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Original Article

MNX1-AS1/PABPC1 Activates Notch Signaling Pathway to Promote Progression of Lung Cancer

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Abstract:

Background MNX1-AS1 is a pan-cancer lncRNA overexpressed in lung cancer. However, the detailed molecular mechanism through which MNX1-AS1 regulates non-small cell lung cancer (NSCLC) remains unclear.

Aims: To explore the role and mechanism of lncRNA MNX1-AS1 and its related downstream signaling pathways in the occurrence and development of NSCLC.

Methods: RT-qPCR was used to analyze the expression of MNX1-AS1 in NSCLC tissues and cell lines, and the roles of MNX1-AS1 and Poly (A)-binding protein cytoplasmic 1 (PABPC1) in the proliferation and invasion of NSCLC cells were assessed using CCK-8 and Transwell assays. The regulatory relationship between MNX1-AS1 and PABPC1 was confirmed by RNA pulldown and RIP assays. Western blotting was used to detect proteins related to the Notch1 signaling pathway. A xenograft tumor model was constructed to verify these results *in vivo*.

Results: MNX1-AS1 was found to be significantly overexpressed in NSCLC through bioinformatic screening. Elevated levels of MNX1-AS1 enhance the proliferation and invasion of NSCLC cells. MNX1-AS1 interacts with PABPC1, which positively correlates with the proliferation and invasion of NSCLC cells. MNX1-AS1/PABPC1 activates the downstream Notch1 signaling pathway to promote NSCLC development. *In vivo*, MNX1-AS1 promoted tumor growth in an NSCLC model, whereas sh-PABPC1 or Notch signaling pathway inhibitor (DAPT) significantly inhibited the tumorigenic ability of MNX1-AS1.

Conclusions: MNX1-AS1/PABPC1 complex mediated the activation of the Notch1 signaling pathway to promote the occurrence and development of NSCLC.

Keywords: MNX1-AS1; PABPC1 ; Notch signaling pathway; NSCLC

1. Introduction

According to the 2022 global cancer statistics, lung cancer was the most frequently diagnosed cancer, with 2.5 million new cases, and was also the leading cause of cancer death,with an

estimated 1.8 million deaths[1]. Lung cancer is the most common and deadliest tumor worldwide,with two main types: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) [2, 3]. Despite some success with targeted therapies and immunotherapy, the 5-year survival rate for NSCLC patients with NSCLC remains significantly low[4, 5]. Therefore, it is essential to improve clinical treatment to conduct in-depth research on the occurrence and development mechanisms of NSCLC.

With the continuous development of biotechnology, several lncRNAs with critical roles in tumor progression have been identified in lung cancer[6]. For example, SLCO4A1-AS1 reduces lung cancer cell migration and invasion by antagonizing TOX4/NTSR1 signaling[7]. High expression of CASC11 promotes the development of lung cancer by upregulating CDK1 expression via binding to miR-302[8]. NNT-AS1 is upregulated in lung cancer and participates in the progression of lung cancer via NNT-AS1 the miR-3666/E2F2 regulatory axis [9]. MNX1-AS1 is a pan-cancer lncRNA expressed in various cancers, including breast cancer, hepatocellular carcinoma, and lung cancer[10]. Elevated MNX1-AS1 expression plays multiple roles in tumorigenesis. For example, MNX1-AS1 upregulates the phosphorylation of Stat3 by enhancing the interaction between p-JAK and Stats to promote the aggressiveness of triple-negative breast cancer[11]. A previous study showed that MNX1-AS1 facilitates COMMD8 expression by sponging miR-218-5p and promotes hepatocellular carcinoma progression[12]. The c-Myc/MNX1-AS1/IGF2BP1 positive feedback loop accelerates cell cycle progression and promotes the continuous proliferation of lung cancer cells, which may serve as a potential biomarker and therapeutic target in NSCLC[13]. Moreover, MNX1-AS1 recruits POU2F2 to the nucleus and activates MYO1G expression to promote the stem cell-like properties of lung cancer cells[14]. However, the detailed molecular mechanism through which MNX1-AS1 regulates NSCLC remains unclear. Therefore, online databases and in vitro and in vivo experiments were combined to study the role of MNX1-AS1 and its downstream and related pathways in NSCLC.

