Am J Transl Res 2020;12(3):857-866
www.ajtr.org /ISSN:1943-8141/AJTR0100995

Original Article

LncARSR promotes non-small-cell lung cancer progression via regulating PTEN/Akt

Jie Ying[1*], Jian Yang[1*], Yingzi Liu[2]

[1]Clinical Research Center, Xuyi People's Hospital, Xuyi 211700, Jiangsu, China; [2]Department of Occupational Disease, Daqing People's Hospital, Daqing 163316, Heilongjiang, China. [*]Co-first authors.

Received July 17, 2019; Accepted August 28, 2019; Epub March 15, 2020; Published March 30, 2020

Abstract: LncRNAs have been suggested to be key modulators in many biological and pathological processes. LncARSR, a recently identified lncRNA, plays crucial roles in the progression of several cancers. However, the role of lncARSR in NSCLC is uninvestigated. In the present study, it was demonstrated that lncARSR expression was higher in NSCLC tissues than in noncancerous tissues. The expression of lncARSR was higher in four NSCLC cell lines than in a normal lung bronchial epithelial line. Further investigation demonstrated that increased lncARSR expression promoted NSCLC cell migration and growth and induced epithelial-mesenchymal transition in A549 cells. Moreover, ectopic expression of lncARSR suppressed PTEN expression and induced Akt phosphorylation in A549 cells. The expression level of PTEN was higher in NSCLC samples than in adjacent non-tumor specimens. PTEN expression was negatively correlated with lncARSR in NSCLC specimens. Furthermore, we demonstrated that overexpression of lncARSR induced NSCLC cell growth and migration via regulating the PTEN/Akt signaling pathway. These results suggest that lncARSR acts as an oncogene in NSCLC development and could serve as a new potential therapeutic target.

Keywords: NSCLC, lncARSR, PTEN, Akt

Introduction

Lung tumors rank as the leading cause of tumor-related deaths worldwide [1-4]. NSCLC accounts for approximately 85% of lung tumor cases [5-7]. Despite developments in chemotherapeutic and surgical interventions, the five-year survival rate for NSCLC patients remains unsatisfactory, and the recurrence rate in these patients is high due to tumor metastasis and chemoresistance development [4, 8-10]. Many genome-wide studies on NSCLC have been performed, such as gene expression profiling, copy number analysis and DNA sequencing [11-15]. However, the detailed mechanisms of NSCLC remain poorly understood. Thus, it is crucial to seek novel therapeutic targets for NSCLC.

LncRNAs are more than two hundred nucleotides (nts) in length with no or limited protein-coding capacity, and they regulate gene expression at the post-transcriptional level [16-22]. LncRNAs play roles in biological and pathological processes, such as development, metastasis, angiogenesis, proliferation, metabolism and invasion [23-28]. Deregulated lncRNA expression has been identified in almost all types of human malignancies, such as gastric cancer, urinary bladder carcinoma, glioblastoma, osteosarcoma, and NSCLC [19, 20, 27, 29-31]. Recent evidence has shown that lncARSR plays a role in the progression of several cancers [32-35]. Qu et al. [35] first indicated that lncARSR was associated with a poor sunitinib reaction in renal carcinoma. Overexpression of lncARSR induced sunitinib resistance by binding miR-449/miR-34 to induce c-MET and AXL expression in renal cell carcinoma cells. Moreover, Qu and colleagues found that lncARSR was overexpressed in renal tumor-initiating cells (T-ICs) and that knockdown of lncARSR abolished the tumorigenicity, metastasis and self-renewal of these renal tumor-initiating cells. Forced expression of lncARSR promoted T-IC characteristics in RCC cells by combining with YAP to impede LATS1-induced YAP

phosphorylation and induce YAP nuclear translocation [34]. However, the role of lncARSR in NSCLC remains uninvestigated.

In the present study, we found that lncARSR was overexpressed in NSCLC tissues. Further investigation indicated that ectopic lncARSR expression induced NSCLC cell migration, growth and EMT.

Materials and methods

Specimens and cell transfection

NSCLC and matched non-tumor samples were collected from 40 NSCLC patients at the Fifth Hospital of Harbin Medical University and Daqing People's Hospital. These samples were immediately snap-frozen. None of the patients received any radiotherapy or chemotherapy. Written informed consent was obtained from the patients, and our research was approved by the Clinical Ethics Committee of the Fifth Hospital of Harbin Medical University and Daqing People's Hospital. Lung bronchial cells (16HBE) and four lung tumor cell lines (SPC-A1, A549, H23 and H1299) were purchased from the Chinese Academy of Sciences of Shanghai (Shanghai). pcDNA-lncARSR and scrambled vector were obtained from GenePharma (Shanghai, China). A549 cell transfection was performed with Lipofectamine 2000 following the manufacturer's instructions.

Cell invasion, cycle and growth assays

For the cell growth assay, cells were grown in 96-well plates. Cell proliferation was detected using a CCK-8 kit (Beyotime, China). The proliferation rate was measured at 0, 1, 2, and 3 days post-transfection, and the absorbance (450 nM) was measured on a microtiter reader. For the cell cycle assay, cells were collected, washed with PBS and fixed overnight with ethyl alcohol at 4°C. RNase A was added to the cells, which were then washed with cold PBS and incubated with propidium iodide. The signal was measured by FACS. For the invasion analysis, a Transwell chamber with Matrigel (Bioscience, CA, USA) was used. The cells were cultured in the upper transwell chamber with no serum, and complete medium was added to the lower chambers. After 24 hours of incubation, the non-invasive cells were removed with a cotton swab, and the invasive cells were fixed with ethanol and stained with crystal violet. The invaded cells were captured by photomicrograph and counted.

qRT-PCR

Total RNA from NSCLC specimens and cell lines was acquired with a Trizol kit (Invitrogen, Technologies). qRT-PCR was performed to analyze the expression of lncRNA, miRNA and mRNA with SYBR PCR reagent (Takara, Dalian, China) on a Bio-Rad PCR system following the manufacturer's instructions. For gene expression quantification, the relative CT method (2^{-DCT} method) was used.

