



miR-137 represses migration and cell motility by targeting COX-2 in non-small cell lung cancer

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Background: Lung cancer is a common malignant tumor, with, non-small cell lung cancer (NSCLC) accounting for about 80–85% of cases. This study investigated the expression of miR-137 in NSCLC tissues and cells and its effects on the migration and invasion of NSCLC cells and related mechanisms.

Methods: We collected the neoplastic and paracancerous tissues of NSCLC patients, detected the expression of miR-137 in NSCLC tissues and cell lines by real-time quantitative polymerase chain reaction (RT-qPCR), and analyzed the correlation between miR-137 expression and the clinicopathological features and survival of NSCLC. Following transfection with miR-137 mimic or inhibitor in NSCLC cell lines (A549 or H1299) to upregulate or downregulate the expression of miR-137, transwell assay was employed to detect the effects of miR-137 on migration or invasion. Online software was employed to predict and analyze the target gene of miR-137, and luciferase reporter gene system was adopted to validate it. The effects of miR-137 on the expressions of COX-2 and Epithelial-Mesenchymal Transition (EMT) related proteins were investigated by Western blot.

Results: Compared to paracancerous tissues and BEAS-2B cells, the expressions of miR-137 in NSCLC tissues, A549 and H1299 cells were dramatically down-regulated ($P < 0.01$). After transfection with miR-137 mimic or inhibitor in A549 and H1299 cells, the miR-137 expressions were markedly up-regulated or down-regulated ($P < 0.01$), respectively. The number of migrating or invading cells was observably decreased or increased ($P < 0.01$) after transfected with mimic or inhibitor, respectively, while relative luciferase activity was evidently decreased in cells co-transfected with miR-137 mimic and wild type recombinant vector of 3'UTR of COX-2. While the expressions of COX-2 and E-cadherin were both substantially reduced in A549 cells treated with miR-137 mimic, that of vimentin was substantially raised. The expression of miR-137 correlated with smoking history, lymph node metastasis, and TNM clinical stage, and patients with high miR-137 expression had apparent longer survival.

Conclusions: The expression of miR-137 was significantly down-regulated in NSCLC tissues and cells, and correlated with NSCLC progress. miR-137 suppressed the migration and invasion of NSCLC cells through regulating EMT relative proteins by targeting COX-2. miR-137 is expected to become a novel biomarker and therapeutic target of NSCLC.

Keywords: miR-137; COX-2; non-small cell lung cancer (NSCLC); Epithelial-Mesenchymal Transition (EMT); migration

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Introduction

Lung cancer is one of the most common malignant tumors globally, and has become the leading cause of death from malignant tumors in the urban Chinese population (1). According to the pathological characteristics and differentiation degree of cancer cells, lung cancer can be divided into small cell lung cancer (SCLC) (15%) and non-small cell lung cancer (NSCLC) (85%) (2), the latter which includes squamous cell carcinoma (SCC), adenocarcinoma, and large cell carcinoma. Compared with small cell carcinoma, the growth and division of NSCLC cells are slower, and diffusion and metastasis are relatively late (3). About 75% of NSCLC sufferers are diagnosed at an advanced stage, and the 5-year survival rate is very low (4,5). The pathogenesis of lung cancer is complex and understanding its potential molecular mechanisms is of great significance to improve the survival rate of patients and reduce mortality from the disease (6).

MicroRNA (miRNA) is a kind of non-coding single stranded RNA molecule with a length of about 22 nucleotides encoded by endogenous genes. miRNAs participate in the regulation of post transcriptional gene expression in animals and plants (7,8), and are both important regulatory factors in tumors and closely related to the occurrence and development of lung cancer (9,10). After abnormal expression, miRNA can be used as carcinogenic miRNA or tumor suppressor miRNA to regulate the expression of signal pathway genes and affect the proliferation, migration, invasion, and metastasis of lung cancer cells (9,11).

More than 50% of human miRNAs are in special chromosomal regions, which are amplified, deleted, or translocated during tumor development. miRNAs play an important role in the occurrence and evolution of tumors (12) by regulating the physiological processes of cells such as apoptosis, cell proliferation, cell cycle control, DNA repair, and metabolism, and negatively regulating the expression of genes and proteins as carcinogens or tumor suppressors (9,13,14). miR-137 has been proven to hold a tumor suppressor gene function, and its antitumor effect has been confirmed in a variety of cancers (15,16). In our previous study, its promoter methylation was associated with NSCLC cell migration and prognosis (17). And, the A549 cells were

treated with cigarette smoking extract for 16 weeks, miR-137 was one of the miRNAs with significantly different expression. In this study we investigated the expression of miR-137 in NSCLC tissues and cells and its effect on the migration and invasion of NSCLC cells and related mechanisms. We present the following article in accordance with the MDAR reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2177/rc>).

