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Regular paper

LINC00313/miR-4429 axis provides novel biomarkers for the diagnosis and prognosis of non-small cell lung cancer

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Background: Increasing evidence suggests that the LncRNA/miRNA axis plays a key role in many types of tumorigenesis. However, the potential role and clinical value of LINC00313/miR-4429 in non-small cell lung cancer (NSCLC) remain elusive and need further study. The aim of this study was to investigate the role of LINC00313/miR-4429 axis in NSCLC. Methods: The expression of LINC00313 and miR-4429 in serum, tissues and cell lines of NSCLC patients were detected by reverse transcription-quantitative PCR. The diagnostic value was evaluated by receiver operating characteristic (ROC) curve analysis and the prognostic value was analyzed by Kaplan-Meier survival analysis and Cox regression. Result: The expression of LINC00313 was significantly up-regulated while the expression of miR-4429 was down-regulated in NSCLC serum, tissue and cell lines. A negative correlation was found between LINC00313 and miR-4429 in patients with NSCLC. ROC curves showed that LINC00313 and miR-4429 had high diagnostic value and Kaplan-Meier curve results showed that high expression of LINC00313 and low expression of miR-4429 predicted poor prognosis. Conclusion: In summary, our data show that the ectopic expression of LINC00313 and miR-4429 has promising clinical significance in the diagnosis and prognosis of NSCLC. The LINC00313/miR-4429 axis may provide novel biomarker for NSCLC treatment.

Keywords: Non-small-cell lung cancer, LINC00313, miR-4429, diagnosis, prognosis

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Abbreviations: NSCLC, non-small cell lung cancer; ROC, receiver operating characteristics; FBS, fetal bovine serum; RT-qPCR, reverse transcription quantitative PCR

INTRODUCTION

Lung cancer is one of the most common cancers with the highest mortality rate in the world (de Sousa & Carvalho, 2018). More than 90 million people worldwide are at risk of developing lung cancer, which has been a major health problem threatening people all over the world for many years (Vosa *et al.*, 2013). Non-small-cell lung cancer (NSCLC) accounts for ~80% of all cases of lung cancer (Torre *et al.*, 2015). NSCLC is generally treated by surgery, chemotherapy, radiotherapy or comprehensive treatment (Farhat & Houhou, 2013). Although the advent of targeted therapy has significantly improved patient outcomes, prolonging disease control time and improving 5-year overall survival remain poor (Anagnostou & Brahmer, 2015). Therefore, it is urgent to improve the treatment level of NSCLC and to find new biomarkers to improve the diagnostic efficiency and poor prognosis of NSCLC.

LncRNA and miRNAs are considered as new class of tumor biomarkers because their expression levels change in some cancers. (Esquela-Kerscher & Slack, 2006, Peng *et al.*, 2017). For instance, Li and others (Li *et al.*, 2015) found that the expression level of lncRNA LINC00313 was upregulated in lung cancer tissues and LINC00313 was associated with the survival of lung cancer. LINC00313 acts as an oncogene of papillary thyroid cancer through sponging miR-4429, which suggests that LINC00313 may successfully serve as a therapeutic target for papillary thyroid cancer (Wu *et al.*, 2018). MiR-4429 has been studied in some cancers such as renal cell carcinoma (Pan *et al.*, 2019), gastric cancer (He *et al.*, 2019), and cervical cancer (Sun *et al.*, 2020). However, the expression and clinical value of miR-4429 in NSCLC and its relationship with LINC00313 in NSCLC have not been reported.

The aim of this study was to analyze the expression levels of LINC00313 and miR-4429 in serum, tissues and cells of NSCLC, and to further analyze the clinical significance of abnormally expressed LINC00313/miR-4429 axis in the diagnosis and prognosis of NSCLC. The results of this study may provide promising new biomarkers for the treatment of NSCLC.

