### Original Article LncRNA LOXL1-AS1 promotes invasion and proliferation of non-small-cell lung cancer through targeting miR-324-3p

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**Abstract:** LncRNAs are played crucial roles in athogenesis of NSCLC. LOXL1-AS1 involved in development of several tumors. So far, there is no study about expression and function pattern of the LOXL1-AS1 in NSCLC. In this reference, we firstly proved that LOXL1-AS1 was overexpressed in NSCLC cell lines (H23, A549, H1299 and SPC-A1) compared to 16HBE cell. The expression of LOXL1-AS1 was overexpressed in NSCLC specimens than adjacent control specimens. We found that 29 of 40 cases showed higher LOXL1-AS1 expression in NSCLC samples as compared to adjacent control specimens. Ectopic expression of LOXL1-AS1 promoted H1299 cell and H23 cell proliferation. LOXL1-AS1 overexpression promoted ki-67 and cyclin D1 expression in the NSCLC cell. Overexpression of LOXL1-AS1 promoted cell invasion and induced N-cadherin and Vimentin expression and suppressed E-cadherin expression in the NSCLC cell. LOXL1-AS1 acts as one sponge for miR-324-3p in NSCLC cell. Moreover, the expression of miR-324-3p was lower in NSCLC specimens than adjacent control specimens. Further correlation assay indicated a negative association between miR-324-3p and LOXL1-AS1 expression. miR-324-3p restoration attenuates the function of LOXL1-AS1 overexpression on NSCLC cell. These results indicated that LOXL1-AS1 enhanced NSCLC cell proliferation and invasion via sponging miR-324-3p in NSCLC cell.

Keywords: Non-small cell lung cancer, IncRNA, LOXL1-AS1, miR-324-3p

#### Introduction

Lung cancer is the leading and the most common reason of tumor-related death in males and the second most common cause of tumorrelated deaths in females. Among this desease, eighty percent is classified as the non-small cell lung cancer (NSCLC), including lung squamous cell carcinoma, lung adenocarcinoma and large cell lung cancer [1-5]. It is difficult for us to diagnosis of NSCLC at the early stage; the most cases are diagnosed at the advanced or middle stage [6-10]. The 5-year survival of advanced stage NSCLC patients is still dissatisfied [2, 11, 12]. It is important to search biological diagnosis markers and novel therapies for NSCLC.

Long noncoding RNAs (IncRNAs) are a family of transcripts, >200 nt in length, are non-protein

or limited coding transcripts [13-16]. A growing number of discoveries shows that deregulated expression of IncRNAs are found in a lot of tumors such as osteosarcoma, glioma, colorectal cancer, ovarian cancer, hepatocellular carcinoma, bladder cancer and lung cancer [17-24]. Increasing studies indicated that IncRNAs acts vital roles in cell physiology including cell growth, differentiation, cell metabolism, invasion, migration and cell immune [25-28]. Recent evidences found that a new IncRNA LOXL1-AS1 acted crucial roles in progression of different tumors [29-31]. For instance, Wang et al [29]. indicated that LOXL1-AS1 knockdown attenuates glioblastoma mesenchymal characteristics via regulating NF-KB pathway. Gao et al [30]. showed that LOXL1-AS1 expression was upregulated in the medulloblastoma samples and LOXL1-AS1 knockdown suppressed D283 and D341 cell colony formation and prolifera-



Figure 1. LOXL1-AS1 was overexpressed in NSCLC cell lines. A. The expression of LOXL1-AS1 in NSCLC cell lines (H23, A549, H1299 and SPC-A1) and 16HBE cell was detected by qRT-PCR analysis. B. The expression of LOXL1-AS1 in NSCLC cell lines (H23, A549, H1299 and SPC-A1) and 16HBE cell was measured by PCR assay.

tion partly through regulating PI3K-AKT signal pathway. Long et al [31]. indicated that LOXL1-AS1 induced prostate tumor cell cycle and growth via regulating CCND1 and miR-541-3p. So far, there is no study about expression and function pattern of the LOXL1-AS1 in NSCLC.

In our research, we measured LOXL1-AS1 expression level in the NSCLC cell and tissues. We also showed that ectopic expression of LOXL1-AS1 promoted cell proliferation, invasion and induced EMT progression in the NSCLC cell partly through regulating miR-324-3p.

