Long noncoding RNA LINC-PINT inhibits non-small cell lung cancer progression through sponging miR-218-5p/PDCD4

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\textbf{ABSTRACT}

Long noncoding RNA, long intergenic non-protein-coding RNA p53-induced transcript (LINC-PINT) was showed to be involved in cancer development. However, the biological effect of LINC-PINT on non-small cell lung cancer (NSCLC) remains unknown. Here, we aimed to investigate the role and underlying mechanism of LINC-PINT in NSCLC. Quantitative real-time polymerase chain reaction (qRT-PCR) was used to measure the level of LINC-PINT in NSCLC tissues and cell lines. Cell counting kit-8 (CCK-8), flow cytometry, migration and transwell invasion assays were used to investigate cell proliferation, cell cycle, cell migration and invasion, respectively. The targets of LINC-PINT were verified by both luciferase reporter assay and RNA immunoprecipitation assay. Tumour xenografts were used to reveal the effect of LINC-PINT on tumourigenesis \textit{in vivo}. We observed that LINC-PINT expression increased in both NSCLC tissues and cell lines. Function assays exhibited that LINC-PINT reduced NSCLC cell proliferation, cell cycle, cell migration and invasion \textit{in vitro}. We also indicated that LINC-PINT mediated inhibitory effect on cell proliferation, cell cycle, cell migration and invasion by miR-208a-3p/programmed cell death 4 (PDCD4) in NSCLC cells. These findings indicated that LINC-PINT functions as a tumour-suppressor that exerts important regulatory roles in NSCLC progression by sponging miR-208a-3p/PDCD4.

\textbf{Introduction}

Lung cancer is the most common type of diagnosed cancer and also the leading cause of cancer deaths worldwide [1,2]. The main type of lung cancer is non-small cell lung cancer (NSCLC). Although the surgery, chemotherapy, radiotherapy and immunotherapy therapy have advanced, the 5-year survival rate of NSCLC patients is still only about 15\% [3–7]. Therefore, further underlying NSCLC progression and developing are necessary [8].

Long noncoding RNAs (lncRNAs) are a number of nonprotein-coding transcripts, which were longer than 200 nucleotides [9]. lncRNAs have key roles in various tumours and cell lines [10–12]. Many of lncRNAs have been regarded as diagnostic or prognostic markers for NSCLC. Downregulation of IncRNA RHPN1-AS1 induces gefitinib resistance through miR-299-3p/TNFSF12 in NSCLC [13]. LncRNA FEZF-AS1 [14] and IncRNA HOXA11-AS is associated with advanced clinical stages in NSCLC [15]. LncRNA Dicer5 mediates CSC-like properties through regulating miR-330-5p/CD44 in NSCLC [16]. LncRNA LINC-PINT has been shown to be involved in multiple types of diseases, such as gastric cancer [17], glioblastoma [18], acute lymphoblastic leukemia [19] and pancreatic cancer [20]. However, the biological role and mechanism of LINC-PINT in NSCLC still unclear.

Thus, we explored the LINC-PINT levels in NSCLC tissues and cell lines and detected its biological function in NSCLC by both \textit{in vitro} and \textit{in vivo} assay.

\textbf{Materials and methods}

\textbf{Patients and samples}

Thirty-six paired tumour tissues and matched adjacent non-cancerous tissues were harvested from patients with NSCLC who were undergoing surgery at the Department of Thoracic Surgery, First People’s Hospital of Yunnan Province. Prior to enrollment, all patients supplied the written informed consent. All of the samples were immediately frozen in liquid nitrogen for further experiments. This study was approved by the Institutional Ethics Committee of the First People’s Hospital of Yunnan Province (Application 2019–001-01).
Cell culture
The NSCLC cell lines A549, H226, SPCA1, H358 and normal human bronchial epithelial cell BEAS-2B were purchased from the Cell Bank of the Chinese Academy of Science (Shanghai, China) and seeded in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS; Gibco, Carlslbad, CA, USA) in a humidified incubator at 37 °C with 5% CO₂.