Western blot analysis

Cells and specimens were collected and lysed in RIPA buffer with a proteinase inhibitor (Beyotime, China), and the protein concentrations were assessed using a BCA kit (Beyotime, China). Equal protein amounts were separated by 12% SDS PAGE and then transferred to PVDF membranes (Millipore, USA). After blocking with milk, the membranes were incubated with primary antibodies (N-cadherin, E-cadherin and vimentin), followed by hybridization with an HRP-conjugated antibody. The protein signals were visualized using enhanced chemiluminescence (ECL) reagents (Pierce, USA).

Statistical analysis

The data are shown as the mean ± SD (standard deviation) and were obtained at least in triplicate. The data were measured and analyzed with SPSS (SPSS Inc., Chicago, IL). One-way ANOVA or Student's t-test was performed for data analyses. $P < 0.05$ was set to indicate statistical significance.

Results

LncARSR expression was upregulated in NSCLC tissues

As demonstrated in **Figure 1A**, lncARSR expression was higher in the cancerous tissues of 31 NSCLC patients (31/40, 77.5%) than in the adjacent noncancerous tissues. In general, the expression level of lncARSR was higher in NSCLC samples than in adjacent noncancerous samples (**Figure 1B**). In addition, we showed that lncARSR expression was higher in four NSCLC cell lines (A549, H23, H1299 and SPC-A1) than in 16HBE cells (**Figure 1C**).

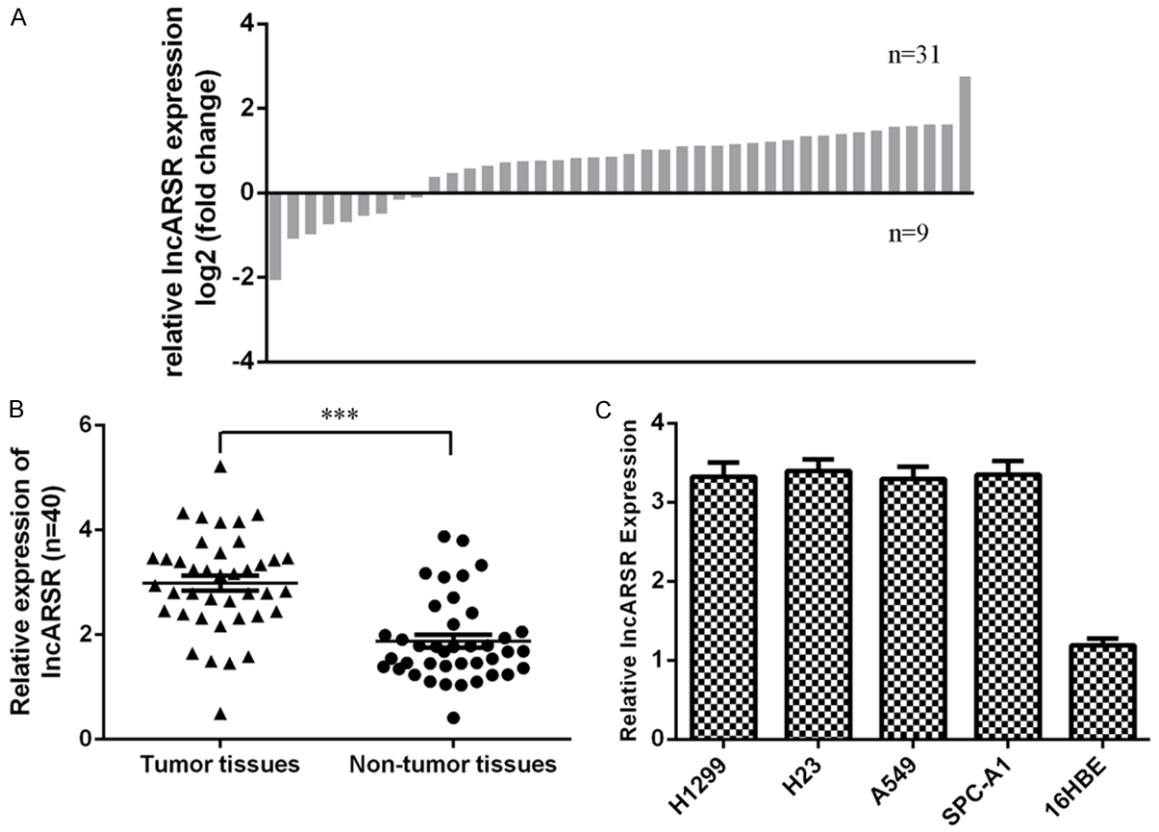

Figure 1. LncARSR expression was upregulated in NSCLC tissues. A. LncARSR expression levels in NSCLC tissues and adjacent noncancerous tissues were detected by qRT-PCR. The data are shown as log2. B. The expression level of lncARSR was higher in NSCLC samples than in adjacent noncancerous samples. C. LncARSR expression levels in four NSCLC cell lines (H1299, H23, A549 and SPC-A1) and a lung bronchial epithelial cell line (16HBE) were determined using qRT-PCR. ***P < 0.001.

Ectopic lncARSR expression promoted NSCLC cell migration and growth

To evaluate the effect of lncARSR on the growth and migration of NSCLC cells, lncARSR was overexpressed in A549 cells by transfection with pcDNA-lncARSR (**Figure 2A**). CCK-8 assays indicated that lncARSR overexpression induced A549 cell proliferation (**Figure 2B**). In line with this finding, lncARSR upregulation increased the expression levels of cyclin D1 (**Figure 2C**) and Ki-67 (**Figure 2D**) in A549 cells. We used a wound healing migration assay and found that lncARSR overexpression induced A549 cell migration (**Figure 2E**).