#### Materials and methods

## Specimen collection and cell culture and transfection

Thirty-five pairs of lung adenocarcinoma specimen were collected from the YanTaiShan Hospital. Our study was approved by the clinical Ethics Committee of YanTaiShan Hospital. written informed consent was obtained from all patients. Human bronchial epithelial cell line (16HBE) and lung adenocarcinoma cell lines (H23, A549, H1299 and SPC-A1) were obtained from Cell Source of the Chinese Academy of Sciences of Shanghai. These cells were maintained in RPMI 1640 medium supplemented with penicillin-streptomycin and FBS (GIBCO, Invitrogen). pcDNA3.1 -IncRNA-LOXL1-AS1 vector and pcDNA3.1-control vector, miR-324-3p mimic and scramble were synthesized from GenePharma Company (Shanghai, China). Cell transfection was carried out by using Lipofectamine 2000 (Invitrogen, USA) following to the manufacturer's indications.

# Quantitative real-time PCR (qRT-PCR)

Total cellular or tissue RNA was extracted by using Trizol kit (Takara, China) according to indications. Real-time PCR (qRT-PCR) was carried out by using SYBR-Green PCR reagent on the ABI 7900HTSequence System (Applied Biosystems) to measure the expression of IncRNA, miRNA and mRNA. The expression level was counted by using the Ct method and U6 or GAPDH

was used as the control. For primers, LOXL1-AS1, 5'-TTC CCA TTT ACC TGC CCG AAG-3' and 5'-GTC AGC AAA CAC ATG GCA AC-3'; GAPDH, 5'-GGA AGG ACT CAT GAC CAC AGT CC-3' and 5'-TCG CTG TTG AAG TCA GAG GAG ACC-3'.

#### Proliferation assay and matrigel invasion assay

A total number of lung adenocarcinoma cells were cultured in the 96-well plate. Cell proliferation was calculated by using CCK-8 analysis following to the manufacturer's protocol. The absorbance at 450 nm was measured on the microplate reader. For cell invasion, cells were cultured in the upper chamber (pre-coated with Matrigel, BD) with no-serum medium. FBS was added into the lower chamber. After 48 hours, invasive cells were fixed and then stained with crystal violet.

#### Statistical analysis

The value was shown as mean  $\pm$  SD (standard deviation) and Statistical assay was carried out using the SPSS program (Version 17.0; SPSS Inc.). Two-tailed Student's t-test and one-way ANOVA were used for signicant differences between groups. *P* value <0.05 was considered to be statistical significant.

#### Results

## LOXL1-AS1 was overexpressed in NSCLC cell lines

To study whether LOXL1-AS1 was dysregulated in NSCLC, qRT-PCR assay was carried out to find the expression of LOXL1-AS1 in NSCLC cell lines. As indicated in **Figure 1A**, expression of



**Figure 2.** LOXL1-AS1 was overexpressed in NSCLC samples. A. The expression of LOXL1-AS1 was overexpressed in NSCLC specimens than adjacent control specimens. B. Twenty-nine of 40 cases showed higher LOXL1-AS1 expression in NSCLC samples as compared to adjacent control specimens.

LOXL1-AS1 was overexpressed in NSCLC cell lines (H23, A549, H1299 and SPC-A1) compared to 16HBE cell. In line with this, the LOXL1-AS1 expression was upregulated in NSCLC cell lines compared to 16HBE cell uisng RT-PCR (**Figure 1B**).

#### LOXL1-AS1 was overexpressed in NSCLC samples

The LOXL1-AS1 expression level was analyzed in 40 paired NSCLC specimens and adjacent control specimens. The expression of LOXL1-AS1 was overexpressed in NSCLC specimens than adjacent control specimens (**Figure 2A**). In additional, we found that 29 of 40 cases showed higher LOXL1-AS1 expression in NSCLC samples as compared to adjacent control specimens (**Figure 2B**). LOXL1-AS1 overexpression induced cell growth in NSCLC cell

LOXL1-AS1 expression was overexpressed in the H1299 cell (**Figure 3A**) and H23 cell (**Figure 3B**) after transfection with pcDNA-LOXL1-AS1 vector. Ectopic expression of LOXL1-AS1 promoted H1299 cell (**Figure 3C**) and H23 cell (**Figure 3D**) proliferation. Furthermore, elevated LOXL1-AS1 expression enhanced ki-67 expression both in H1299 cell (**Figure 3E**) and H23 cell (**Figure 3F**). In addition, we found that LOXL1-AS1 overexpression promoted cyclin D1 expression both in H1299 cell (**Figure 3G**) and H23 cell (**Figure 3H**).

### Ectopic expression of LOXL1-AS1 enhanced cell invasion and ECM in NSCLC cell

Cell invasion capacity was detected by transwell. It was shown that overexpression LOXL1-AS1 promoted H1299 cell invasion (Figure 4A and 4B). The expression of N-cadherin was upregulated in H1299 cell after treated with pcDNA-LOXL1-AS1 (Figure 4C). Ectopic expression of LOXL1-AS1 promoted Vimentin (Figure 4D) expression and suppressed E-cadherin (Figure 4E) expression in H1299 cell.