Plasmid construction and transfection
miR-208a-3p mimics, miR-208a-3p inhibitor, pcDNA-LINC-PINT and pcDNA-NC were obtained from Shanghai GenePharma Co., Ltd. (Shanghai, China). Transfection was used by Lipofectamine 3000 reagents (Invitrogen, Carlsbad, CA, USA) followed the protocol description.

Quantitative RT-PCR
Total RNA was extracted by using TRIzol RNA extraction kit (Invitrogen, Carlsbad, CA). RNA was reverse-transcribed by the Prime Script TM RT Master Mix (TaKaRa Bio Technology Dalian, China) and quantitative PCR (qPCR) was detected by qPCR kits (Invitrogen, Carlsbad, CA). U6 or β-actin was used as the endogenous control for normalization. Relative gene level was analyzed by using 2⁻ΔΔCt.

Cell proliferation assay
Cell Counting Kit-8 (Beyotime Institute of Biotechnology, Jiangsu, China) was used to detect cell proliferation. The infected cells (2000 cells/well) were seeded in 96-well plates. The absorbance of wells was measured for 0–72 h at 450 nm by a microplate reader (Bio Tek Instruments, Winooski, VT, USA).

Flow cytometric analysis
The infected cells were fixed in 70% ethanol at 4 °C overnight. Then, cells were added to RNase A (1 mg/ml) and propidium iodide (PI, 0.1 mg/ml, Sigma-Aldrich) at dark for 30 min. Cell cycle distribution was assessed by a FACScan flow cytometer (BD Biosciences, NJ, USA). The percentage of cells was investigated by FlowJo (USA).

Cell migration and invasion assay
Cell migration and invasion were detected by 24-well Transwell chambers with 8-μm-pore size membrane (Corning Incorporated, Corning, NY, USA). Cells (2 × 10⁵) with 500 μl RPMI 1640 were added to the upper well. In the lower chambers, 700 μl of RPMI 1640 with 10% FBS was incubated for 24 h. The cells on the lower surface of the membrane were stained with Calcein-AM. Stained cells were visualized by a fluorescence microscope (200× magnification). For cell invasion assay, the chambers were precoated with Matrigel for 30 min.

Dual-luciferase reporter assay
Firstly, LINC-PINT sequences with the wild-type (WT) or mutated-type (MT) of miR-208a-3p binding sites were synthesized by Shanghai GenePharma Co., Ltd. (Shanghai, China) and then were cloned to pGLO vector (Promega, Madison, WI, USA), which were named as: WT-LINC-PINT and MT-LINC-PINT, respectively. Cells were cotransfected with miR-208a-3p mimic or miR-NC and WT-LINC-PINT or MT-LINC-PINT plasmids for 48 h. The luciferase activities were detected using the dual-luciferase reporter assay kit (Promega, Madison, WI, USA).

RNA immunoprecipitation (RIP) assay
The EZ-Magna RIP RNA-binding protein immunoprecipitation kit (Millipore Corp., Billerica, MA, USA) was used. Cells were lysed by RIPA buffer and added to magnetic beads associated with mouse IgG or human anti-Ago2 antibody (Sigma-Aldrich). RNA expression was measured by qRT-PCR.

In vivo functional assays in mouse models
Balb/C nude mice were maintained at the Laboratory Animal Center of Medical School of Kunming University of Science and Technology. All animal experiments were approved by the Institutional Animal Care and Use Committee of Medical School of Kunming University of Science and Technology. The control cells and pcDNA-LINC-PINT A549 cells (2 × 10⁵) were subcutaneously injected into the nude mice flanks (n = 5). The volume (V) of the tumour was detected every 7 days. The mice were killed after 35 days, and the tumours were harvested, weighed and stored in liquid nitrogen.

Statistical analysis
Each experiment was repeated three times. Data are expressed as the mean ± SD. The statistically significant differences between untreated control and drug-treated cells were evaluated using Student’s 1-tailed t test. In all figures “*” indicates P < .05, whereas “***” indicates P < .001.