Methods

Patients and tissues

We obtained the paraffin embedded cancerous and paracancerous tissues of 10 NSCLC patients (four with squamous cell cancer and six with adenocarcinoma) who attended the Subei People's Hospital in 2012. The tissues of ten patients with benign lung lesions were also collected. To further assay the relationship between miRNA expression and the clinicopathological features of NSCLC, a further 56 NSCLC cancerous tissues embedded with paraffin collected between 2008 to 2009 were also obtained. No patient had received chemotherapy before surgical excision, and the resected tissues were embedded with paraffin after being fixed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research was approved by the Ethics Committee of the Subei People's Hospital of Jiangsu Province, and written informed consent was obtained from all patients prior to participation.

RNA isolation and real-time quantitative polymerase chain reaction (RT-qPCR)

Total RNA was extracted and purified from paraffin embedded tissues using an RNeasy FFPE Kit (Univ-Bio Company, Shanghai, China), with Trizol applied to isolate total RNA from cultured cells. cDNA was synthesized using a miRcute miRNA cDNA synthesis kit (Tiangen, Biotech, Beijing, China). Primers were synthesized by the Shenggong Company (Shanghai, China), and their sequences are listed in *Table 1*. SYBR Green and specific primers of miR-137 and U6 were employed to detect the expression of miR-137,

Table 1 Primers for RT-qPCR

Gene	Primer sequence (5'-3')
miR-137	Forward: CAAGGCTTGTTAACTGTAAC
	Reverse: TCTGTCAATGTCTGAATAAATG
U6	Forward: CTCGCTTCGGCAGCACATATACT
	Reverse: ACGCTTCACGAATTTGCGTGTC

RT-qPCR, real-time quantitative polymerase chain reaction.

and U6 was applied as internal reference.

Transwell assay

A transwell chamber with or without matrigel was employed to investigate the effect of miR-137 on the migration or invasion of NSCLC cells. Briefly, the H1299 or A549 cells were digested and subcultured into the upper chamber with or without matrigel after 24 hours of transfection with miR-137 mimic or inhibitor. After a further 24 hours, a cotton swab was adopted to wipe out the cells not passing through polycarbonate membranes, while those passing through pore membranes were fixed with 4% paraformaldehyde and stained with Giemsa for 20 min. The cells were observed with a Leica microscope and analyzed by ImageJ.

Cell culture and transfection

BEAS-2B (Human bronchial epithelial cells), NCI-H1299 cells, and A549 cells (human NSCLC cell line) were obtained from Procell Life Science & Technology Co., Ltd. (Wuhan, China), and were cultured in a 37 °C and 5% CO₂ constant-temperature incubator with RPMI-1640 medium containing 10% fetal calf serum (HyClone, ThermoFisher, Shanghai). Every second day, the cells were digested with trypsin and subcultured, and during their logarithmic growth period, were transfected according to the following protocol.

The miR-137 mimic, mimic negative control, miR-137 inhibitor, inhibitor negative control, COX-2 siRNA, and scramble siRNA were synthesized by RiboBio Co., Ltd (Guangzhou, China). The coding sequence of COX-2 was cloned into lentivirus vector GV492 to obtain the recombinant overexpression vector Lv-COX-2, which was provided by Vigen Biotechnology (Zhengjiang, China). The mimic, inhibitor, or siRNA was transfected into H1299 or A549 cells with lipofectamine 2000 (Invitrogen, Shanghai, China). In brief, the cells were digested with trypsin and

cultured into a 6-well plate with 50,000 cells/well before 24 hours of transfection. The miR-137 mimic, inhibitor (50 pmol), or COX-2 siRNA (100 pmol) were diluted in OPTI-MEM and transfected into NSCLC cells, and Lv-COX-2 was transfected into A549 cells at a multiplicity of infection (MOI) of 5.