Poly (A)-binding protein cytoplasmic 1 (PABPC1) is present in the cytoplasm of eukaryotic cells and plays an important role in various cellular activities[15, 16]. PABPC1 is aberrantly expressed in numerous tumors and contributes to carcinogenesis[17, 18]. The study demonstrated that PABPC1 promotes cell proliferation, metastasis, and epithelial-to-mesenchymal transition, partly by activating the PI3K/AKT signaling pathway[19]. However, the role of PABPC1 in NSCLC remains largely unexplored in NSCLC.

The Notch signaling pathway has been demonstrated to regulate and play an important role in cancer progression of cancer[20]. The Notch signaling pathway is necessary for maintaining homeostasis, and its aberrant activity has been implicated in the onset and progression of NSCLC[21]. In addition, a study has been demonstrated that PABPC1 acts as a crucial molecule in the activation of the Notch signaling pathway[22]. In this study, we investigated the role and mechanism of MNX1-AS1 in the occurrence and development of NSCLC. The regulatory relationship between MNX1-AS1/PABPC1 and the Notch signaling pathway was explored. The results of this study provide unique insights and a theoretical basis for the treatment of NSCLC.

Materials and Methods

Database Analysis

The expression of MNX1-AS1 in NSCLC tissues was analyzed using Gene Expression Profiling Interactive Analysis (GEIPIA) and Starbase databases.

Clinical Specimens and Cell Culture

Forty paired human NSCLC tissues and adjacent lung tissues were obtained from patients with NSCLC who underwent surgical resection and were confirmed by postoperative pathological sections at the 988th Hospital of Joint Logistics Support Forces, PLA from June 2019 to June 2022. No radiotherapy, chemotherapy, or other tumor-specific treatments were administered before surgery. The study was approved by the Medical Ethics Committee of the 988th Hospital of the PLA Joint Logistic Support (988YY20230002LLSP). All subjects or their relatives signed written informed consent forms on a voluntary basis after being fully informed.

Various NSCLC cell lines (A549, H1299, HCC827 and H1650) were obtained from the Shanghai Cell Bank of the Chinese Academy of Sciences. The cells were cultured in RPMI-1640 medium (Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS; Gibco, USA) and 1% penicillin/streptomycin (Solarbio, China) at 37℃ and 5% CO_2 saturated humidity.

Specific overexpression plasmids, shRNAs, and their negative controls were constructed by Tsingke (Beijing, China). Cells in the logarithmic growth phase were used for transfection. All transfection assays were performed using Lipofectamine^{TM} 2000, according to the manufacturer's instructions. For pathway exploration, a γ-secretase inhibitor that blocks the Notch pathway, DAPT(2μmol/L) was used to treat cells in the different groups[23].

RT-qPCR Assay

Total RNA from tissues and cells was isolated using TRIzol reagent and reverse-transcribed according to the instructions of the cDNA reverse transcription kit. RT-qPCR was performed according to the instructions of a SYBR Premix Ex Taq II Kit on a 7900HT Fast Real-Time PCR System (Applied Biosystems, USA), with cDNA as the template. Relative expression was calculated using the $2^{-\Delta\Delta Ct}$ method with GAPDH as an internal reference.

CCK-8 Assay

NSCLC cells in each group were incubated in 96-well plates at 2×10^3 cells/well with three replicate wells. After culturing for 24, 48, and 72 h, the CCK-8 solution (10 μl) was added to each well and incubated for 4 h. Optical density (OD) at 450 nm was measured using a microplate reader (Thermo Fisher, USA).

Transwell Assay

Briefly, cells in each group were resuspended in FBS-free RPMI-1640 medium at a density of 1×10^5 cells/ml. 100μl The cell suspension was seeded in the upper chamber, which was pre-covered with Materigel. And 500μl of RPMI-1640 complete medium with 20% FBS was added to the lower chamber. After culturing for 24 h, the cells attached to the lower chamber were fixed with methyl alcohol after removing the cells in the inner layer with a cotton swab. The cells were stained with 0.1% crystal violet (Solarbio Co. Ltd., Beijing, China). Stained cells were counted and photographed under a microscope in five random visual fields for each group.

Western blot Assay

Cells or tissues from each group were lysed using RIPA lysis buffer containing 1% phenylmethylsulfonyl fluoride (Beyotime, Jiangsu, China), and the total protein was obtained from the supernatant after centrifugation. Proteins were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred to polyvinylidene difluoride membranes (Millipore, USA). After blocking, the membranes were incubated with primary antibodies: PABPC1, HEY1, HES1, NOTCH1, N-cadherin, Vimentin overnight at 4℃, followed by a 2h incubation with secondary antibodies. Proteins were visualized using an ECL kit. GAPDH was used as an internal control.