METHODS

Cell culture

NSCLC cell lines (SK-MES-1, A549) and a normal lung cell line (NHBE) were purchased from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China). All cells were incubated in Dulbecco's modified Eagle medium (Invitrogen, Thermo Fisher Scientific, Inc, Waltham, Massachusetts) supplemented with 10% fetal bovine serum (FBS, Gibco), 100 U/mL penicillin and 100 μg/mL streptomycin (Thermo Fisher, Waltham, MA, USA) in a humidified atmosphere with 5% CO_2 at 37°C.

Patients and sample collection

Blood and tissue samples from 128 NSCLC patients who underwent tumor resection at Affiliated Hospital of Weifang Medical University from January 2012 to May 2014 were analyzed. Venous blood samples were collected before surgery, and tumor tissues and adjacent normal tissues (3 cm from the edge of tumor tissues) were collected during the surgery. All patients met the follow-

ing inclusion criteria: (1) all patients underwent resection in Affiliated Hospital of Weifang Medical University; (2) no patients received anticancer treatment before surgery; (3) no history of asbestos exposure; (4) all patients had complete medical records. In addition, 64 healthy volunteers provided blood samples as healthy controls. Healthy volunteers came from a group who underwent routine health examinations at Affiliated Hospital of Weifang Medical University and confirmed no history of cancer. Serum from collected blood samples was separated by centrifugation and were stored at –80ºC for the future use. The collected tumor tissues and adjacent normal tissues were rapidly preserved in liquid nitrogen. All patients participated in a 5-year telephone follow-up after surgery to record patient survival for subsequent survival analysis.

Cell transfection

A LINC00313 overexpression vector pcDNA3.1-LINC00313 was constructed, and the overexpression vector or empty vector pcDNA3.1 was transfected into NSCLC cell lines A549 and SK-MES-1 using transfection reagent Lipofectamine 3000 (Invitrogen, Carlsbad, CA, USA) following the manufacturer's protocols. LINC00313 expression level was detected 48 h after transfection to evaluate transfection efficiency.

RNA extraction

Total RNA in serum, tissues and cells was extracted using GenElute Total RNA Purification Kit (Sigma-Aldrich), and RNA concentration and quality were analyzed using NanoDrop 2000 (Thermo Fisher Scientific, Waltham, MA, USA), where the absorbance ratio OD260/OD280 results close to 2.0 of RNA can be used for subsequent reverse transcription.

Reveres transcription quantitative PCR (RT-qPCR)

The expression of LINC00313 and miR-4429 were measured by qRT-PCR, which was carried out using a SYBR green I Master Mix kit (Invitrogen, Carlsbad, CA, USA) on a 7500 Real-Time PCR System (Applied Biosystems, USA). The level of LINC00313 and miR-4429 were calculated using the $2^{-\Delta\Delta Ct}$ method and normalized to the level of U6 or GAPDH, respectively. The oligonucleotide primer sequences were as follows:

LINC00313 forward: 5'-TTGCGTGACAGTTTCCACTC-3';
LINC00313 reverse: 5'-CTCCCTTCTGCGGTCATTTC-3';
miR-4429 forward: 5'-ATTATTGGGGCTGGGCG-3';
miR-4429 reverse: 5'-CAGTGCAGGGTCCGAGGT-3';
and U6 forward: 5'-TGCGGGTGCTCGCTTCGGCAGC-3';
U6 reverse: 5'-CCAGTGCAGGGTCCGAGGT-3';
GAPDH forward: 5'-CTGGGCTACACTGAGCACC-3';
GAPDH reverse: 5'-AGTGGTCGTTGAGGGCAATG-3.

