

Original Article

MiR-130a inhibits cell proliferation and migration via targeting TGFA in non-small cell lung cancer cells

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Abstract: Background: MicroRNAs are important modulators for cell growth, invasion and metastasis and are involved in proliferation and migration of human non-small cell lung cancer (NSCLC). In this study, we tried to investigate the role of miR-130a-TGFA axis in NSCLC cells. Methods: Quantitative real-time polymerase chain reaction (qRT-PCR) was used to detect the expression of miR-130a in NSCLC tissues and cells. Western blot was performed to examine the protein level of TGF- α . Cell proliferation and migration were detected by MTT assay and Transwell migration assay, respectively. The luciferase assay was conducted to confirm whether TGFA was a target of miR-130a. A xenotransplanted tumor model of lung cancer cells was established through subcutaneously infected with A549 cells or H1299 cells. Results: Lower expression of miR-130a was observed in lung cancer tissues and cells compared to that in the corresponding controls. The expression of miR-130a in lung cancer tissues was negatively correlated with the expression of TGFA. MiR-130a overexpression suppressed the cell proliferation and migration of lung cancer cells. MiR-130a negatively regulated the expression of TGFA. TGFA knockdown reversed the effect of miR-130a inhibitors on cell proliferation and migration. In the xenotransplanted tumor model of lung cancer cells, miR-130a overexpression significantly suppressed the tumor growth. Conclusion: These findings indicate that the miR-130a-mediated TGFA gene silencing plays an important role in proliferation and migration of NSCLC, which might facilitate a better understanding of the molecular mechanisms of lung cancer progression.

Keywords: miR-130a, proliferation, migration, TGFA, non-small cell lung cancer cells

Introduction

Lung cancer is one of the most frequently diagnosed cancers, leading to the largest number of cancer-related deaths worldwide [1]. Recent data indicated that the 5-year survival rate of patients with lung cancer is only 15%. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers, including adenocarcinoma and squamous cell carcinoma [2]. Compared with the small cell lung cancer, NSCLC is characterized by relatively slow growth rate and late early metastasis, which made it difficult to be diagnosed [3]. Most of patients have advanced stage tumors when lung cancer is diagnosed [4]. Thus, it is an urgent need to explore the effective biomarkers and therapeutic strategies for the treatment of lung cancer.

Transforming growth factor- α (TGF- α), as a ligand for the epidermal growth factor receptor

(EGFR), is encoded by the TGFA gene. The binding of TGF- α to EGFR could initiate a series of biological processes including cell growth, differentiation and development [5]. TGF- α also contributes to cell migration and invasion, for example, in prostate cancer and breast cancer [6, 7]. Furthermore, increased expression of TGF- α has been observed to be related with poor prognosis in many malignancies, such as gastric cancer, endometrial cancer and pancreatic cancer [8-10]. In patients with lung adenocarcinoma, high TGFA gene expression was strongly correlated with poor survival [11]. However, the regulation mechanism of TGFA in NSCLC has not been fully elucidated.

MicroRNAs (miRNAs) are small non-coding RNAs that post-transcriptionally regulate gene expression through binding to the 3'-untranslated region (UTR) of the target mRNA, triggering either translation repression or mRNA deg-

radiation [12]. It has been well-known that miRNAs are closely associated with the progression of carcinogenesis, functioning as tumor suppressors or oncogenes [13]. A large number of miRNAs have been found to contribute to the pathologic process of NSCLC and might be related to clinicopathologic characteristics or patient prognosis [14]. Among the identified miRNAs, miR-130a plays a crucial role in tumor pathogenesis. MiR-130a is not only implied to impact cell proliferation, apoptosis, invasion, migration, but also involved in angiogenesis and the development of chemoresistance in cancer cells [15-17]. Gao et al. reported that miR-130a was observed to be downregulated in the squamous cell lung carcinoma tissues compared with normal tissues, which indicated the important role of miR-130a in NSCLC [18]. However, the molecular mechanism of miR-130a-mediated TGFA on cell proliferation and migration in NSCLC has been poorly understood.

In this study, we investigated the expression level of miR-130a in NSCLC tissue samples and cancer cells. Epigenetic modulation and repression of miR-130a was performed to explore its function on cell proliferation and migration, as well as the regulation of TGFA in lung cancer cells.