LncARSR overexpression induced epithelial-mesenchymal transition (EMT): Furthermore, we found that lncARSR overexpression inhibited the expression of the epithelial marker E-cadherin (**Figure 3A**). The expression levels of mesenchymal markers, vimentin and N-cadherin, were increased in A549 cells after treatment with pcDNA-lncARSR (**Figure 3B** and **3C**). In sum, we confirmed that E-cadherin was downregulated and that N-cadherin and vimentin were upregulated in A549 cells after incubation with pcDNA-lncARSR (**Figure 3D**).

LncARSR activated AKT signaling in NSCLC cells: As indicated in **Figure 4A**, ectopic expression of lncARSR suppressed the mRNA expression of PTEN. In line with this finding, ectopic expression of lncARSR decreased PTEN protein expression in A549 cells (**Figure 4B**). Furthermore, increased expression of lncARSR induced Akt phosphorylation in A549 cells (**Figure 4C**).

LncARSR expression was negatively correlated with PTEN expression

We first measured the expression of PTEN in NSCLC samples. As demonstrated in **Figure**

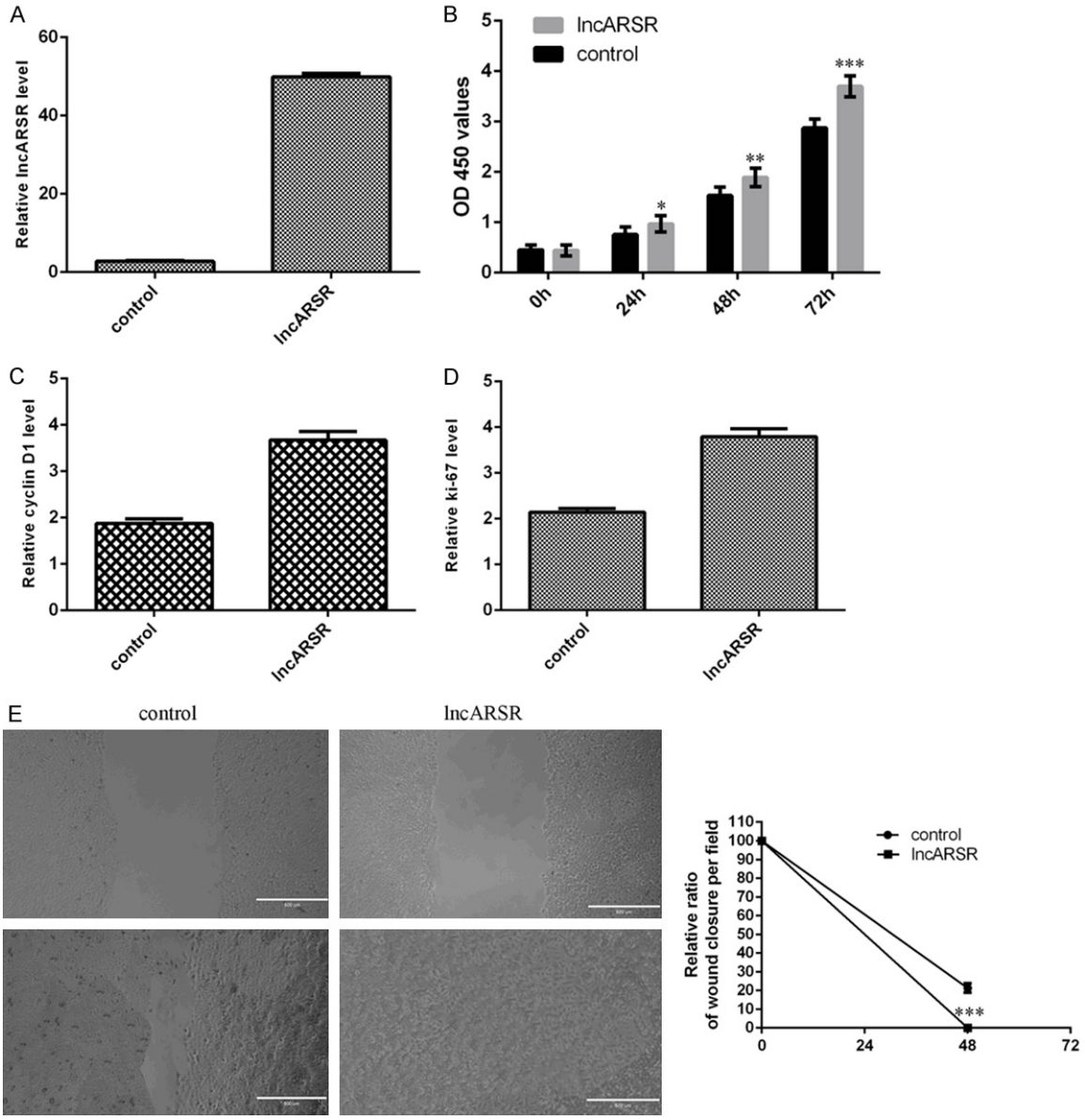

Figure 2. Ectopic expression of lncARSR promoted NSCLC cell growth and migration. A. The expression level of lncARSR in A549 cells after transfection with pcDNA-lncARSR was measured using qRT-PCR. B. CCK-8 assays were performed to measure cell proliferation. C. The mRNA expression of cyclin D1 was detected by qRT-PCR. D. The mRNA expression of Ki-67 was measured by using qRT-PCR. E. A wound healing migration assay showed that lncARSR overexpression induced A549 cell migration. The relative ratio of wound closure is shown. *P < 0.05, **P < 0.01 and ***P < 0.001.

5A, PTEN expression was lower in the cancerous tissues of 30 NSCLC patients (30/40, 75%) than in their adjacent noncancerous tissues. In general, the expression level of PTEN was lower in NSCLC samples than in adjacent noncancerous samples (**Figure 5B**). Moreover, the expression level of PTEN was negatively correlated with lncARSR in the NSCLC specimens (**Figure 5C**).