#### LOXL1-AS1 acts as one sponge for miR-324-3p in NSCLC cell

The LOXL1-AS1 has a putative binding site of miR-324-3p by using StarBase v2.0 (Figure 5A). miR-324-3p expression was overexpressed in the H1299 cell (Figure 5B) and H23 cell (Figure 5C) after transfection with miR-324-3p mimic. To study whether miR-324-3p can interact with the LOXL1-AS1, LOXL1-AS1 mutant luciferase construct (mut) and wild type (WT) were created. The luciferase activity were decreased in the treatment of miR-324-3p and inhibitory function was abolished when miR-324-3p binding sites were mutated both in H1299 cell and H23 cell (Figure 5D). Furthermore, we showed that overexpression of LOXL1-AS1 suppressed miR-324-3p expression both in H1299 cell (Figure 5E) and H23 cell (Figure 5F).

## miR-324-3p was downregulated in NSCLC samples

The miR-324-3p expression level was analyzed in 40 paired NSCLC specimens and adjacent control specimens. The expression of miR-324-

#### LOXL1-AS1 promotes invasion and proliferation of non-small-cell lung cancer



**Figure 3.** LOXL1-AS1 overexpression induced cell growth in NSCLC cell. A. The expression of LOXL1-AS1 in the H1299 cell after transfection with pcDNA-LOXL1-AS1 was detected by qRT-PCR assay. B. The expression of LOXL1-AS1 in the H23 cell after transfection with pcDNA-LOXL1-AS1 was detected by qRT-PCR assay. C. Ectopic expression of LOXL1-AS1 promoted H1299 cell growth. D. Overexpression of LOXL1-AS1 induced cell proliferation in H23 cell. E. The expression level of ki-67 was measured by qRT-PCR assay. F. Elevated LOXL1-AS1 expression enhanced ki-67 expression. G. The expression level of cyclin D1 was analyzed by qRT-PCR assay. H. Elevated LOXL1-AS1 expression enhanced xi-67 expression. \*P<0.01 and \*\*\*P<0.001.



**Figure 4.** Ectopic expression of LOXL1-AS1 enhanced cell invasion and ECM in NSCLC cell. A. Overexpression of LOXL1-AS1 promoted H1299 cell invasion. B. The relative invasive cells were shown. C. The expression of N-cadherin was upregulated in H1299 cell after treated with pcDNA-LOXL1-AS1. D. The expression of Vimentin was detected by qRT-PCR analysis. E. The expression of E-cadherin was detected by qRT-PCR analysis. \*\*\*P<0.001.



**Figure 5.** LOXL1-AS1 acts as one sponge for miR-324-3p in NSCLC cell. A. The LOXL1-AS1 has a putative binding site of miR-324-3p by using StarBase v2.0. B. miR-324-3p expression was overexpressed in the H1299 cell after transfection with miR-324-3p mimic. C. The expression of miR-324-3p in the H23 cell was analyzed by qRT-PCR analysis. D. The luciferase activity was decreased in the treatment of miR-324-3p and inhibitory function was abolished when miR-324-3p binding sites were mutated both in H1299 cell and H23 cell. E. Overexpression of LOXL1-AS1 suppressed miR-324-3p expression in H1299 cell. F. The expression of miR-324-3p was detected by qRT-PCR in the H23 cell.

3p was lower in NSCLC specimens than adjacent control specimens (Figure 6A). In additional, we found that 24 of 40 cases showed lower miR-324-3p expression in NSCLC samples as

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compared to adjacent control specimens (**Figure 6B**). Further correlation assay indicated a negative association between miR-324-3p and LOXL1-AS1 expression (**Figure 6C**).

miR-324-3p restoration attenuates the function of LOXL1-AS1 overexpression on NSCLC cell

We next tested whether biological effects of LOXL1-AS1 were attributed to its modulation of miR-324-3p. Ectopic expression of miR-324-3p decreased cell growth in the LOXL1-AS1-over-expressing H1299 cell (Figure 7A). miR-324-3p overexpression suppressed the cyclin D1 (Figure 7B) and ki-67 expression (Figure 7C) in the LOXL1-AS1-overexpressing H1299 cell. Elevated expression of miR-324-3p decreased cell invasion in LOXL1-AS1-overexpressing H1299 cell (Figure 7D and 7E).