Materials and methods

Patient samples

A total of 60 NSCLC tissues and the adjacent normal tissues were collected in the First Affiliated Hospital of Zhengzhou University hospital from January 2014 to December 2015. The procedure was approved by the Ethical Committee of Zhengzhou University and written informed consent was obtained from all enrolled patients in this study. All the patients did not receive radiotherapy or chemotherapy or any other treatment before and after operation. The tissues were snap-frozen in liquid nitrogen for the further analysis.

Cell culture and transfection

Human lung cancer cells A549, SPCA-1 and H1299 and the bronchial epithelial cell line BEAS-2B were cultured in RPMI 1640 supplemented with 10% fetal bovine serum (FBS) 100 units/ml of penicillin, and 100 µg/ml of streptomycin at 37°C in a humidified incubator with

5% CO₂. Human lung cancer cell CALU-1 was cultured in DMEM with 10% fetal bovine serum (FBS), L-glutamine and antibiotics (Invitrogen, Carlsbad, CA, USA).

MiR-130a mimic and mimic control (pre-NC), or miR-130a inhibitor and inhibitor control (NC), or pcDNA-TGFA and pcDNA, or si-TGFA and si-control were synthesized by Riobio Co., Ltd. (Guangzhou, China). For transfection, cell lines were cultured to 60% confluence and then transfected using Lipofectamine 2000 (Invitrogen) according to the manufacturer's instruction.

Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted from tissues or cells using TRIzol reagent (Invitrogen) and the concentrations were determined using the Nano-Drop. For quantification of TGFA mRNA, 500 ng of total RNA was reverse transcribed into cDNA using PrimeScript™ RT reagent Kit with gDNA Eraser (Takara, Dalian, China). RT-qPCR analysis was performed with an SYBR Green I real-time PCR kit (GenePharma, Shanghai, China) with the ABI 7300 Real-Time PCR System. For quantification of miRNA, the miScript II RT kit (Qiagen) and the miScript SYBR Green PCR Kit (Qiagen) were used for the reverse transcription and real-time PCR, respectively. The expression of TGFA mRNA was normalized to that of glyceraldehyde phosphate dehydrogenase (GAPDH) mRNA and miR-130a to that of U6 small nuclear RNA (RNU6). The change in expression level was calculated using the 2^{-ΔΔCt} method.

Western blot analysis

Total proteins were extracted from cells with ice-cold RIPA lysis buffer and the concentrations were measured using the protein assay kit (Beyotime, Shanghai, China). Protein samples (40 µg) were separated on 10% SDS-PAGE gels and transferred to polyvinylidene fluoride membranes (Bio-Rad). After blocked with 5% nonfat dry milk for 1 h, the membranes were incubated with primary antibodies against TGF-α (1:500, Proteintech, Proteintech Group, USA) and GAPDH (1:2000, Proteintech, Proteintech Group, USA) overnight at 4°C. After three washes with 1×TBST for 15 min each time, the membranes were incubated with secondary antibodies conjugated to HRP for 2 h.