RIP Assay

The interaction between PABPC1 and MNX1-AS1 was analyzed using the Megna RIP RNA-Binding Protein Immunoprecipitation Kit (Millipore). A549 and H1299 cells were collected at 90% confluence and cross-linked with 254 nm ultraviolet light, followed by lysis in RIP lysis buffer. The lysates were co-precipitated with magnetic beads pre-incubated with anti-PABPC1 or IgG antibodies (Abcam, USA). The co-precipitated RNAs were quantitatively assessed using RT-qPCR.

RNA Pull-down Assay

The magnetic beads were incubated with biotin-labeled MNX1-AS1 sense or antisense probes for 3h to prepare probe-coated magnetic beads. Then, A549 and H1299 cells were collected and lysed using ultrasound, followed by an overnight incubation with the probe-coated magnetic beads at 4℃. The magnetic beads were washed and the target proteins were purified and eluted. RNA-protein interactions were assessed by western blotting.

Animal Experiments

Animal experiments were conducted in accordance with the guidelines for the care of laboratory animals and the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Forty BALB/c nude mice were purchased from the Henan Experimental Animal Center (SCXK (Yu)2021-0009), to establish the xenograft tumor model, with 8 mice in each group. Tumor cells were implanted into the right armpit of mice. The diameters of the A549 cell-derived tumors were measured every 7 days, and the volume was calculated using the formula $0.5\times length\times width^2$. The mice were euthanized by cervical dislocation on day 28^{th}. And the xenograft tumors were excised and weighed. The expression of key molecules in the Notch1 signaling pathway in xenograft tumors was detected using western blotting.

Statistical Analysis

IBM SPSS20.0 and GraphPad Prism8.0 software was used for statistical analysis. If the measurement data were normally distributed, they were described as mean±standard deviation, using *t*-test or ANOVA. $P<0.05$.

Results

MNX1-AS1 was up-regulated in NSCLC tissues

The expression of MNX1-A1 was analyzed using two online databases and was detected in tissues and cells. Analysis of data from The Cancer Genome Atlas (TCGA) and Starbase databases showed that MNX1-AS1 expression was higher in NSCLC tissues than in normal tissues (Figure 1A and B). MNX1-AS1 was expressed at a high level in NSCLC tissues and cells (Figure 1C and D), which was similar to the data from the TCGA and Starbase databases. Among these NSCLC cell lines, A549 and H1299, which had the highest MNX1-AS1 levels, were used for further experiments.

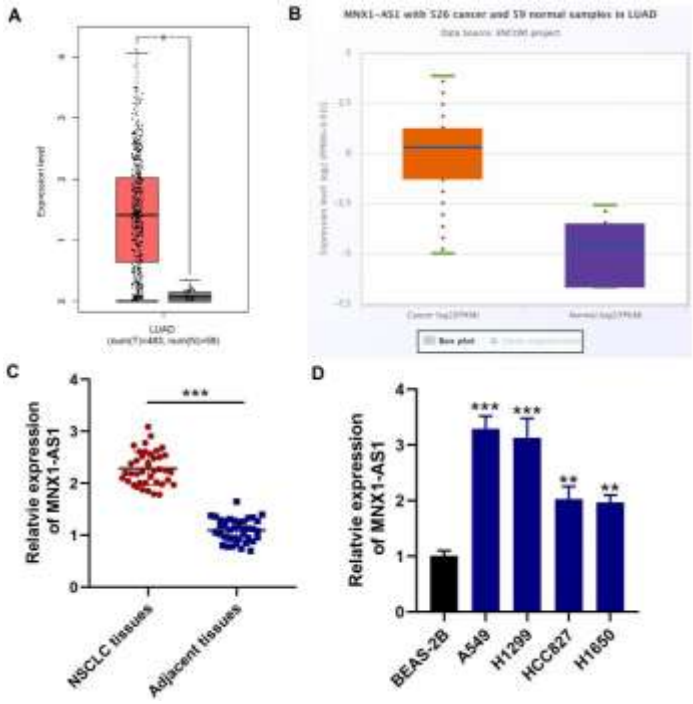

Figure 1 The expression of MNX1-AS1 in databases, tissues and cells.