#### Discussion

Accumulating references indicated that Inc-RNAs play critical roles in development of tumors [32-34]. In this research, we firstly proved that LOXL1-AS1 was overexpressed in NSCLC cell lines (H23, A549, H1299 and SPC-A1) compared to 16HBE cell. Then, the LOXL1-AS1 expression level was analyzed in 40 paired NSCLC specimens and adjacent control specimens. The expression of LOXL1-AS1 was overexpressed in NSCLC specimens than adjacent control specimens. In additional, we found that 29 of 40 cases showed higher LOXL1-AS1 expression in NSCLC samples as compared to adjacent control specimens. Ectopic expression of LOXL1-AS1 promoted H1299 cell and H23 cell proliferation. LOXL1-AS1 overexpression promoted ki-67 and cyclin D1 expression in the NSCLC cell. Overexpression of LOXL1-AS1 promoted cell invasion and induced N-cadherin and Vimentin expression and suppressed E-cadherin expression in the NSCLC cell. LOXL1-AS1 acts as one sponge for miR-324-3p in NSCLC cell. Moreover, the expression of miR-324-3p was lower in NSCLC specimens than adjacent control specimens. We



**Figure 7.** miR-324-3p restoration attenuates the function of LOXL1-AS1 overexpression on NSCLC cell. A. The cell growth was analyzed by using CCK-8 assay in the H1299 cell. B. The expression level of cyclin D1 was detected using qRT-PCR analysis. C. The expression level of ki-67 was detected using qRT-PCR analysis. D. Elevated expression of miR-324-3p decreased cell invasion in LOXL1-AS1-overexpressing H1299 cell. E. The relative invasive cells were shown. \*P<0.05, \*\*P<0.01 and \*\*\*P<0.001.

found that 24 of 40 cases showed lower miR-324-3p expression in NSCLC samples as compared to adjacent control specimens. Further correlation assay indicated a negative association between miR-324-3p and LOXL1-AS1 expression. miR-324-3p restoration attenuates the function of LOXL1-AS1 overexpression on NSCLC cell. These results indicated that LOXL1-AS1 enhanced NSCLC cell proliferation and invasion via sponging miR-324-3p in NSCLC cell.

Increasing evidences found that a new IncRNA LOXL1-AS1 acted crucial roles in progression of different tumors [29-31]. For instance, Wang and workmate showed that LOXL1-AS1 knockdown attenuates glioblastoma mesenchymal characteristics via regulating NF-κB pathway [29]. Gao et al [30]. showed that LOXL1-AS1 expression was upregulated in the medulloblastoma samples and LOXL1-AS1 knockdown suppressed D283 and D341 cell colony formation and proliferation partly through regulating PI3K-AKT signal pathway. Long et al [31]. indicated that LOXL1-AS1 induced prostate tumor

cell cycle and growth via regulating CCND1 and miR-541-3p. Chen and colleague found that LOXL1-AS1 overexpression increased osteosarcoma cell growth, invasion and migration [35]. So far, there is no study about expression and function pattern of the LOXL1-AS1 in NSCLC. We found that LOXL1-AS1 was overexpressed in NSCLC cell and tissues. Ectopic expression of LOXL1-AS1 promoted cell proliferation, invasion and induced EMT progression in the NSCLC cell.

Although IncRNA LOXL1-AS1 was shown to act as one oncogene in NSCLC, the mechanism about how LOXL1-AS1 involved in progression of NSCLC remains unclear. Growing studies suggested that IncRNAs regulated cell functions through interacting with miRNA [36-38]. For examples, Li et al [39]. found that IncRNA LINCO0978 induced cell invasion and growth in NSCLC via suppressing miR-6754-5p. Xia et al [40]. showed that IncRNA HOXD-AS1 increased NSCLC cell invasion and migration via modulating miR-133b expression. Tang and colleague showed that MALAT1 induced NSCLC cell inva-

sion and migration through regulating miR-206 [41]. Moreover, Zhang et al [42]. showed that LOXL1-AS1 regulated cholangiocarcinoma development through modulating miR-324-3p expression. In line with this, we showed that LOXL1-AS1 has a putative binding site of miR-324-3p by using StarBase v2.0. The luciferase activity was decreased in the treatment of miR-324-3p and inhibitory function was abolished when miR-324-3p binding sites were mutated both in H1299 cell and H23 cell. Furthermore, we showed that overexpression of LOXL1-AS1 suppressed miR-324-3p expression both in H1299 cell and H23 cell. The expression of miR-324-3p was lower in NSCLC specimens than adjacent control specimens. Further correlation assay indicated a negative association between miR-324-3p and LOXL1-AS1 expression. miR-324-3p restoration attenuates the function of LOXL1-AS1 overexpression on NSCLC cell.

Summarily, it has shown that LOXL1-AS1 was overexpressed in NSCLC cell and samples and ectopic expression of LOXL1-AS1 promoted cell proliferation, invasion and induced EMT progression in the NSCLC cell partly through regulating miR-324-3p. These results indicated that LOXL1-AS1 enhanced NSCLC cell proliferation and invasion via sponging miR-324-3p in NSCLC cell.

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#### Disclosure of conflict of interest

None.

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