The Akt signaling pathway was responsible for lncARSR-induced proliferation and migration in NSCLC cells

To further study whether the PTEN/Akt signaling pathway participated in lncARSR-induced proliferation and migration in NSCLC cells, we treated lncARSR-overexpressing A549 cells with the PI3K/Akt inhibitor LY294002. CCK-8

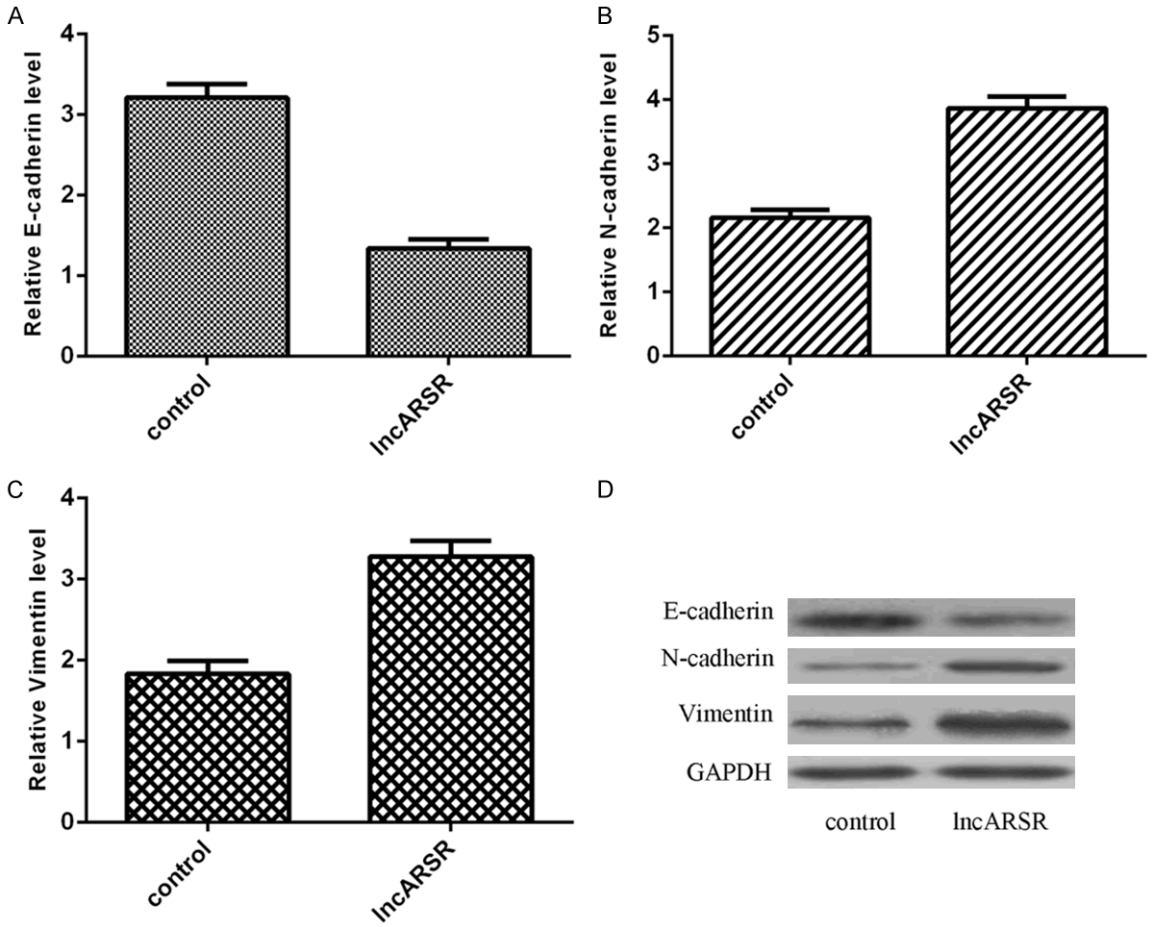

Figure 3. LncARSR overexpression induced epithelial-mesenchymal transition (EMT). A. LncARSR overexpression inhibited the expression of the epithelial marker E-cadherin. B. The mRNA expression of N-cadherin was detected by qRT-PCR. C. The mRNA expression of vimentin was detected by qRT-PCR. D. The protein expression of E-cadherin was decreased, and that of N-cadherin and vimentin was increased in A549 cells after treatment with pcDNA-lncARSR. GAPDH was used as a loading control.

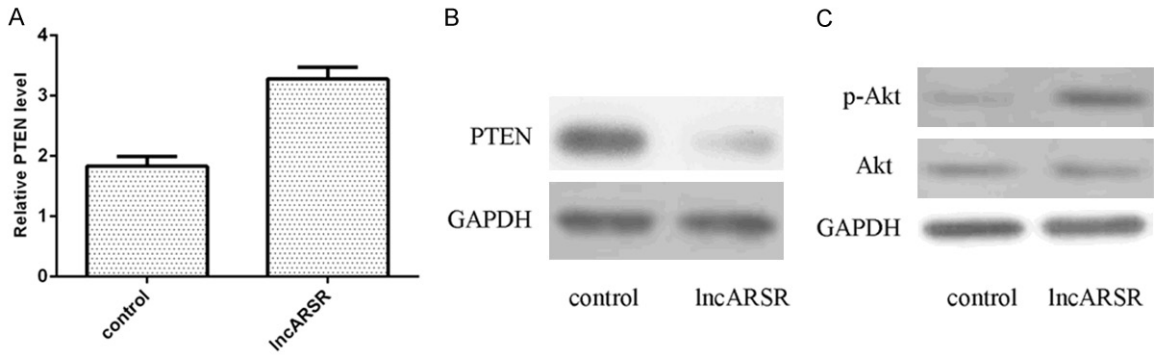

Figure 4. LncARSR activated AKT signaling in NSCLC cells. A. Ectopic expression of lncARSR suppressed the mRNA expression of PTEN. B. The protein expression of PTEN was detected by Western blotting. C. Increased expression of lncARSR induced Akt phosphorylation in A549 cells. GAPDH was used as a loading control.

analysis indicated that cell proliferation was suppressed after treating lncARSR-overexpressing A549 cells with LY294002 (**Figure 6A**). Treatment with LY294002 reversed the increases in cyclin D1 and Ki-67 induced by lncARSR overexpression (**Figure 6B** and **6C**).