Luciferase reporter gene assay

The online software miRanda (<http://www.microrna.org/microrna/getMirnaForm.do>) was employed to analyze the target genes of miR-137, and as a predictive result, COX-2 (PTGS2) was a target gene of miR-137. The 3'UTR of COX-2 with or without miR-137 binding mutation site was cloned into pGL3 vector, and the constructed recombinant vector pGL3-PTGS2 (WT) or pGL3-PTGS2 (MT) was co-transfected with miR-137 mimic into the logarithmic growth phase of HEK293 cells. After 48 hours transfection, the luciferase was detected using a Luciferase Assay system (Promega Biotech, Beijing, China).

Western blot

The NSCLC H1299 or A549 cells were collected after 72 hours transfection with miR-137 mimic, COX-2 siRNA, or Lv-COX-2, respectively. RIPA lysis solution was applied to extract total protein, and a BCA assay kit was used to quantify its concentration. Total proteins with 50 µg/lane were separated by SDS-PAGE electrophoresis, then transblotted into PVDF membrane. After blocking, the membrane was incubated with rabbit anti-human primary antibodies, COX-2 (1:2,000) (BioVision, Waltham, MA), vimentin (1:2,000) (Merck, Rockville, MD), E-cadherin (1:5,000) (Abcam, Waltham, MA), and β-actin (1:5,000) (Beyotime Biotechnology, Haimen, China), overnight at 4 °C, respectively. Membranes were then reacted with goat HRP-conjugated anti-rabbit secondary antibody (sigma, St. Louis, MO) for 1 hour at 37 °C following washing with TBST. The bands were visualized by enhanced chemiluminescence (ECL) reagent using a Tanon 5200 image system (Tanon, Shanghai, China) and quantified using ImageJ.

Statistical analysis

All data are presented as mean ± standard deviation (SD). Student's *t* two-tailed tests were employed to perform comparison between two groups, and one-way ANOVA with post hoc Holm-Sidak correction was performed for

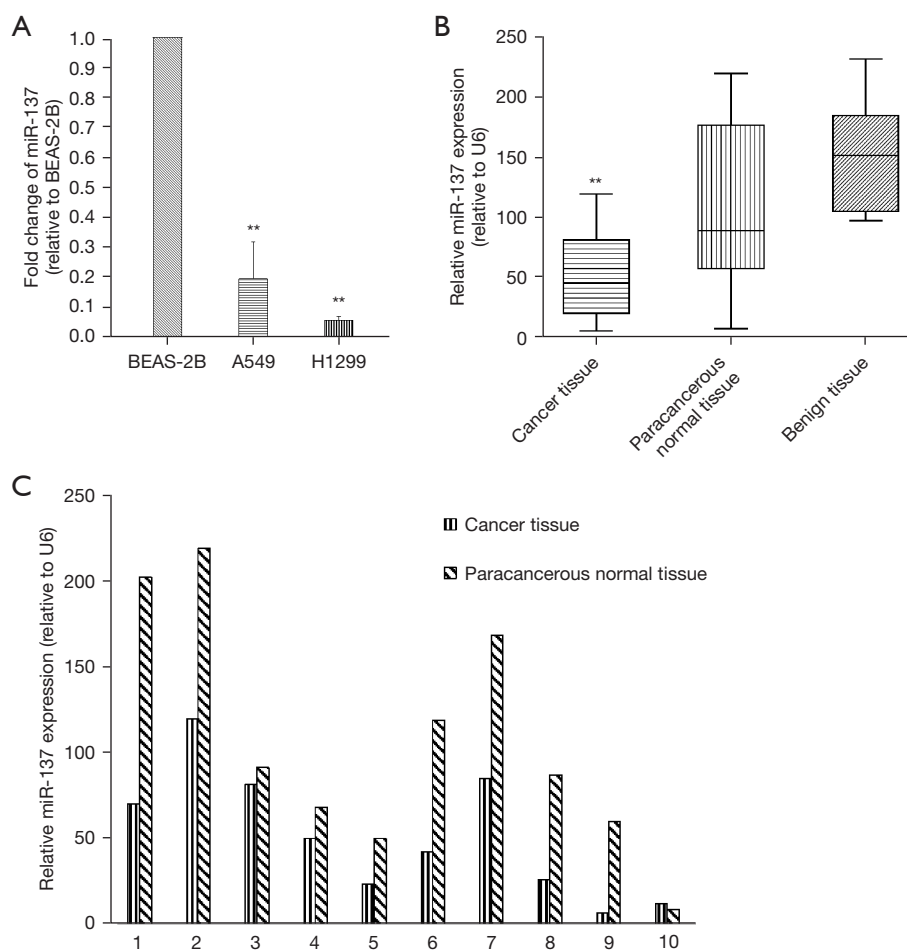


Figure 1 Expression of miR-137 in NSCLC cell lines and tissues. (A) miR-137 was expressed in NSCLC cell lines (A549 and H1299). **, $P < 0.01$ versus BEAS-2B cells. (B) miR-137 was expressed in tissues. **, $P < 0.01$ versus paracancerous normal tissues. (C) miR-137 was expressed in ten pairs of NSCLC tissues and corresponding paracancerous normal tissues, respectively. NSCLC, non-small cell lung cancer.