A: MNX1-AS1 was upregulated in the LUAD tissue in TCGA database; B: MNX1-AS1 expression was higher in the LUAD tissue than in the normal tissues based on the Starbase database; C: MNX1-AS1 is expressed at a high level in NSCLC tissues; D: MNX1-AS1 is expressed at a high level in NSCLC cells. LUAD, lung adenocarcinoma. *** P<0.001, ** P<0.01, * P<0. 05.

MNX1-AS1 act as an oncogene and accelerates the progression of NSCLC

To explore the role of MNX1-AS1 in NSCLC progression, MNX1-AS1 overexpression plasmid (pcDNA3.1-MNX1-AS1) and shRNA plasmid (sh-MNX1-AS1) were transfected into NSCLC cells. The expression of MNX-AS1 was regulated (Figure 2A). Silencing MNX1-AS1 inhibited the proliferation of A549 and H1299 after 24h. However, MNX1-AS1 overexpression significantly promoted cell proliferation (Figure 2B). Transwell assays demonstrated that silencing MNX1-AS1 inhibited the invasion of cells, whereas overexpression yielded opposite results (Figure 2C). Therefore, MXN1-AS1 acts as an oncogene and accelerates NSCLC progression.

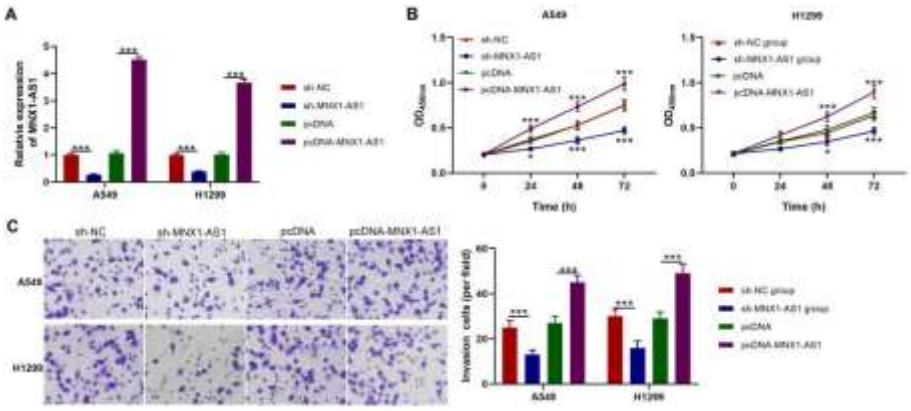

Figure 2 The effect of MNX1-AS1 on the behavior of NSCLC cells.

A: MNX1-AS1 expression was regulated by sh-MNX1-AS1 or pcDNA-MNX1-AS1; B: MNX1-AS1 promoted cell proliferation in both A549 and H1299 cells as detected by CCK-8 assay; C: MNX1-AS1 promoted cell invasion in both A549 and H1299 cells as detected by Transwell assay. *** P<0.001, * P<0.05.

MNX1-AS1 upregulated PABPC1 expression

To uncover the specific mechanism by which MNX1-AS1 exerts its oncogenic function, we previously found that PABPC1 was a potential downstream target of MNX1-AS1 from the high-throughput sequence data of the RNA-RNA interactome. Starbase also revealed an interaction between MNX1-AS1 and PABPC1 (Figure 3A). Therefore, we determined that PABCP1 is a putative MNX1-AS1 binding protein. RNA pull-down experiments showed that the specific precipitation of PABPC1 was pulled down by MNX-AS1 (Figure 3B). Moreover, RIP experiments demonstrated that MNX1-AS1 was more enriched in complexes precipitated with the ant-PABPC1 antibody, compared to the control IgG (Figure 3C).

After sh-MNX1-AS1 or pcDNA-MNX1-AS1 transfection, the expression of PABPC1 was downregulated when MNX1-AS1 was silenced, whereas it was upregulated when MNX1-AS1 was overexpressed (Figure 3D). Moreover, alterations in PABPC1 protein levels in NSCLC cells following the modulation of MNX1-AS1 was validated by western blotting (Figure 3E). These results suggested that MNX1-AS1 mediates its pathological effects in NSCLC cells by directly interacting with PABPC1.