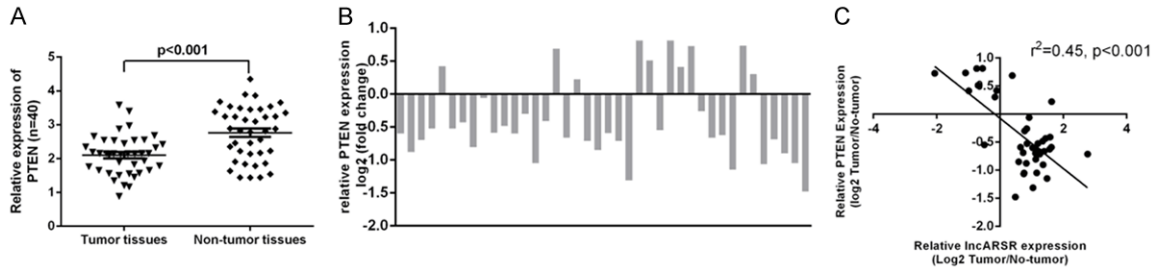

Figure 5. Negative correlation between lncARSR and PTEN expression in NSCLC tissues. A. PTEN expression was downregulated in the cancerous tissues of 30 NSCLC patients (30/40, 75%) compared to that in the adjacent noncancerous tissues. B. The expression level of PTEN was lower in NSCLC samples than in adjacent noncancerous samples. C. The PTEN expression level was negatively correlated with the lncARSR expression level in NSCLC tissues.

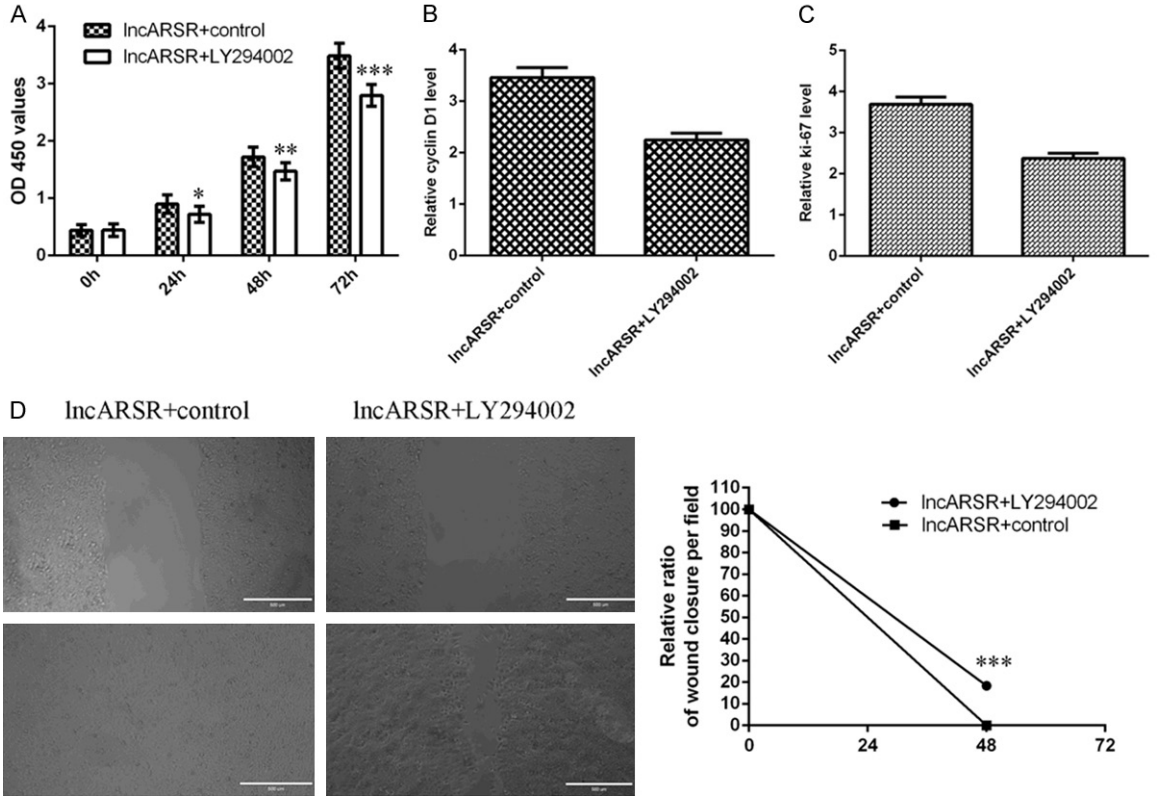

Figure 6. The Akt signaling pathway was responsible for lncARSR-induced proliferation and migration in NSCLC cells. A. CCK-8 assays were performed to measure cell proliferation. B. The mRNA expression of cyclin D1 was detected by qRT-PCR. C. The mRNA expression of Ki-67 was measured by using qRT-PCR. D. Ectopic expression of lncARSR promoted A549 cell migration, which was abolished by LY294002. The relative ratio of wound closure is shown. *P < 0.05, **P < 0.01 and ***P < 0.001.

Furthermore, overexpression of lncARSR increased A549 cell migration, which was abolished by LY294002 (**Figure 6D**).