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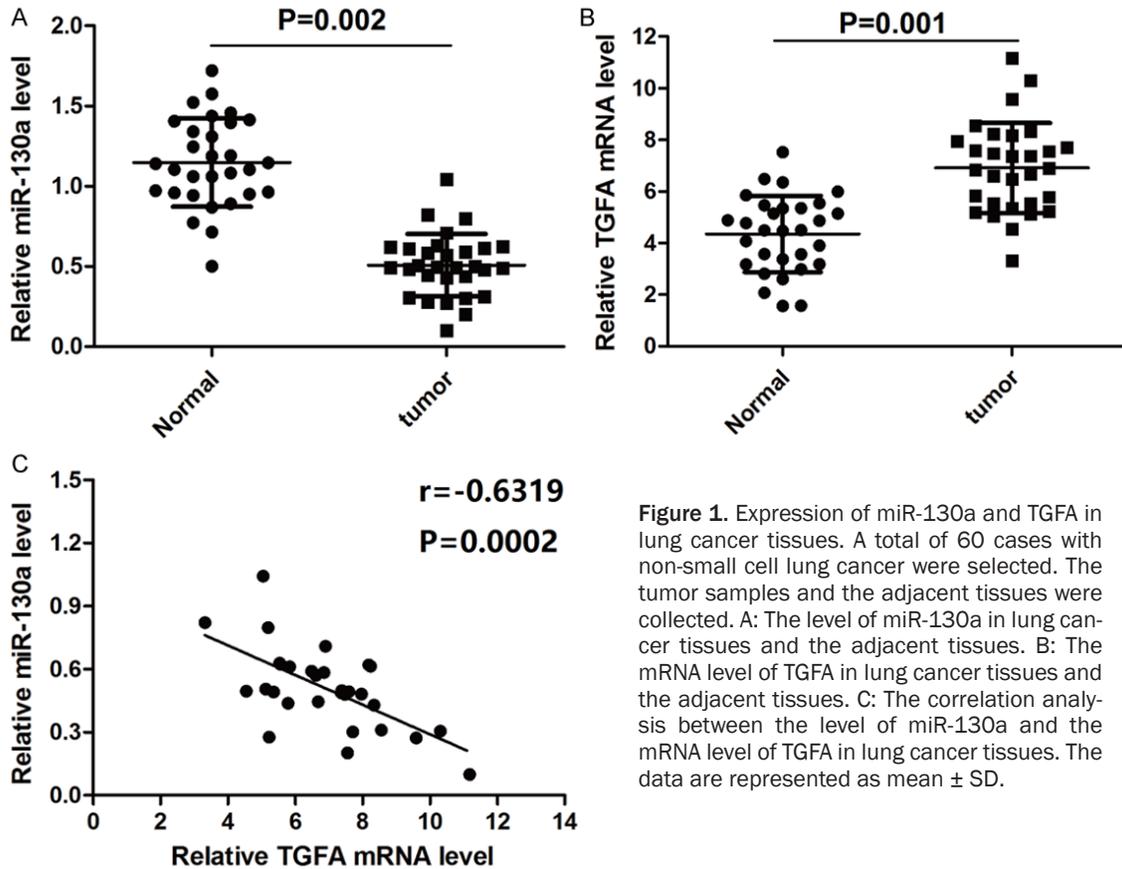


Figure 1. Expression of miR-130a and TGFA in lung cancer tissues. A total of 60 cases with non-small cell lung cancer were selected. The tumor samples and the adjacent tissues were collected. A: The level of miR-130a in lung cancer tissues and the adjacent tissues. B: The mRNA level of TGFA in lung cancer tissues and the adjacent tissues. C: The correlation analysis between the level of miR-130a and the mRNA level of TGFA in lung cancer tissues. The data are represented as mean \pm SD.

The bands were visualized using ECL Plus detection reagent (Santa Cruz Biotechnology). GAPDH was used as an endogenous protein for normalization.

Cell viability assay

A549 or H1299 cells were seeded in 24-well plates overnight and then transfected with miR-130a mimic (or Pre-NC) or miR-130a inhibitor (or NC). After 48 h, cells (2×10^3 cells/well) were seeded into 96-well plates for a 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT) assay, and incubated at 37°C for 72 h. Then, 10 μl MTT (0.5 mg/ml; Sigma, Shanghai, China) was added to each well (20 μl /well), and the cells were maintained at 37°C for another 4 h. The precipitate was dissolved in 100 μl DMSO (Sigma, Shanghai, China). After shaking for 15 min, the absorbance at 570 nm was measured using a microplate reader.

Transwell migration assay

The Transwell chamber with 8 μm pores (Corning, USA) was used for the cell migration assay.

After 24 h of transfection, A549 or H1299 cells (2×10^5 /ml) in serum-free medium were placed into the upper chamber with gelatin-coated polycarbonate membrane filter RMPI1640 with 20% FBS was added to the lower chamber. After 24 h incubation, the membranes were fixed with methanol and stained with 0.1% crystal violet. The migration was determined by counting the penetrated cells under a microscope at $\times 100$ magnification of 6 random fields in each well. Each experiment was performed in triplicate.

Dual-luciferase reporter assay

The wild-type and mutant TGFA 3'-UTR were amplified by PCR and cloned in pMIR-REPORT (Ambion) with firefly luciferase. The wild-type or mutants of TGFA 3' UTR luciferase reporters together with pRL-TK Vector (Promega, Madison, WI) were co-transfected into A549 cells with miR-130a mimics, or miR-130a inhibitors or the controls by lipofectamine 2000. After 48 h of transfection, the firefly and Renilla luciferase were measured according to the manufac-

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Table 1. Comparison of several clinicopathologic factors and expression levels of miR-130a in non-small cell lung carcinoma specimen

Factors	Total number of Patients (n)	MiR-130a expression		P-value
		High (n=30)	Low (n=30)	
Age				
<60	31	13	18	0.698
>60	29	17	12	
Sex				
Female	14	8	6	0.543
Male	46	22	24	
Tumor differentiation				
Well/moderately	28	13	15	0.342
Poorly	32	17	15	
Clinical stages				
I-II	31	12	19	0.065
III	29	18	11	
Tumor Size				
<5 cm	32	22	10	0.042
>5 cm	28	8	20	
Lymph node metastasis				
Absent	16	2	14	0.008
Present	44	28	16	
Smoking				
No	25	12	13	0.438
Yes	35	18	17	

turer's protocols (Promega). The firefly luciferase activities were normalized to Renilla luciferase activities.