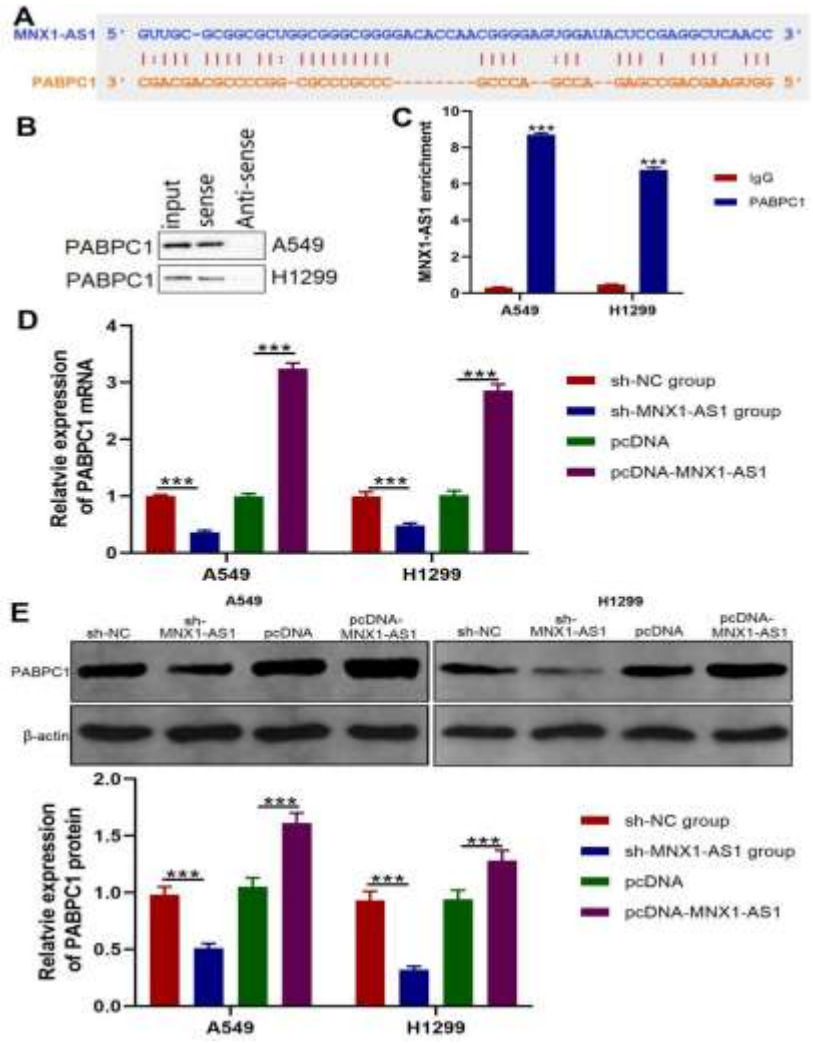

Figure 3 MNX1-AS1 targeted and positively regulated PABPC1.

A: The interaction between MNX1-AS1 and PABPC1was predicted the Starbase database; B: RNA pull-down assay detected the interaction between MNX1-AS1 and PABPC1 in A549 and H1299 cells; C: RIP assay detected the interaction between PABPC1 and MNX1-AS1 in A549 and H1299 cells; D: PABPC1 mRNA expression detected by RT-qPCR; E: PAPBC1 protein expression detected by western blotting. *** P<0.001.

Sh-PABPC1 significantly suppressed the effect of MNX1-AS1 on the behaviour of NSCLC cells

To study the potential biological role of PABPC1 in NSCLC cells, with an overexpression plasmid and shRNA plasmid targeting PABPC1 were transfected into A549 and H1299 cells, respectively. Silencing PABPC1 inhibited the proliferation of A549 and H1299 cells, whereas overexpression of PABPC1 yielded the opposite results (Figure 4A). Transwell assays demonstrated that silencing PABPC1 inhibited the invasion abilities of A549 and H1299 cells, while overexpression of PABPC1 significantly promoted the invasion of NSCLC cells (Figure 4B). These results indicated that PABPC1 has a potential oncogenic role in NSCLC.

The roles of MNX1-AS1 and sh-PABPC1 were investigated in NSCLC cells. Based on transfection, the cells were divided into three groups: control, MNX1-AS1, and MNX1-AS1+sh-PABPC1. After 48h, the proliferation in MNX1-AS1 group was higher than control group, while sh-PABPC1 reduced the proliferative effects of MNX1-AS1 overexpression in NSCLC cells (Figure 4C). Invasion was accelerated by MNX1-A1 and inhibited by sh-PABPC1(Figure 4D). These results demonstrated that sh-PABPC1 significantly suppressed the effect of MNX1-AS1 on the behavior of NSCLC cells.