Results
LINC-PINT is downregulated in NSCLC tissues and cell lines
The levels of LINC-PINT were assessed in NSCLC tissue (n = 36) and adjacent non-tumour tissues using qRT-PCR. Our data showed that LINC-PINT expression reduced in NSCLC tissues compared to adjacent non-tumour tissues (P < .01; Figure 1(A)). The low expression of LINC-PINT was also found in NSCLC cell lines, including A549, H226, SPCA1 and H358 compared to normal human bronchial epithelial cell BEAS-2B (all P < .05, Figure 1(B)). A549 cell line presented the lowest LINC-PINT level and was elected for all the subsequent studies. These results indicated that LINC-PINT may function as a suppressor involved in NSCLC tumourigenesis.
LINC-PINT inhibits NSCLC cell proliferation and cell cycle in vitro

To explore the role of LINC-PINT in NSCLC oncogenesis, we upregulated LINC-PINT expression by transfected pcDNA-LINC-PINT plasmid into A549 cell. The results showed that LINC-PINT expression increases in the pcDNA-LINC-PINT group compared to the pcDNA-NC group ($P < .01$, Figure 2(A)). The CCK8 assay demonstrated that overexpression of LINC-PINT inhibits A549 cell proliferation (Figure 2(B)). Then, the cell cycle was detected by flow cytometry. The result revealed that overexpression of LINC-PINT increases the percentage of G1 phase cell and decreases the percentage of S phase cell in A549 cell ($P < .01$, Figure 2(C)).

LINC-PINT inhibits NSCLC cell migration and invasion

To investigate the effect of LINC-PINT on A549 cell migration and invasion, the migration and Matrigel invasion assays were used. The migration analysis demonstrated that overexpression of LINC-PINT decreased A549 cell migration (Figure 3(A)). The Matrigel invasion assay exhibited that overexpression of LINC-PINT reduced A549 cell invasion (Figure 3(B)).

miR-208a-3p is a direct target of LINC-PINT in NSCLC cells

The subcellular distribution of lncRNA modulate their function, the location of LINC-PINT in A549 cell cytoplasm and the nucleus was determined by qRT-PCR. As shown in

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**Figure 1.** The expression of LINC-PINT in NSCLC. (A) The level of LINC-PINT in NSCLC tissues ($n = 36$) compared with adjacent non-tumour tissues was assessed by qRT-PCR. (B) The relative level of LINC-PINT was assessed by qRT-PCR in NSCLC cell lines and BEAS-2B cell. $*P < .05$, $**P < .01$.

**Figure 2.** LINC-PINT inhibits NSCLC cell proliferation and cell cycle. (A) The level of LINC-PINT in NSCLC cell transfected with pcDNA-LINC-PINT or pcDNA-NC were analyzed by qRT-PCR. (B) The effect of LINC-PINT on A549 cell proliferation was evaluated by CCK8 assay. (C) The effect of LINC-PINT on A549 cell cycle was determined by flow cytometry. $*P < .05$, $**P < .01$. 
Figure 4(A), LINC-PINT was mostly expressed in the cell cytoplasm. LncRNA in the cytoplasm regulates gene expression by sponging miRNAs, serving as competing endogenous RNAs (ceRNAs). Thus, we hypothesized that LINC-PINT modulates NSCLC progression by sponging miRNAs. It has been showed that miR-208a-3p is a potential downstream target of LINC-PINT. To explore whether miR-208a-3p was a potential target of LINC-PINT in A549 cell, the luciferase reporter assay was used. The data showed that miR-208a-3p mimic reduced the wild-type LINC-PINT (WT-LINC-PINT) luciferase activity but not that of the mutant LINC-PINT (MT-LINC-PINT) luciferase activity in A549 cell (Figure 4(B)). Next, RNA immunoprecipitation (RIP) assay showed that LINC-PINT and miR-208a-3p were enriched in A549 cell (Figure 4(C)).