In vivo tumorigenesis model

For the *in vivo* experiment, the xenotransplanted tumor model of lung cancer cells was established. A549 cells transfected with Len-miR-130a mimic or H1299 cells transfected with Len-miR-130a inhibitor were subcutaneously injected into the right hindlimbs of BALB/c nude mice (n=6 for each). Len-miR-130a mimic or Len-miR-130a inhibitor or the corresponding controls were obtained from Riobio Co., Ltd. (Guangzhou, China). Tumor volume was monitored every 7 days and measured the tumor length (L) and width (W) with a vernier caliper. The volume was calculated using the formula $0.5 \times L \times W^2$. The animal experiments were manipulated according to protocols and approved by Zhengzhou University Experimental Animal Care Commission.

Statistical analysis

Statistical analyses were performed in SPSS 17.0 for Windows (SPSS Inc.). The data are presented as mean \pm standard deviation (SD). Student's *t*-test or one-way analysis of variance was applied to estimate the difference among groups. A *P*-value <0.05 was considered significant.

Results

The expression of miR-130a in lung cancer tissues and its clinical significance

The expression of miR-130a was detected by qRT-PCR in 60 tumor tissues (n=60) and the matched adjacent non-tumor tissues (n=60). As shown in **Figure 1A**, lower expression of miR-130a was observed in tumor tissues than that in the control tissues. We also tested the mRNA level of TGFA in tumor tissues. As compared with adjacent non-tumor tissues, the mRNA level of TGFA was greatly upregulated in the tumor tissues (**Figure 1B**). Correlation analysis showed that the expression of miR-130a in lung cancer tissues was

negatively correlated with the expression of TGFA (**Figure 1C**).

To detect the clinical significance of miR-130a expression in lung cancer, the 60 patients were divided into low expression of miR-130 (n=30) group or high expression of miR-130 (n=30) group according to the cutoff value. As shown in **Table 1**, low expression of miR-130 in NSCLC patients was significantly correlated with lymph node metastasis (*P*=0.008) and large tumor size (*P*=0.042). These data revealed the significant roles of miR-130 in the development of NSCLC.

MiR-130a is downregulated and TGFA is up-regulated in lung cancer cells

We further detected the expression of miR-130a and TGFA in human lung cancer cells A549, SPCA-1, CALU1 and H1299 and in the control cell bronchial epithelial cell line BEAS-2B. As shown in **Figure 2A**, the level of miR-

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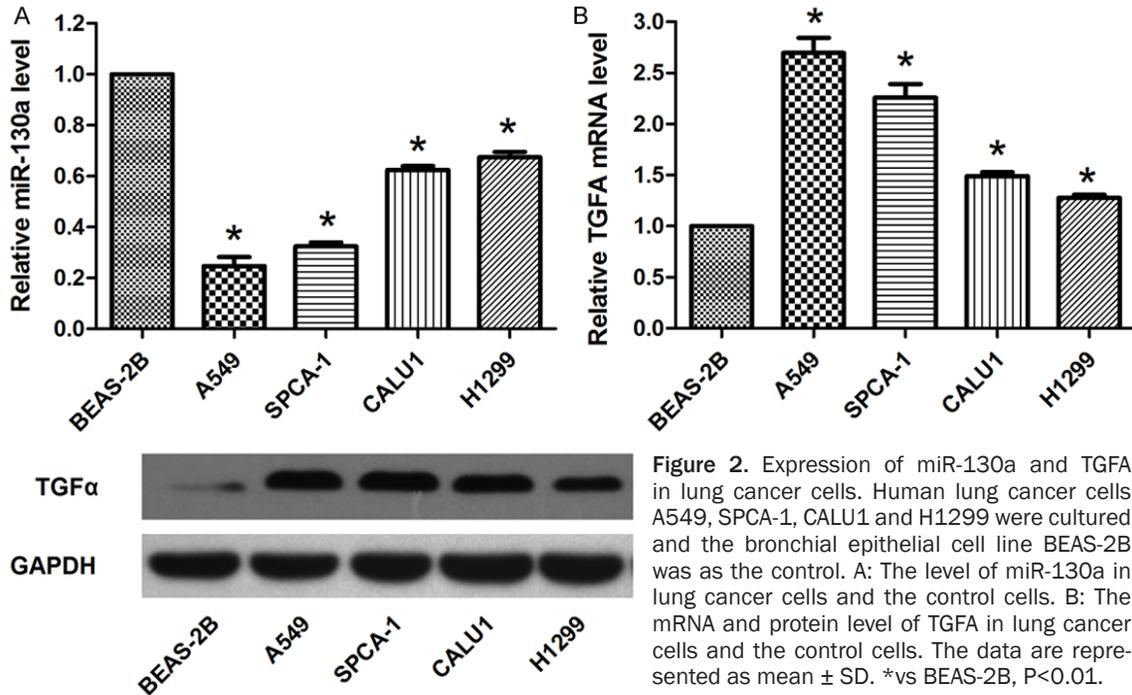