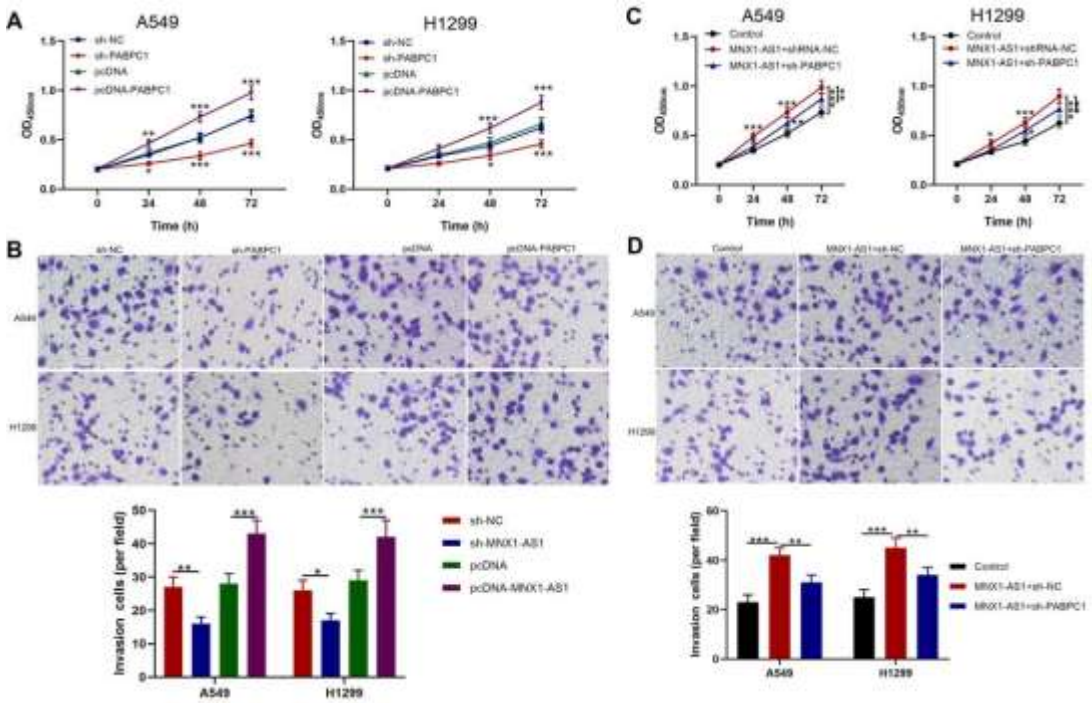

Figure 4 Effect of PABPC1 on the behavior of NSCLC cells and knockdown of PABPC1 inhibited the effect of MNX1-S1 on the behavior of NSCLC cells.

A: PABPC1 promoted cell proliferation in both A549 and H1299 cells as detected by CCK-8 assay; B: PABPC1 promoted cell invasion both in

A549 and H1299 cells as detected by Transwell assay; C: sh-PABPC1 reduced the proliferative effects of MNX1-AS1 in A549 and H1299 cells; D: sh-PABPC1 suppressed the invasive effects of MNX1-AS1 in A549 and H1299 cells. *** $P<0.001$, ** $P<0.01$, * $P<0.05$.

MNX1-AS1/PABPC1 regulated the Notch1 signaling pathway mediating tumorgenesis

To detect the effect of the MNX1-AS1/PABPC1/Notch signaling pathway, a western blot assay was performed to detect the expression of key molecules in the Notch1 signaling pathway, including, NOTCH1, HES1 and HEY1. The results showed that overexpression of MNX1-AS1 or PABPC1 significantly increased the expression of key molecules in the Notch1 signaling pathway, whereas a Notch-specific inhibitor (DAPT) significantly suppressed the promoting effect of MNX1-AS1 or PABPC1 overexpression on their expression (Figure 5A). These results indicated that MNX1-AS1/PABPC1 is involved in the Notch1 signaling pathway.

The role of the MNX1-AS1–PABPC1/Notch axis *in vivo* was also investigated. Changes in the tumor volume and weight were evaluated. As shown in Figure 5B and 5C, MNX1-AS1 and PABPC1 improved tumor growth, whereas DAPT significantly inhibited the tumorigenic ability of MNX1-AS1 and PABPC1. RT-qPCR assay was performed to detect the expression of proliferation (CyclinA1 and PCNA) and invasion (E-cadherin)-related genes in xenograft tumor tissues, and the results and tendencies were consistent with the experiments *in vitro* (Figure 5D). These results demonstrated that MNX1-AS1/PABPC1 regulates the Notch1 signaling pathway, mediating tumorigenesis *in vivo*.