Moreover, overexpression of LINC-PINT reduced miR-208a-3p expression in A549 cell (Figure 4(D)). Furthermore, miR-208a-3p inhibitor increased LINC-PINT expression, while miR-208a-3p mimics reduced LINC-PINT expression in A549 cell (Figure 4(E)). Next, we revealed the expression of miR-208a-3p in NSCLC tissues and cell lines by qRT-PCR. The data showed that the expression of miR-208a-3p upregulated in both NSCLC tissues and cell lines (Figure 4(F,G)).

To determine whether the effects of LINC-PINT on NSCLC were mediated by miR-208a-3p, A549 cell were transfected with pcDNA-LINC-PINT plasmid and miR-208a-3p mimics; then cell proliferation, cycle progression, migration and invasion were examined by CCK8, flow cytometry, migration and Matrigel invasion assays, respectively. The data showed miR-208a-3p mimics partially suppress the effect of LINC-PINT on cell proliferation, cycle progression, migration and invasion (all \( P < .05 \); Figure 4(H–K)), implying that miR-208a-3p mediate the roles of LINC-PINT in NSCLC cell.

**PDCD4 mediates the suppressive effects of LINC-PINT on NSCLC cell**

The past study showed that miR-208a-3p inhibits cell growth and invasion by PDCD4 signal. To determine whether LINC-PINT modulates the expression of PDCD4 via miR-208a-3p. The results presented that the mRNA levels of PDCD4 decreased in the miR-409-3p mimic group relative to the control group, whereas, it increased in the miR-409-3p inhibitor group (Figure 5(A)). Moreover, LINC-PINT overexpression A549 cell was transfected with miR-208a-3p mimics. As shown in Figure 5(B), overexpression of LINC-PINT increased PDCD4 expression compared with pcDNA-NC group. However, LINC-PINT induced PDCD4 was reversed by miR-208a-3p mimics in A549 cell. These results suggested that miR-208a-3p/PDCD4 might be the target of LINC-PINT in NSCLC cell.

To detect whether the effects of LINC-PINT on NSCLC were mediated by PDCD4, A549 cell were transfected with pcDNA-LINC-PINT and PDCD4 inhibitor; then cell proliferation, cycle progression, migration and invasion were measured by CCK8, flow cytometry, migration and Matrigel invasion assays, respectively. The results presented that transfection with PDCD4 inhibitor partially rescued the effect of LINC-PINT on cell proliferation, cycle progression, migration and invasion (all \( P < .05 \); Figure 5(C–F)), suggesting that PDCD4 mediates the effects of LINC-PINT on NSCLC cells.
LINC-PINT inhibits the tumourigenesis of NSCLC in vivo

To assess the effect of LINC-PINT on NSCLC tumourigenesis in vivo, overexpression of LINC-PINT A549 cells were subcutaneously inoculated into Balb/C mice, and tumour growth was measured. Tumour growth was slower in the pcDNA-LINC-PINT group than in the pcDNA-NC group (Figure 6(A)). The mice were killed for 35 days, and the tumours were harvested and weighed. We found that the tumour size and weight reduce in the pcDNA-LINC-PINT group (Figure 6(B)).

Moreover, qRT-PCR data showed that LINC-PINT expression increases \((P < .05; \text{Figure 6(C)})\), whereas the expression of miR-208a-3p decreases in the pcDNA-LINC-PINT group (Figure 6(D)).

Discussion

Recently, dysregulation of lncRNAs have been shown to be involved in carcinogenesis and tumour development and can be used as a cancer therapeutic or prognostic biomarker [21–23]. Currently, we observed that LINC-PINT expression in
Figure 5. PDCD4 targets LINC-PINT in A549 cell. (A) The expression of PDCD4 was detected in A549 cell transfected with miR-NC, miR-338-3p mimic, miR-338-3p inhibitor and anti-miR-NC by qRT-PCR. (B) The level of PDCD4 was detected in A549 cell transfected with pcDNA-LINC-PINT and miR-338-3p mimic by qRT-PCR. (C–F) Cell proliferation, cell cycle, migration and invasion were detected in A549 cells transfected with pcDNA-LINC-PINT and PDCD4 inhibitor. \*P < .05, \**P < .01.