Discussion

Our findings demonstrated that lncARSR expression was higher in NSCLC tissues than in non-tumor tissues. LncARSR expression was also higher in four NSCLC cells (A549, H23, H1299 and SPC-A1) than in lung 16HBE cells. Further investigation suggested that lncARSR upregulation promoted NSCLC cell proliferation and migration and induced EMT in A549 cells. We found that ectopic lncARSR expression suppressed PTEN expression and induced Akt

phosphorylation in A549 cells. Moreover, the expression level of PTEN was higher in NSCLC samples. The PTEN expression level was negatively correlated with lncARSR expression in NSCLC specimens. Furthermore, we demonstrated that ectopic lncARSR expression promoted NSCLC cell migration and proliferation via regulating the PTEN/Akt signaling pathway. These results suggest that lncARSR plays an oncogenic role in NSCLC development and might serve as a new potential therapeutic target.

Recent evidence has demonstrated that lncARSR plays crucial roles in the development of several tumors [32-37]. Qu et al. [35] first demonstrated that lncARSR was associated with a poor chemoresponse to sunitinib treatment in renal cancer. Overexpression of lncARSR induced sunitinib resistance through binding to miR-449/miR-34, thus promoting c-MET and AXL expression in renal cell carcinoma cells. In addition, Qu and colleagues indicated that lncARSR was overexpressed in renal tumor-initiating cells (T-ICs) and that lncARSR knockdown abolished tumorigenicity, metastasis and self-renewal in renal tumor-initiating cells. Forced expression of lncARSR promoted T-IC properties in RCC cells through binding with YAP to inhibit LATS1-induced YAP phosphorylation and induce YAP nuclear translocation [33, 34]. Li and colleagues indicated that lncARSR was overexpressed in HCC. Increased expression of lncARSR induced HCC cell resistance to doxorubicin treatment via regulating the PTEN-PI3K/Akt pathway. Shu et al. [32]. proved that lncARSR expression was increased in ovarian cancer and associated with lymph node metastasis, poor survival, FIGO (International Federation of Gynecology and Obstetrics) staging and histological grade. Overexpression of lncARSR induced cell progression via the β-catenin/Wnt pathway in ovarian cancer. Our research indicated that lncARSR expression was upregulated in NSCLC samples and NSCLC cell lines. Further study showed that ectopic lncARSR expression enhanced NSCLC cell proliferation and induced EMT progression in NSCLC cells.

LncRNAs are important posttranscriptional modulators of the majority of human genes [38-40]. Previous evidence suggested that ectopic lncARSR expression induced chemoresistance to doxorubicin in HCC cells via PTEN-PI3K/Akt signaling pathway regulation [33]. The PTEN gene, located on chromosome 10q, consists of 9 exons and a 5-Kb variable exon [41]. PTEN was found to act as a tumor suppressor gene in the progression of several tumors [42-44]. PTEN was also shown to be involved in cell migration, proliferation, invasion and metabolism [45]. Loss of the PTEN gene in the PI3K/Akt pathway is frequently found in NSCLC [46-48]. We demonstrated that increased expression of lncARSR inhibited PTEN expression and induced Akt phosphorylation in A549 cells. Moreover, we reported that PTEN expression was higher in NSCLC samples than in adjacent noncancerous specimens. PTEN expression was negatively correlated with lncARSR expression in NSCLC samples. Furthermore, we demonstrated that ectopic lncARSR expression induced cell migration and proliferation via regulating the PTEN/Akt signaling pathway.

In summary, we showed that the expression level of lncARSR was higher in NSCLC specimens and cells and that ectopic lncARSR expression induced NSCLC cell proliferation, migration and invasion via the PTEN/Akt pathway. These results suggest that lncARSR plays an oncogenic role in the initiation and progression of NSCLC and might serve as a novel therapeutic target.

Disclosure of conflict of interest

None.

Address correspondence to: Yingzi Liu, Department of Occupational Disease, Daqing People's Hospital, Daqing 163316, Heilongjiang, China. E-mail: liuying1zi@163.com

References

[1] Gu H, Yang T, Fu S, Chen X, Guo L and Ni Y. MicroRNA-490-3p inhibits proliferation of A549 lung cancer cells by targeting CCND1. Biochem Biophys Res Commun 2014; 444: 104-108.

[2] She K, Yan H, Huang J, Zhou H and He J. miR-193b availability is antagonized by LncRNA-SNHG7 for FAIM2-induced tumour progression in non-small cell lung cancer. Cell Prolif 2018; 51.

[3] Huang CS, Liu SG, Wang HJ, Zhang ZC, Yang Q and Gao F. LncRNA PVT1 overexpression is a