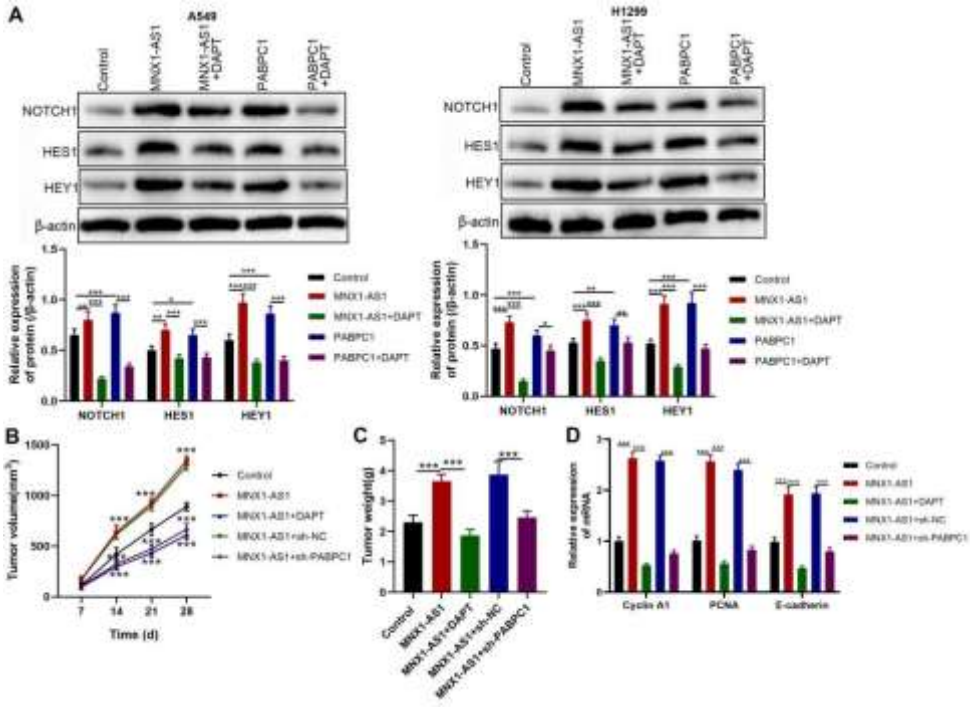

Figure 5 MNX1-AS1/PABPC1 functions in NSCLC by regulating the Notch1 signaling pathway

A: Protein expression of NOTCH, HES1, and HEY1 in the Notch1 signaling pathway; B: Changes in tumor volume; C: Changes in tumor weight; D: mRNA expression of proliferation- and invasion-related genes (CyclinA1, PCNA, and E-cadherin) in xenograft tumor tissues. *** $P<0.001$, ** $P<0.01$, * $P<0.05$.

Discussion

With advancements in high-throughput sequencing and bioinformatics technologies, a growing number of lncRNAs are continuously being screened and validated for their expression and functions, and they are believed to participate in various biological processes in a highly regulated manner. Furthermore, a large number of dysregulated lncRNA expressions have been implicated in the occurrence and progression of cancer. In this study, MNX1-AS1 expression in NSCLC was significantly elevated, as revealed by bioinformatic methods. The high expression of MNX1-AS1 was also validated in tumor tissues and cells through RT-qPCR analysis, indicating its diagnostic value as a biomarker for NSCLC, which is consistent with the results of previous research[24].

Moreover, MNX1-AS1 promotes cell proliferation, migration, and invasion in many malignancies. For example, MNX1-AS1 promotes cell proliferation, migration, and invasion and inhibits apoptosis in ovarian cancer cells through the miR-744-5p/SOX12 axis[25]. MNX1-AS1 promotes laryngeal squamous cell carcinoma cell proliferation, migration, and invasion by competitively binding to miR-370 to regulate FOXM1[26]. In a previous study, MNX1-AS1 was shown to act as a ceRNA, regulating the miR-34a/SIRT1 axis to mediate cell proliferation, migration, and invasion, and to suppress cell apoptosis in lung adenocarcinoma progression[27]. In this study, sh-MNX1-AS1 suppressed cell proliferation and invasion, whereas cell proliferation and invasion were accelerated by MNX1-AS1 overexpression, indicating that MNX1-AS1 promoted cell proliferation and invasion in NSCLC. Moreover, MNX1-AS1 accelerated tumorigenic ability *in vivo*, which is consistent with a previous report.