Figure 6. LINC-PINT inhibits the tumourigenesis of NSCLC in vivo. (A, B) The volume and weights of tumour was determined after transfected pcDNA-LINC-PINT or pcDNA-NC for 35 days. (C) The level of LINC-PINT in xenograft tumours were analyzed by qRT-PCR. (D) The level of miR-338-3p in xenograft tumours were analyzed by qRT-PCR. \*P < .05, \**P < .01.
NSCLC tissues and cell lines were downregulated. Overexpression of LINC-PINT inhibited NSCLC cell proliferation, cycle progression, migration and invasion in vitro. LINC-PINT inhibited NSCLC tumorigenesis in vivo. Taking these together, these results revealed that LINC-PINT might have a suppressive role in NSCLC through miR-208a-3p/PDCD4.

Many studies have reported that IncRNAs might play crucial roles in the initiation and development of NSCLC [24,25]. Long noncoding RNA HOXD-AS1 promoted migration and invasion of NSCLC by targeting miR-133b/MMP9 signalling [26]. LncRNA MALAT1 promoted NSCLC proliferation, migration and invasion through regulating miR-206/Akt/mTOR axis [27]. LINC00339 promoted NSCLC tumorigenesis by sponging miR-145 [28]. Thus, investigating the biological function and underlying molecular mechanism of IncRNAs would be beneficial for NSCLC treatment. LINC-PINT expression reduces in many types of cancers, including gastric cancer [17], glioblastoma [18] and acute lymphoblastic leukemia [19]. However, the effect of LINC-PINT on the occurrence and progression of NSCLC has not been elucidated.

In the present study, we examined LINC-PINT expression in NSCLC tissues and cell lines. We found that LINC-PINT expression was downregulated in both NSCLC samples and cell lines. For functional experiments, overexpression of LINC-PINT inhibited proliferation, cell cycle, migration and invasion of NSCLC cells. The data also revealed that overexpression of LINC-PINT suppresses tumour growth in vivo models. These data suggested that LINC-PINT functions as a suppressor in NSCLC carcinogenesis.

In the present study, both dual luciferase reporter and RIP assay were used to confirm miR-208a-3p as a target of LINC-PINT in NSCLC cell. We found that the expression of miR-208a-3p was higher in NSCLC samples compared to the normal tissues. Moreover, we also showed that miR-208a-3p mimic reduced LINC-PINT expression, whereas miR-208a-3p inhibitor induced LINC-PINT expression in NSCLC cell. Notably, miR-208a-3p mimics rescued the role of LINC-PINT in cell proliferation, cycle progression, migration, and invasion of NSCLC. These results implied that LINC-PINT inhibits NSCLC progression by sponging miR-208a-3p.

Then, we found that LINC-PINT induces PDCD4 expression, whereas overexpression of LINC-PINT induction of PDCD4 was reversed by miR-208a-3p mimics in A549 cell. Importantly, PDCD4 inhibitor rescued the effect of LINC-PINT on NSCLC cell proliferation, cycle progression, migration and invasion. These results implied that LINC-PINT suppresses NSCLC progression through PDCD4.

**Conclusion**

In summary, the levels of LINC-PINT downregulated in human NSCLC tissues and cell lines. Moreover, we also revealed that overexpression of LINC-PINT in NSCLC cell suppresses cell proliferation, cell cycle, migration and invasion in vitro. Furthermore, LINC-PINT was involved in the progression of NSCLC by miR-208a-3p/PDCD4 signal. These findings indicated that LINC-PINT could serve as a new target for NSCLC.

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**Disclosure statement**

No potential conflict of interest was reported by the authors.

**Availability of data and materials**

The datasets supporting the conclusions of this article are included within the article.

**Ethical approval**

This study was approved by the ethics committees of First People's Hospital of Yunnan Province (Application 2019–001-01).

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