multiple comparisons. GraphPad Prism 8 was employed to analyze the data, Kaplan-Meier and log-rank tests were adopted to analyze the disease-free survival and overall survival effected by miR-137. $P < 0.05$ was determined as statistically significant.

Results

Expression of miR-137 in NSCLC tissues and cells

We used RT-qPCR to investigate the expression of miR-137 in NSCLC tissues and cells, with BEAS-2B, a human normal bronchial epithelial cells, as control. The results showed the expression of miR-137 was dramatically down-regulated in NSCLC cell lines (H1299 and A549), compared to BEAS-2B ($P < 0.01$) (Figure 1), and as

anticipated, was markedly down-regulated in cancerous tissues compared with paracancerous normal tissues and benign lung tissues ($P < 0.01$) (Figure 1B). The expression analysis of miR-137 in ten pairs of cancerous tissues and paracancerous normal tissues is shown in Figure 1C.

Relationship between miR-137 expression and clinicopathological characteristics of NSCLC

As stated above, the expression of miR-137 was down-regulated in NSCLC tissues and cells, and we further investigated this relationship in 56 NSCLC cancerous tissues. The results showed the expression of miR-137 was correlated with smoking history, lymph node metastasis, and TNM clinical stage ($P = 0.032$, $P = 0.01$ and $P = 0.015$,

Table 2 Characteristics of 56 patients with NSCLC by miR-137 expression levels

Characteristics	miR-137 expression levels		P ^a
	Expression value of miR-137	Low, N	
Gender			0.388
Male	329.3±241.0	21	22
female	265.4±195.5	7	6
Age, years			0.362
<60	327.1±251.7	13	11
≥60	305.0±218.2	15	17
Smoking status			0.032
0	412.5±262.6	7	11
<1 pack/day	340.1±252.4	6	7
≥1 pack/day	230.4±163.9	15	10
Histological type			0.288
Adenocarcinoma	344.2±252.3	15	16
Squamous cell	277.6±200.9	13	12
T-status			0.053
T1	383.2±241.4	11	19
T2	239.3±200.3	14	7
T3	217.4±187.0	3	2
T4	-	0	0
N-status			0.010
N0	378.0±222.7	12	19
N1	312.4±265.3	7	7
N2	137.8±83.0	9	2
N3	-	0	0
TNM			0.015
I	399.6±230.8	9	17
II	285.0±202.2	9	8
III	182.5±209.0	10	3
IV	-	0	0
Differentiation			0.272
Well	415.9±220.2	4	7
Moderate	290.2±218.2	18	16
Poor	288.0±272.9	6	5

^a, P values for one way analysis of variance (ANOVA) tests. Data were presented as mean ± SD. NSCLC, non-small cell lung cancer; T-status, tumor status; N-status, nodes status; TNM, tumor-nodes-metastases; SD, standard deviation.

respectively), while there was no apparent relationship with gender, age, histological type of tumor, tumor size, or tumor differentiation ($P>0.05$) (Table 2).

Effect of miR-137 on migration and invasion in NSCLC cells

To investigate the effect of miR-137 on the migration and invasion of NSCLC cells, the synthesized miR-137 mimic and inhibitor were subjected to transfection. After 48 hours transfection, the analytical results of RT-qPCR showed miR-137 expression was substantially increased or decreased in NSCLC cells transfected with miR-137 mimic or inhibitor (both $P<0.01$), respectively, compared to the negative control. The synthesized miR-137 mimic and inhibitor were then adopted for application in the following experiments.

Metastasis of various organs can occur in the late stage of lung cancer, which often brings great suffering to patients and threatens their lives. Transwell assay was employed to detect the influence of migration or invasion by miR-137 and showed its overexpression by mimic markedly restrained the migration or invasion of A549 and H1299 cells. Conversely, miR-137 expression down-regulated by inhibitor significantly facilitated migration or invasion. These results are shown in Figure 2.

