler Thromb Vasc Biol 40: 697-713, 2020.
33. Luan X and Wang Y: LncRNA XLOC_006390 facilitates cervical cancer tumorigenesis and metastasis as a ceRNA against miR-331-3p and miR-338-3p. J Gynecol Oncol 29: e95, 2018.

34. Zhao W, Geng D, Li S, Chen Z and Sun M: LncRNA HOTAI influences cell growth, migration, invasion, and apoptosis via the miR-20a-5p/HMG1 axis in breast cancer. Cancer Med 7: 842-855, 2018.

35. Chen J, Jiang T, Yu B, Li T, Zhao P, Yuan L and Qi J: Upregulation of microRNA-1303 is a potential prognostic marker of non-small cell lung cancer. Cancer Biomark 28: 439-446, 2020.

36. Liang Y, Song X, Li Y, Chen B, Zhao W, Wang L, Zhang H, Liu Y, Han D, Zhang N, et al: LncRNA BCRT1 promotes breast cancer progression by targeting miR-1303/PTBP3 axis. Mol Cancer 19: 85, 2020.

37. Zheng L, Liu YT, Wu CP, Jiang JT, Zhang L, Wang ZL and Wang QY: Long non-coding RNA linc01433 promotes tumorigenesis and progression in esophageal squamous cell carcinoma by sponging miR-1301. Eur Rev Med Pharmacol Sci 24: 4785-4792, 2020.

38. Cheng T, Shuang W, Ye D, Zhang W, Yang Z, Fang W, Xu H, Gu M, Xu W and Guan C: SNHG16 promotes cell proliferation and inhibits cell apoptosis via regulation of the miR-1303-p/STARD9 axis in clear cell renal cell carcinoma. Cell Signal 84: 110013, 2021.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.