Statistical analysis

Student's t test was used for comparison between two groups, and one-way ANOVA followed by Tukey's test was used for comparison among multiple groups. The relationship between the expression level of LINC00313 and miR-4429 in tumor tissues and patient clinicopathological data was tested using Chi-square test. The receiver operating characteristic (ROC) curve was established according to the expression level of serum LINC00313 or miR-4429 to evaluate the diagnostic value of LINC00313/miR-4429 axis. Kaplan-Meier method was used to establish patient survival curves, and log-rank test was used to compare the differences between survival curves. Cox regression analysis was used to evaluate the prognostic value of LINC00313 and miR-4429 in predicting patient 5-year survival. All the statistical analyses were performed using SPSS 21.0 (IBM Corp.) and GraphPad Prism version 7.0 software (GraphPad Software, Inc.), and a difference was considered statistically significant when $P<0.05$.

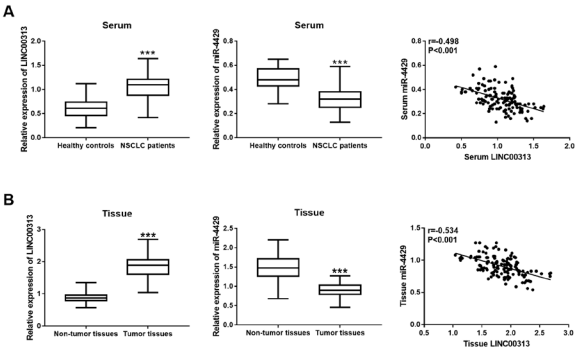

Figure 1. Expression of the LINC00313 and miR-4429 in NSCLC serum and tissue samples.
(**A**) LINC00313 expression level was upregulated and miR-4429 expression level was downregulated in NSCLC serum, and the expression levels of both were negatively correlated. (**B**) LINC00313 expression level was upregulated, and miR-4429 expression level was downregulated in NSCLC tissue, and the expression levels of both were negatively correlated.

RESULTS

Expression of the LINC00313 and miR-4429 in NSCLC serum and tissue samples

Our experimental results showed that serum LINC00313 expression level was upregulated, but serum miR-4429 expression level was downregulated in the patients with NSCLC compared with healthy controls (both $P<0.001$), and the levels of LINC00313 and miR-4429 were negatively correlated (r=–0.498, $P<0.001$) (Fig. 1A). Similarly, NSCLC tissues also upregulated LINC00313 and downregulated miR-4429 levels than adjacent normal tissues (both $P<0.001$), and a significantly negative

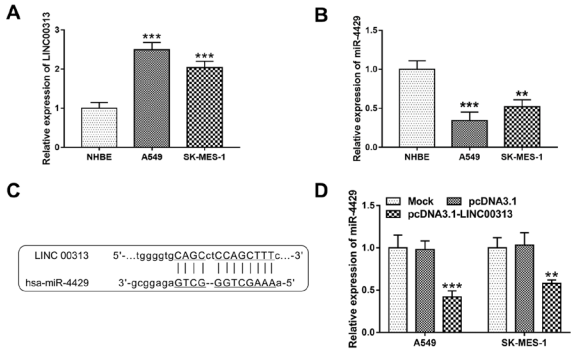

Figure 2. Overexpression of LINC00313 inhibits miR-4429 expression in NSCLC cells.
(**A**) Compared with normal NHBE cells, the expression level of NSCLC cell line LINC00313 was enhanced. (**B**) Decreased expression of miR-4429 was observed in NSCLC cell lines compared with normal NHBE cells. (**C**) The putative binding sites between LINC00313 and miR-4429. (**D**) Upregulating of LINC00313 expression in NSCLC cell lines inhibits the expression of miR-4429.