poor prognostic biomarker and regulates migration and invasion in small cell lung cancer. Am J Transl Res 2016; 8: 5025-5034.
[4] Ye M, Zhang J, Miao Q and Yao L. Curcumin promotes apoptosis by activating the p53-miR-192-5p/215-XIAP pathway in non-small cell lung cancer. Cancer Lett 2015; 357: 196-205.
[5] Shan N, Shen L, Wang J, He D and Duan C. MiR-153 inhibits migration and invasion of human non-small-cell lung cancer by targeting ADAM19. Biochem Biophys Res Commun 2015; 456: 385-391.
[6] Wang Y, Xu L and Jiang L. miR-1271 promotes non-small-cell lung cancer cell proliferation and invasion via targeting HOXA5. Biochem Biophys Res Commun 2015; 458: 714-719.
[7] Wang R, Chen XF and Shu YQ. Prediction of non-small cell lung cancer metastasis-associated microRNAs using bioinformatics. Am J Cancer Res 2015; 5: 32-51.
[8] Yao S, Zhao T and Jin H. Expression of MicroRNA-325-3p and its potential functions by targeting HMGB1 in non-small cell lung cancer. Biomed Pharmacother 2015; 70: 72-79.
[9] Stahlhut C and Slack FJ. Combinatorial action of microRNAs let-7 and miR-34 effectively synergizes with erlotinib to suppress non-small cell lung cancer cell proliferation. Cell Cycle 2015; 2014: 2171-80.
[10] Bar J, Gorn-Hondermann I, Moretto P, Perkins TJ, Niknejad N, Stewart DJ, Goss GD and Dimitroulakos J. miR Profiling identifies cyclin-dependent kinase 6 downregulation as a potential mechanism of acquired cisplatin resistance in non-small-cell lung carcinoma. Clin Lung Cancer 2015; 16: e121-9.
[11] Yu H, Jiang L, Sun C, Li Guo L, Lin M, Huang J and Zhu L. Decreased circulating miR-375: a potential biomarker for patients with non-small-cell lung cancer. Gene 2014; 534: 60-65.
[12] Ge H, Li B, Hu WX, Li RJ, Jin H, Gao MM and Ding CM. MicroRNA-148b is down-regulated in non-small cell lung cancer and associated with poor survival. Int J Clin Exp Pathol 2015; 8: 800-805.
[13] Guo H, Li Q, Li W, Zheng T, Zhao S and Liu Z. miR-96 downregulates RECK to promote growth and motility of non-small cell lung cancer cells. Mol Cell Biochem 2014; 390: 155-60.
[14] Liu H, Park J, Manning C, Goehlmann HW and Marshall DJ. Metastatic signature in lung cancer is associated with sensitivity to anti-integrin alphaV monoclonal antibody intetumumab. Genes Chromosomes Cancer 2014; 53: 349-357.
[15] Apopa P, Alley L, Penney R, Arnaoutakis K, Steliga M, Jeffus S, Bircan E, Gopalan B, Jin J, Patumcharoenpol P, Jenjaroenpun P, Wongsurawat T, Shah N, Boysen G, Ussery D, Nookaew I, Fagan P, Bebek G and Orloff MS. PARP1 is up-regulated in non-small cell lung cancer tissues in the presence of the cyanobacterial toxin microcystin. Front Microbiol 2018; 9: 1757.
[16] Yu Y, Yang J, Li Q, Xu B, Lian Y and Miao L. LINC00152: a pivotal oncogenic long non-coding RNA in human cancers. Cell Prolif 2017; 50.
[17] Wang G, Pan J, Zhang L, Wei Y and Wang C. Long non-coding RNA CRNDE sponges miR-384 to promote proliferation and metastasis of pancreatic cancer cells through upregulating IRS1. Cell Prolif 2017; 50.
[18] Li J, Lian Y, Yan C, Cai Z, Ding J, Ma Z, Peng P and Wang K. Long non-coding RNA FOXP4-AS1 is an unfavourable prognostic factor and regulates proliferation and apoptosis in colorectal cancer. Cell Prolif 2017; 50.
[19] Zhang YY, Yang R, Lian JC and Xu HY. LncRNA Sox2ot overexpression serves as a poor prognostic biomarker in gastric cancer. Am J Transl Res 2016; 8: 5035-5043.
[20] Ye KS, Wang SK, Zhang HH, Han H, Ma B and Nan W. Long noncoding RNA GAS5 suppresses cell growth and epithelial-mesenchymal transition in osteosarcoma by regulating the miR-221/ARHI pathway. J Cell Biochem 2017; 118: 4772-4781.
[21] Li H, Liu X, Zhang L and Li XQ. LncRNA BANCR facilitates vascular smooth muscle cell proliferation and migration through JNK pathway. Oncotarget 2017; 8: 114568-114575.
[22] Ba ZW, Gu LL, Hao SN, Wang XF, Cheng ZP and Nie G. Downregulation of lncRNA CASC2 facilitates osteosarcoma growth and invasion through miR-181a. Cell Prolif 2018; 51.
[23] Fu X, Zhang L, Dan L, Wang K and Xu Y. LncRNA EWSAT1 promotes ovarian cancer progression through targeting miR-330-5p expression. Am J Transl Res 2017; 9: 4094-4103.
[24] Huan JL, Xing L, Lin QH, Xui H and Qin XJ. Long noncoding RNA CRNDE activates Wnt/beta-catenin signaling pathway through acting as a molecular sponge of microRNA-136 in human breast cancer. Am J Transl Res 2017; 9: 1977-1989.
[25] Liu J, Song ZW, Feng C, Lu YL, Zhou Y, Lin Y and Dong CY. The long non-coding RNA SUMO1P3 facilitates breast cancer progression by negatively regulating miR-320a. Am J Transl Res 2017; 9: 5594-5602.
[26] Ma X, Li ZH, Li T, Zhu L, Li Z and Tian N. Long non-coding RNA HOTAIR enhances angiogene-