Target gene of miR-137

miRNAs play important roles in multiple life processes, including tumorigenesis and progress, by regulating target genes. As predicted, COX-2 (PTGS2) was a target gene of miR-137, and there were binding sites in the 3'UTR of COX-2, as shown in Figure 3A. The luciferase reporter gene system was adopted to verify COX-2 as the target gene of miR-137, and showed relative luciferase activity dramatically declined in cells co-transfected with miR-137 mimic and pGL3-PTGS2 (WT). This result directly validated COX-2 as the target gene of miR-137 (Figure 3B). The effects of miR-137 on COX-2 were then detected by Western blot and showed COX-2 expression was apparently suppressed in H1299 and A549 cells transfected with miR-137 mimic (Figure 3C).

Mechanism of inhibition of migration and invasion by miR-137 in NSCLC cells

Epithelial-Mesenchymal Transition (EMT) plays a crucial

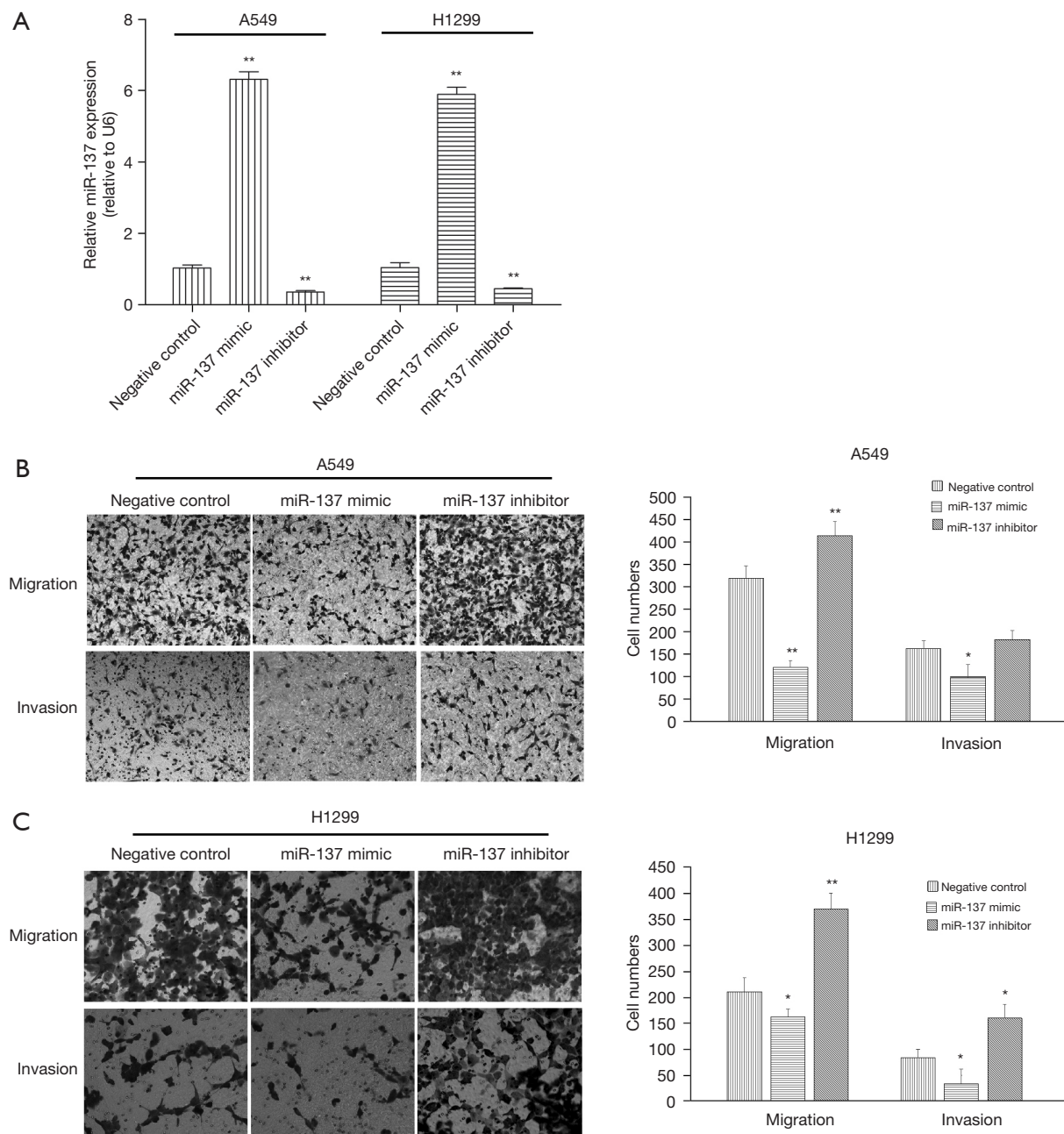


Figure 2 Effect of miR-137 on migration and invasion of non-small cell lung cancer (NSCLC) cells by transwell assay. (A) Expression of miR-137 in NSCLC cell line A549 or H1299 after transfection with miR-137 mimic or inhibitor. (B) Effect of miR-137 on migration and invasion of A549 cells. Stained with Giemsa. 100 \times . (C) Effect of miR-137 on migration and invasion of H1299 cells. Stained with Giemsa. 200 \times . *, $P < 0.05$ and **, $P < 0.01$ versus negative control.