Table 1. Relationship between the LINC00313/miR-4429 axis and clinicopathological characteristics in NSCLC patients

Variables	Cases (n=128)	LINC00313 expression		*P*	miR-4429 expression		*P*
		Low (n=60)	High (n=68)		Low (n=65)	High (n=63)	
Age							
< 60 years	47	21	26	0.705	27	20	0.251
≥ 60 years	81	39	42		38	43	
Gender							
Male	77	36	41	0.973	40	37	0.746
Female	51	24	27		25	26	
Tumor size							
< 3 cm	71	39	32	0.042	39	32	0.295
≥ 3 cm	57	21	36		26	31	
Smoking history							
No	52	24	28	0.892	27	25	0.831
Yes	76	36	40		38	38	
Differentiation							
Well-Moderate	72	40	32	0.026	43	29	0.022
Poor	56	20	36		22	34	
Lymph node metastasis							
Negative	75	42	33	0.014	44	31	0.034
Positive	53	18	35		21	32	
TNM stage							
I-II	69	40	29	0.007	42	27	0.014
III-IV	59	20	39		23	36	

correlation was also found between the two molecules (r=–0.534, *P*<0.001) (Fig. 1B).

Overexpression of LINC00313 inhibits miR-4429 expression in NSCLC cells

Previous studies have shown that LINC00313 has a binding site for miR-4429 (Wu *et al.*, 2018). The results of this experiment showed that the expression level of LINC00313 was upregulated and that the expression of miR-4429 was down-regulated in NSCLC cell lines (all *P*<0.01 Fig. 2A and B), which further indicates that the potential direct interaction between LINC00313 and miR-4429 could bind. The binding sequence between LINC00313 and miR-4429 was shown in Fig. 2C. To further confirm the regulatory relationship of LINC00313 with miR-4429, the current study evaluated the expression of miR-4429 in NSCLC cells under the overexpression of LINC00313 by pcDNA3.1-LINC00313. The results showed that the overexpression of LINC00313 could significantly decrease the expression level of miR-4429 in NSCLC cells (*P*<0.05 Fig. 2D). The above results indicated a potential axis of LINC00313/miR-4429 in NSCLC.

Relationship between the LINC00313/miR-4429 axis and clinicopathological characteristics in NSCLC patients

This study then explored the role of LINC00313 and miR-4429 in the development of NSCLC by analyzing the relationship between LINC00313 and miR-4429 and patient clinical data. The findings from this analysis were summarized in Table 1. SPSS analysis showed that the expression level of LINC00313 was related to tumor size (*P*=0.042), differentiation (*P*=0.026), lymph node metastasis (*P*=0.014) and TNM stage (*P*=0.007), and that the expression level of miR-4429 is related to differentiation (*P*=0.022), lymph node metastasis (*P*=0.034) and TNM stage (*P*=0.014). In contrast, no association was found between the expression levels of miR-4429 and LINC00313 and other parameters, such as gender, age, and smoking history (all *P*>0.05).

Diagnostic value of the LINC00313/miR-4429 axis in NSCLC patients

ROC curves were generated according to the serum levels of LINC00313 and miR-4429 in patients. Also, the LINC00313 had high diagnostic value with an area under the curve of 0.916. Sensitivity was 78.91% and specificity was 90.63% (Fig. 3A). In addition, miR-4429

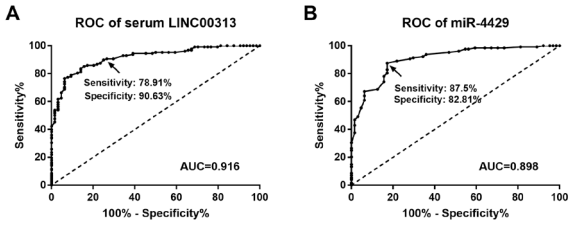

Figure 3. Diagnostic value of the LINC00313/miR-4429 axis in NSCLC patients.
(**A**) A receiver operating characteristic curve based on LINC00313 expression indicated high diagnostic accuracy of LINC00313. AUC: 0.916 (**B**) A receiver operating characteristic curve based on miR-4429 expression indicated high diagnostic accuracy of miR-4429. AUC: 0.898.