sis by induction of VEGFA expression in glioma cells and transmission to endothelial cells via glioma cell derived-extracellular vesicles. Am J Transl Res 2017; 9: 5012-5021.
[27] Zhu HX, Li XC, Song YR, Zhang P, Xiao YJ and Xing YF. Long non-coding RNA ANRIL is up-regulated in bladder cancer and regulates bladder cancer cell proliferation and apoptosis through the intrinsic pathway. Biochem Biophys Res Commun 2015; 467: 223-228.
[28] Ma L, Wang QB, Gong ZD, Xue LD and Zuo ZB. Long noncoding RNA GIHCG enhanced tongue squamous cell carcinoma progression through regulating miR-429. J Cell Biochem 2018; 119: 9064-9071.
[29] Fawzy MS, Ellawindy A, Hussein MH, Khashana MS, Darwish MK, Abdel-Daim MM, Toraih EA. Long non-coding RNA H19, and not microRNA miR-326, is over-expressed and predicts survival in glioblastoma. Biochem Cell Biol 2018; [Epub ahead of print].
[30] Liu J, Wan L, Lu K, Sun M, Pan X, Zhang P, Lu B, Liu G and Wang Z. The long noncoding RNA MEG3 contributes to cisplatin resistance of human lung adenocarcinoma. PLoS One 2015; 10: e0114586.
[31] Zuo ZB, Ma L, Gong ZD, Xue LD and Wang QB. Long non-coding RNA CASC15 promotes tongue squamous carcinoma progression through targeting miR-33a-5p. Environ Sci Pollut Res Int 2018; 25: 22205-22212.
[32] Shu C, Yang DM, Mo YX, Gu JS, Shah N and He J. Long noncoding RNA lncARSR promotes epithelial ovarian cancer cell proliferation and invasion by association with HuR and miR-200 family. Am J Cancer Res 2018; 8: 981-992.
[33] Li YL, Ye Y, Feng BM and Qi Y. Long noncoding RNA lncARSr promotes doxorubicin resistance in hepatocellular carcinoma via modulating PTEN-PI3K/Akt pathway. J Cell Biochem 2017; 118: 4498-4507.
[34] Qu L, Wu ZJ, Li YM, Xu ZP, Liu B, Liu F, Bao Y, Wu DS, Liu JY, Wang AB, Chu XY, Sun YH, Chen C, Zhang ZY and Wang LH. A feed-forward loop between lncARSR and YAP activity promotes expansion of renal tumour-initiating cells. Nat Commun 2016; 7: 12692.
[35] Qu L, Ding J, Chen C, Wu ZJ, Liu B, Gao Y, Chen W, Liu F, Sun W, Li XF, Wang X, Wang Y, Xu ZY, Gao L, Yang Q, Xu B, Li YM, Fang ZY, Xu ZP, Bao Y, Wu DS, Miao X, Sun HY, Sun YH, Wang HY and Wang LH. Exosome-transmitted lncarsr promotes sunitinib resistance in renal cancer by acting as a competing endogenous RNA. Cancer Cell 2016; 29: 653-668.
[36] Zhang M, Chi XM, Qu N and Wang CY. Long noncoding RNA lncARSR promotes hepatic lipogenesis via Akt/SREBP-1c pathway and contributes to the pathogenesis of nonalcoholic steatohepatitis. Biochem Biophys Res Commun 2018; 499: 66-70.
[37] Huang JB, Chen SJ, Cai DL, Bian DQ and Wang FL. Long noncoding RNA lncARSR promotes hepatic cholesterol biosynthesis via modulating Akt/SREBP-2/HMGCR pathway. Life Sci 2018; 203: 48-53.
[38] Wang LN, Lin YN, Meng H, Liu CY, Xue J, Zhang Q, Li CY, Zhang PJ, Cui FA, Chen WW and Jiang AL. Long non-coding RNA LOC283070 mediates the transition of LNCaP cells into androgen-independent cells possibly via CAMK1D. Am J Transl Res 2016; 8: 5219-5234.
[39] Zhang XY, Zhang LX, Tian CJ, Tang XY, Zhao LM, Guo YL, Cheng DJ, Chen XL, Ma LJ and Chen ZC. LncRNAs BCYRN1 promoted the proliferation and migration of rat airway smooth muscle cells in asthma via upregulating the expression of transient receptor potential 1. Am J Transl Res 2016; 8: 3409-3418.
[40] Zhang XY, Tang XY, Ma LJ, Guo YL, Li XS, Zhao LM, Tian CJ, Cheng DJ, Chen ZC and Zhang LX. Schisandrin B down-regulated lncRNA BCYRN1 expression of airway smooth muscle cells by improving miR-150 expression to inhibit the proliferation and migration of ASMC in asthmatic rats. Cell Prolif 2017; 50.
[41] Phin S, Moore M and Cotter P. Genomic rearrangements of pten in prostate cancer. Front Oncol 2013; 3: 240.
[42] Li L, Sun JX, Wang XQ, Liu XK, Chen XX, Zhang B, He ZD, Liu DZ, Chen LX, Wang LW and Huang Z. Notoginsenoside R7 suppresses cervical cancer via PI3K/PTEN/Akt/mTOR signaling. Oncotarget 2017; 8: 109487-109496.
[43] Zhao YF, Wang YH and Wang YQ. Up-regulated miR-500a enhances hepatocarcinoma metastasis by repressing PTEN expression. Biosci Rep 2017; 37.
[44] Szarzyńska-Zawadzka B, Kunz JB, Sędek Ł, Kosmalska M, Zdon K, Biecek P, Bandapalli OR, Kraszewska-Hamilton M, Jaksik R, Drobna M, Kowalczyk JR, Szczepański T, Van Vlierberghe P, Kulozik AE, Witt M, Dawidowska M. PTEN alterations are related to unfavorable prognosis in children with T-Cell acute lymphoblastic leukemia treated according to ALL IC-BFM protocols. Am J Hematol 2019; 94: E93-E96.
[45] Chen C, Chen J, He L and Stiles B. PTEN: tumor suppressor and metabolic regulator. Front Endocrinol (Lausanne) 2018; 9: 338.
[46] Liu J, Xing Y and Rong L. miR-181 regulates cisplatin-resistant non-small cell lung cancer via downregulation of autophagy through the

PTEN/PI3K/AKT pathway. Oncol Rep 2018; 39: 1631-1639.

[47] Zhao M, Xu P, Liu Z, Zhen Y, Chen Y, Liu Y, Fu Q, Deng X, Liang Z, Li Y, Lin X and Fang W. Dual roles of miR-374a by modulated c-Jun respectively targets CCND1-inducing PI3K/AKT signal and PTEN-suppressing Wnt/β-catenin signaling in non-small-cell lung cancer. Cell Death Dis 2018; 9: 78.

[48] De Marco C, Laudanna C, Rinaldo N, Oliveira D, Ravo M, Weisz A, Ceccarelli M, Caira E, Rizzuto A, Zoppoli P, Malanga D and Viglietto G. Specific gene expression signatures induced by the multiple oncogenic alterations that occur within the PTEN/PI3K/AKT pathway in lung cancer. PLoS One 2017; 12: e0178865.