In addition, lncRNAs have been shown to act as ceRNAs and play roles in sponging miRNAs[28]. To further analyze the specific molecular mechanisms of MNX1-AS1 in NSCLC, we demonstrated that MNX1-AS1 exerted its effects not via the ceRNA mechanism but rather by interacting with the PABPC1 protein to regulate the activation of the Notch signaling pathway. The results of this study also confirmed that MNX1-AS1 targets and positively regulates PABPC1 expression. Comparison of the Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) datasets with normal tissues showed notable upregulation of PABPC1 in 31 tumor samples[16]. Previous studies have indicated that PABPC1 is highly expressed in lung cancer, promotes cell proliferation and migration, and plays an important role in lung cancer pathogenesis[16, 29]. The results of this study also confirmed that silencing PABPC1 inhibited the proliferation and invasion of A549 and H1299 cells, whereas overexpression of PABPC1 yielded the opposite results, indicating that PABPC1 has a potential oncogenic role in NSCLC. Furthermore, sh-PABPC1 significantly suppressed the effect of MNX1-AS1 on NSCLC cell behavior.

The evolutionarily conserved Notch signaling pathway plays critical roles in cell communication and function, and is also critically involved in carcinogenesis and cancer progression[30]. Moreover, aberrant activity is markedly linked to NSCLC formation and progression[21]. PABPC1 has been shown to mediate NUMB expression inhibition, ultimately promoting activation of the Notch1 signaling pathway[22]. The present study indicated that the overexpression of MNX1-AS1 or PABPC1 significantly increased the expression of key molecules in the Notch1 signaling pathway, suggesting that the Notch1 signaling pathway is activated by MNX1-AS1 or PABPC1. The results also showed that the Notch signaling pathway inhibitor DAPT suppressed the promoting effect of MNX1-AS1 or PABPC1 overexpression, and inhibited the occurrence and progression of NSCLC *in vivo*. These results demonstrated that MNX1-AS1/PABPC1 regulates

the Notch1 signaling pathway, mediating the occurrence and progression of NSCLC.

However, this study has several limitations. First, although the mechanism through which MNX1-AS1/PABPC2 regulates the Notch1 signaling pathway has been elucidated, numerous specific mechanisms remain to be investigated. PABPC1 can bind to a large number of RNAs and proteins, and more experiments are needed to authenticate the interaction between PABPC1 and the Notch1 signaling pathway. Additionally, the prognosis of patients with NSCLC based on MNX1-AS1 expression requires further validation using multicenter data. Despite these limitations, we believe that the molecular mechanisms and pathways identified in our study will help to understand the carcinogenesis of NSCLC and explore novel treatment strategies.

Conclusions

In summary, through in vitro and in vivo experiments, the data elucidated the interaction between MNX1-AS1 and PABPC1, and the MNX1-AS1/PABPC1 complex mediated the activation of the Notch1 signaling pathway to promote the occurrence and development of NSCLC. Targeting MNX1-AS1 is expected to be a promising strategy for suppressing NSCLC tumorigenesis and may provide broader applications for future NSCLC therapies.

Statements and Declarations

Ethics approval

All procedures in this study were conducted in accordance with the ethical guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the 988th Hospital of Joint Logistics Support Forces, PLA (Approval No.988YY20230002LLSP).

All animal experiments in this study were approved by the Laboratory Animal Ethics Committee of the 988th Hospital of Joint Logistics Support Forces, PLA (Approval No.: 988YY20230002LLSP).

Data Availability

All data generated or analyzed during this study were included in the published article.

Acknowledgement

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Conflict of Interests

The authors have no relevant financial or non-financial interests to disclose.

Authors Contributions

Conceptualization: GF Liu, L Zhou, ZWSun; Methodology: GF Liu, L Zhou, ZWSun, QY Li; Formal analysis and investigation: JH Tang, Y Zhang, YB Zhao, GP Sun, XY Ding, XZ Zhang, SJ Cui; Writing - original draft: GF Liu, L Zhou, JH Tang, Y Zhang, YB Zhao; Writing - review and editing: GF Liu, L Zhou, ZWSun; Funding acquisition: GF Liu; Resources: GP Sun, JH Tang; Supervision: ZW Sun

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