role in embryonic development, tissue reconstruction, and cancer metastasis (18), and whether miR-137 suppressed the migration and invasion by regulating EMT was then examined. The expression influences of E-cadherin and

vimentin by miR-137 were measured by Western blot, and showed the expression of vimentin was dramatically downregulated in A549 cells alone transfected with miR-137 mimic, while that of E-cadherin was dramatically

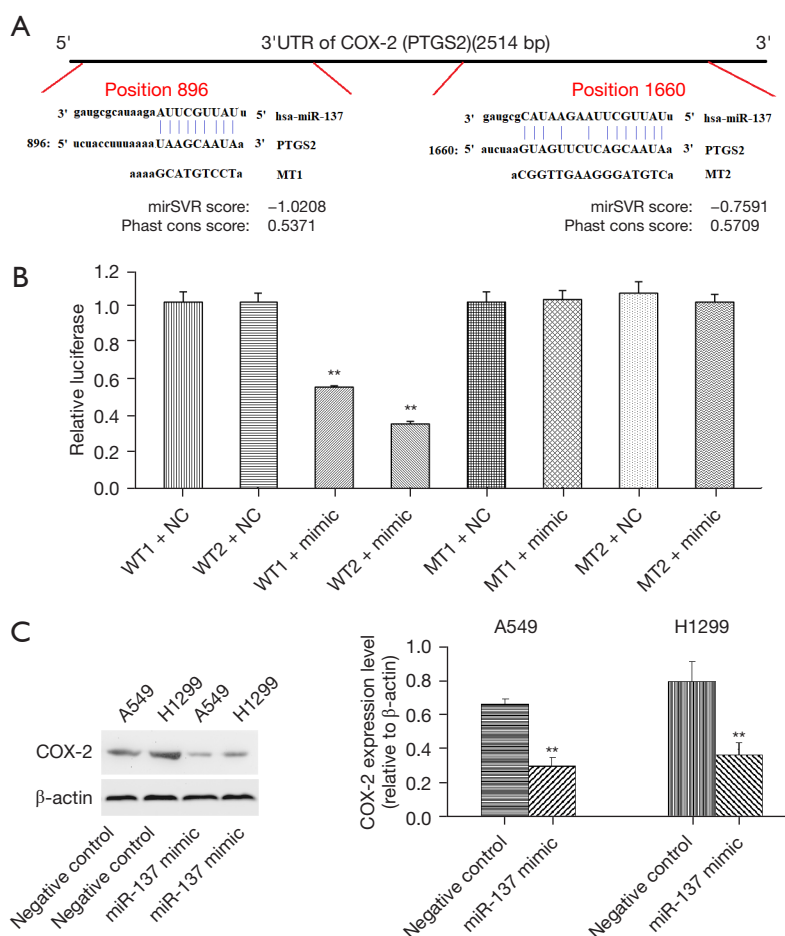


Figure 3 COX-2 was the target gene of miR-137. (A) Diagram of the 3' UTR of COX-2 (PTGS2) representing the predicted complementary sites for the miR-137. (B) Dual-luciferase reporter assay system was employed to validate the target gene of miR-137. (C) Effect of miR-137 on COX-2 by Western blot. **, P<0.01 versus negative control. PTGS2, prostaglandin-endoperoxide synthase 2; MT, mutation; WT, wild type; NC, negative control; Mimic, miR-137 mimic.

upregulated. In addition, when A549 cells were co-transfected with Lv-COX-2 and miR-137 mimic, the expression of vimentin was significantly enhanced, and E-cadherin was reduced (Figure 4).