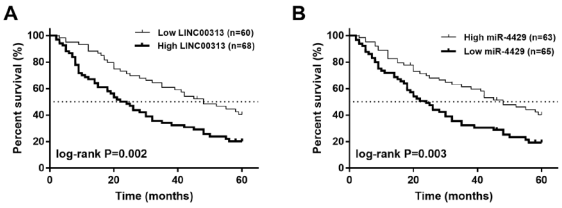

Figure 4. Prognostic value of the LINC00313/miR-4429 axis in NSCLC patients.
(**A**) Survival curves showed that patients with low expression of LINC00313 had higher overall survival rates. (**B**) Survival curves showed that patients with high expression of miR-4429 had higher overall survival rates.

also has a moderate diagnostic value, with a sensitivity of 87.5%, specificity of 82.81%, and an area under the curve of 0.898 (Fig. 3B).

Prognostic value of the LINC00313/miR-4429 axis in NSCLC patients

Because of the abnormal expression levels of LINC00313 and miR-4429 in NSCLC tissue samples, we further evaluated the prognostic significance of LINC00313 and miR-4429 in NSCLC patients. The relationship between LINC00313 and miR-4429 expression levels and overall survival was estimated by plotting Kaplan-Meier survival curves. As shown in Fig. 4A, the results showed that patients with low levels of LINC00313 expression had higher overall survival rate (log-rank P=0.002). However, the patients with high level of miR-4429 expression had better prognosis than those with low level of miR-4429 expression (log-rank P=0.003) (Fig. 4B). In addition, a multivariate Cox analysis showed that LINC00313 (HR=2.290, 95% CI=1.427–3.675, P=0.001) and miR-4429 (HR=2.144, 95% CI=1.291–3.561, P=0.003) were two independent prognostic factors affecting the survival of NSCLC patients (Table 2).

DISCUSSION

NSCLC is a fatal cancer with high mortality and is threatening the health of people all over the world (Chen *et al.*, 2017). Although great progress has been made in the study of NSCLC, the diagnosis and prognosis of its patients are still not optimistic (Vokes *et al.*, 1998). Therefore, there is an urgent need to explore the molecular mechanism of the onset and progression of NSCLC, and to find new noninvasive biomarkers and new targets for effective treatment to improve the diagnostic efficiency and prognosis of patients with NSCLC. LncRNA and miRNA can participate in the initiation and development of NSCLC and act as tumor suppressors or promoters (Cai *et al.*, 2017; Yu *et al.*, 2019; Peng *et al.*, 2019). For instance, studies have shown that PCAT19 negatively regulates the p53 tumor suppressor pathway and promotes cancer cell proliferation in NSCLC patients (Zhang *et al.*, 2019). Gu and others (Gu *et al.*, 2018) found that miR-940 inhibits the proliferation of cancer cells and further inhibits the progression of NSCLC by targeting FAM83F. LncRNA MALAT1 can alter the chemoresistance of NSCLC cells by targeting miR-197-3p and regulating p120-ctn expression, which may help to improve the chemotherapy of NSCLC (Yang *et al.*, 2019). However, the roles of LINC00313 and miR-4429 in NSCLC remain unclear.

LINC00313, located in 21q22.3, was a newly identified lncRNA whose dysregulation had been reported in several tumors (Yin *et al.*, 2018). For instance, the experimental results showed that knockout of LINC00313 could significantly inhibit cell proliferation, migration and invasion. Therefore, LINC00313 may act as an oncogene of papillary thyroid cancer (Yan *et al.*, 2019). Yang and others (Yang *et al.*, 2020) found that LINC00313 overexpression inhibits cell migration, invasion, and tube formation in Kaposi's sarcoma-associated herpesvirus. Similarly, new evidence suggests that miRNAs play an important role in biological processes such as differentiation, cell proliferation, migration, invasion and apoptosis (Shukla *et al.*, 2011). For instance, human studies of glioblastoma have shown that decreased expression of miR-4429 can affect the viability and apoptosis of glioblastoma multiform cells (Liu *et al.*, 2019). Liang et al. found that miR-4429 can directly target FOXM1 in cervical cancer to regulate the proliferation, migration, invasion and apoptosis of cervical cancer cells (Liang *et al.*, 2020). Further studies showed that the expression level of miR-4429 was significantly decreased in NSCLC patients and cells. In this study, qRT-PCR results showed that LINC00313 was overexpressed and miR-4429 was downregulated in NSCLC patients and cells. Pearson experiment showed that the expression level of LINC00313 was negatively correlated with that of miR-4429 in tissues of NSCLC patients and cells. Therefore, miR-4429 and LINC00313 may play a role in the occurrence and development of NSCLC.