Figure 2. Expression of miR-130a and TGFA in lung cancer cells. Human lung cancer cells A549, SPCA-1, CALU1 and H1299 were cultured and the bronchial epithelial cell line BEAS-2B was as the control. A: The level of miR-130a in lung cancer cells and the control cells. B: The mRNA and protein level of TGFA in lung cancer cells and the control cells. The data are represented as mean \pm SD. *vs BEAS-2B, $P < 0.01$.

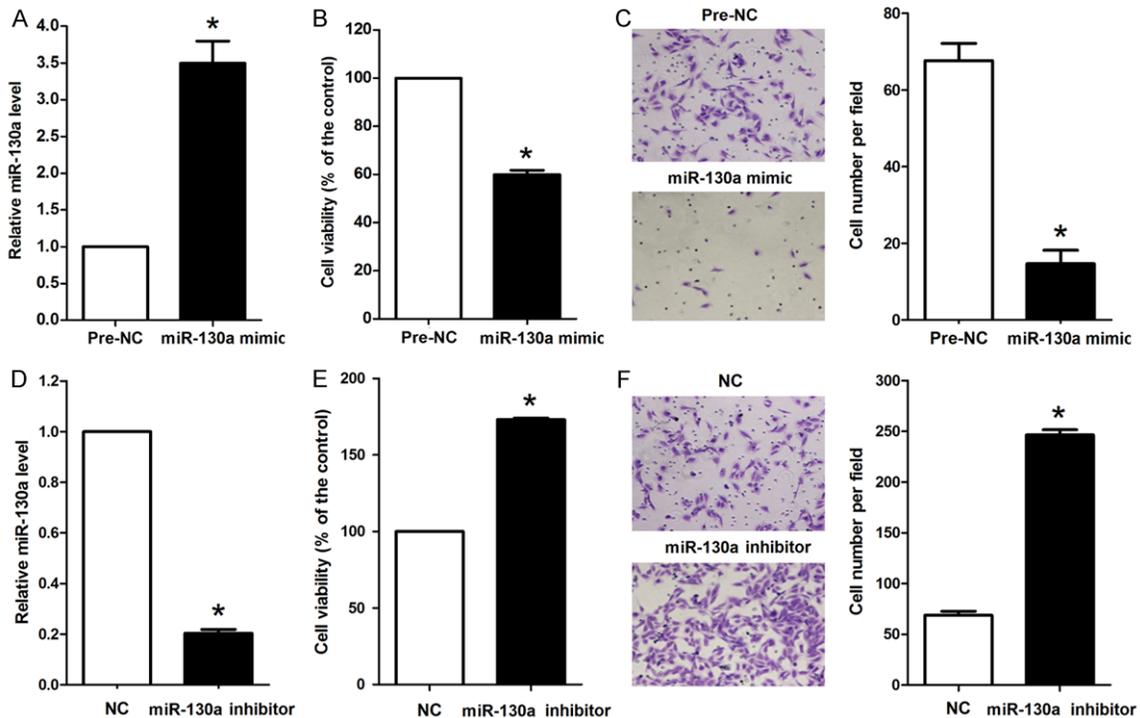


Figure 3. Effect of miR-130a on the cell proliferation and migration of lung cancer cells. A: The level of miR-130a in A549 cells transfected with miR-130a mimic or the control Pre-NC was examined by qRT-PCR. B: The cell viability of A549 cells transfected with miR-130a mimic or the control Pre-NC was detected by MTT assay. C: The cell migration of A549 cells transfected with miR-130a mimic or the control Pre-NC was detected by transwell migration assay. D: The level of miR-130a in H1299 cells transfected with miR-130a inhibitor or the control NC. E: The cell viability of H1299 cells transfected with miR-130a inhibitor or the control NC. F: The cell migration of H1299 cells transfected with miR-130a inhibitor or the control NC. The data are represented as mean \pm SD. *vs control, $P < 0.05$.