Association between miR-137 expression and survival of NSCLC patients

Among the recruited 56 patients with NSCLC, one died of postoperative pneumonia, and the follow-up data of eight patients were lost. A Kaplan-Meier survival curve was applied to analyze the correlation between miR-137 expression and survival in the remaining 47 patients, who were divided based on the relative expression of miR137 into two groups. A high expression group containing 23 patients with miR-

137 expression \geq median and a low expression group containing 24 patients with miR-137 expression < median were established, and as shown in Figure 5, those with high miR-137 expression had apparent longer disease-free survival (P=0.01) and overall survival (P=0.04).

Discussion

miRNAs may act as tumor suppressors or carcinogens in lung cancer by targeting and controlling the expression of multiple signal pathway genes and affecting the proliferation, migration, invasion, and other malignant processes of tumor cells (19,20). In recent years, with the deepening of research, miRNAs have increasingly been recognized as lung cancer biomarkers, and the regulatory

mechanism of lung cancer-related miRNAs in tumors has been found (21,22). However, the self-regulation mechanism of miRNA is unclear, and whether this affects the occurrence and evolution of tumors requires further research and exploration (23,24). At the same time, although the mechanism of miRNA in the occurrence and development of lung cancer has been widely studied, its precise mechanism in regulating the malignant biological

process of lung cancer cells has not been clarified. miRNA has broad clinical application prospects, and is expected to become a key target for molecular targeted therapy of lung cancer (19,25). Studying the potential molecular mechanisms involved is of great significance for the diagnosis, treatment, and prognosis of a variety of malignant tumors, including lung cancer.

In this study, miR-137 expression was dramatically down-regulated in NSCLC tissues and cells, and the results indicated it may be a tumor suppressor of the disease. Further research showed miR-137 suppressed the migration and invasion of NSCLC cells, and its expression correlated with the smoking history, lymph node metastasis, and TNM clinical stage of NSCLC patients.

Prostaglandin E (PGE) plays an important role in human physiological regulation, involving multiple processes such as inflammation, coagulation, cell growth, tumorigenesis, and development (26,27). Cyclooxygenase (COX), also known as prostaglandin peroxidase, is the rate-limiting enzyme in the process of PGE synthesis, and can metabolize arachidonic acid (AA) to form various prostaglandin (PG) products (28). The human body contains two different COX isoenzyme isomers: Constitutive COX-1 and inducible COX-2. While COX-2 is minimally expressed in normal tissue, this can increase as much as 80 fold, and large amounts can be expressed under the stimulation of inflammatory factors, such as IL-1, TNF- α , lipopolysaccharide (LPS), and cAMP, (29), promoting the synthesis of many PGEs and triggering an inflammatory reaction (30). PGEs produced by COX-2 have a variety of biological activities and can participate in

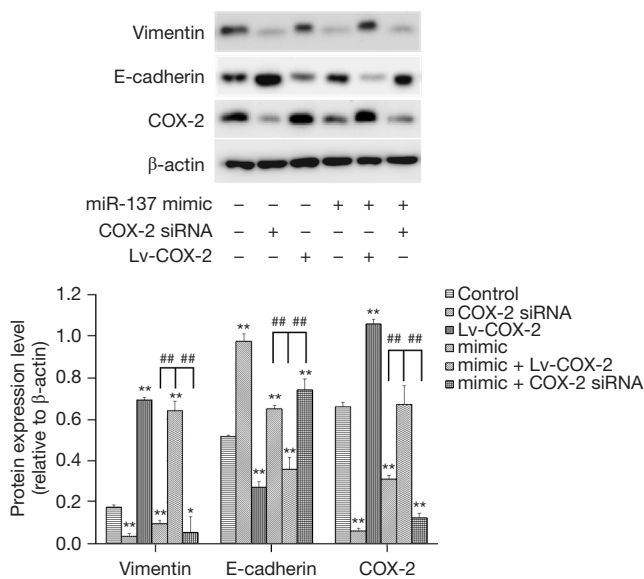


Figure 4 Effect of miR-137 on EMT related proteins in A549 cells by Western blot. *, $P < 0.05$ and **, $P < 0.01$ versus control. #, $P < 0.01$. EMT, Epithelial-Mesenchymal Transition; Mimic, miR-137 mimic.