Previous studies have suggested that LINC00313 may play a role in disease by targeting miR-4429. The data of Wu et al. showed that LINC00313 acted as an oncogene of papillary thyroid cancer through sponging mir-4429, which suggested that LINC00313 might be successfully

Table 2. Cox regression analysis of LINC00313 and miR-4429 expression and clinicopathological features in patients with NSCLC

Indicators	Multiple Cox regression analysis		
	HR	95% CI	*P* value
Age	1.335	0.845–2.111	0.216
Gender	1.083	0.693–1.692	0.727
Tumor size	1.222	0.779–1.918	0.382
Smoking history	1.003	0.647–1.556	0.989
Differentiation	1.385	0.857–2.238	0.183
Lymph node metastasis	1.325	0.846–2.075	0.219
TNM stage	1.857	1.154–3.059	0.014
LINC00313	2.290	1.427–3.675	0.001
miR-4429	2.144	1.291–3.561	0.003

used as a therapeutic target of papillary thyroid cancer (Wu *et al.*, 2018). In this study, we found that LINC00313 and miR-4429 had binding sites, and further experiments showed that overexpression of LINC00313 could inhibit the level of miR-4429. Thus, LINC00313 mediates the occurrence of NSCLC via miR-4429 sponging. In addition, the clinical significance of miR-4429 and LINC00313 was further studied. Kaplan-Meier survival curves showed that patients with high LINC00313 expression had a lower overall survival rate than NSCLC patients with low expression, which was the same as in previous studies (Wu *et al.*, 2018). NSCLC patients with high expression of miR-4429 had better prognosis. In addition, LINC00313 and miR-4429 were independently associated with overall survival, suggesting that LINC00313 and miR-4429 may serve as independent prognostic biomarkers for NSCLC patients. The stability of lncRNA and miRNA expression in blood samples can be used as ideal diagnostic tools for human diseases (Bhan *et al.*, 2017, Moya *et al.*, 2019). Therefore, the significance of LINC00313 and miR-4429 in diagnosis was further studied in this experiment. In our study, ROC curve results showed that LINC00313 and miR-4429 had high diagnostic value, and their AUC values of ROC curve were 0.916 and 0.898, respectively. Therefore, LINC00313 and miR-4429 could be potential diagnostic biomarkers for NSCLC patients.

In summary, the results of this study indicate that LINC00313 and miR-4429 are abnormally expressed in NSCLC patients and cells. LINC00313 and miR-4429 serum can be used as candidate diagnostic biomarkers to differentiate NSCLC patients from healthy people. Moreover, the expression levels of LINC00313 and miR-4429 can be used as prognostic biomarkers for NSCLC patients. This study provides two potential biomarkers for the diagnosis and prognosis of NSCLC and provides research ideas for future research and development of new treatment strategies for NSCLC. There are still many shortcomings in the study, including the role of LINC00313/miR-4429 axis in the pathological mechanism of NSCLC was not further analyzed, which will be the focus of future research.

Declarations

Ethics approval and consent to participate

A signed written informed consent was obtained from each patient and the experimental procedures were all in accordance with the guideline of the Ethics Committee of Affiliated Hospital of Weifang Medical University.

Consent for publication

Written informed consent for publication was obtained from each participant.

Availability of data and material

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

Competing interests

The authors declare that they have no competing interests.

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