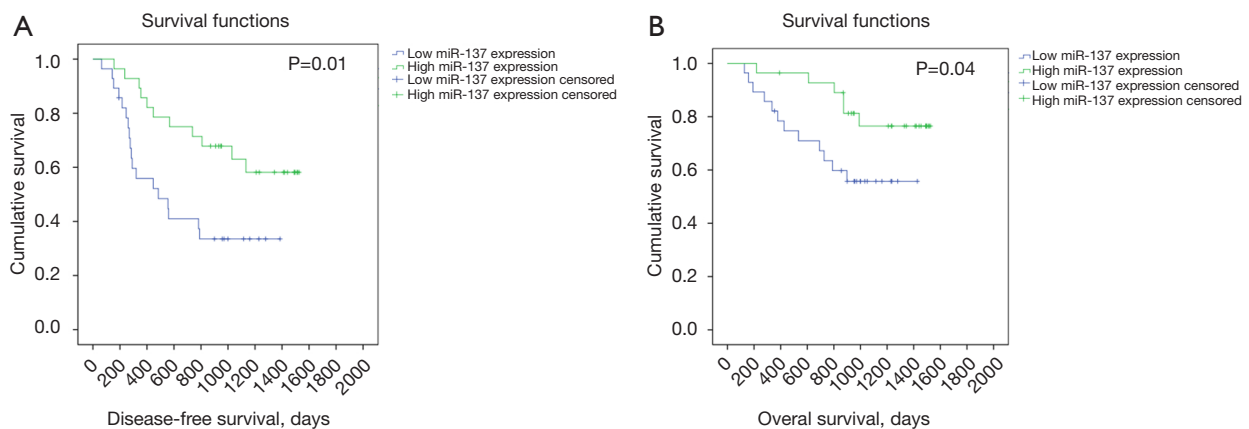


Figure 5 Association between miR-137 expression and survival of NSCLC patients. Kaplan-Meier and log-rank tests were adopted to analyze disease-free survival (A) and overall survival (B) effected by miR-137 expression in NSCLC patients. NSCLC, non-small cell lung cancer.

pathophysiological processes through a variety of pathways including tumor cell growth, metastasis, chemoresistance, and tumor stem cell proliferation (31,32). Therefore, the up regulation of COX-2 expression is considered closely related to inflammation, pain, tumorigenesis, and cancer development.

COX-2 is highly expressed in gastric cancer, esophageal adenocarcinoma, colorectal cancer, and other gastrointestinal tumors, and can promote tumorigenesis and tumor development by regulating the expression of genes related to tumor cell proliferation and apoptosis (33). Both specific and non-specific inhibitors of COX-2, such as nonsteroidal anti-inflammatory drugs (NSAIDs), can induce apoptosis of gastric cancer, colorectal cancer, and pancreatic cancer cells (34). A study on esophageal cancer showed celecoxib could inhibit the expression of COX-2, down regulate the expression of PGE, inhibit the proliferation of esophageal cancer cells, and improve the therapeutic effect of chemotherapy and radiotherapy (35).

The biological role of miRNA is to regulate target genes, and in this study, online software and luciferase reporter gene systems were employed to predict and validate COX-2 as a target gene of miR-137, which observably suppressed it. COX-2 has an oncogene function in lung cancer, and we identified miR-137 as playing a tumor suppressor role by regulating it.

EMT has been widely studied in malignant tumors and is considered to play a crucial role in chemotherapy tolerance and the migration and invasion of cancer cells (18,36). While during EMT, the expression of epithelial markers (E-cadherin) decreased, interstitial markers (N-cadherin and vimentin) increased in cancer tissues (36,37). EMT is observed in the invasion and metastasis of many malignant tumors, including NSCLC (38). In this study, miR-137 suppressed the migration and invasion of NSCLC cells by inhibiting vimentin and promoting E-cadherin.

In summary, the expression of miR-137 was significantly down-regulated in NSCLC tissues and cells. miR-137 suppressed the migration and invasion of NSCLC cells through regulating EMT relative proteins by targeting COX-2, and correlated with the progress of the disease. It is expected to become a novel biomarker and therapeutic target of NSCLC in the future.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2177/rc>

Data Sharing Statement: Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2177/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2177/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The current study was approved by the Institutional Ethics Committee of the Subei People's Hospital of Jiangsu Province. The participants gave informed consent before taking part.

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