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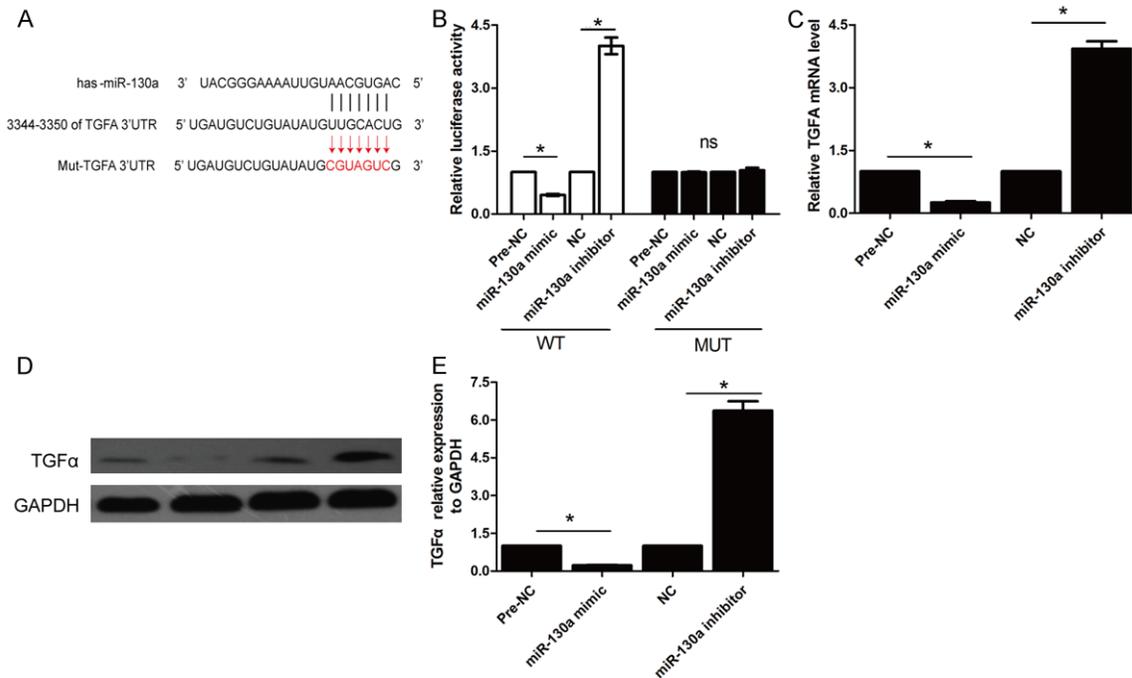


Figure 4. miR-130a regulated the expression of TGFA. A: Bioinformatics software predicted the potential binding between miR-130a and the 3' UTR of TGFA. B: Luciferase reporter assay was performed in A549 cells co-transfected with luciferase reporter containing 3' UTR of TGFA or the mutant and miR-130a mimic or miR-130a inhibitor. C: The mRNA level of TGFA in A549 cells transfected with miR-130a mimic or miR-130a inhibitor. D and E: The protein level of TGFA in A549 cells transfected with miR-130a mimic or miR-130a inhibitor. The data are represented as mean \pm SD. *vs control, $P < 0.05$.

130a was significantly decreased in the studied lung cancer cells compared to that in BEAS-2B cells. In addition, the lowest level of miR-130a was observed in A549 cells and the highest level in H1299 cells among the cancer cells. The mRNA level and protein level of TGFA were significantly higher in the four cancer cells than that in the BEAS-2B cells (Figure 2B). These data indicated that miR-130a was down-regulated and TGFA was upregulated in lung cancer cells.

MiR-130a overexpression suppresses the cell proliferation and migration of lung cancer cells

To investigate the effect of miR-130a on the function of lung cancer cells, studies with loss- or gain-of miR-130a expression was performed. MiR-130a level was increased up to 3.5-fold in the miR-130a mimic-transfected A549 cells compared with pre-ctr (pre-NC)-transfected cells (Figure 3A). MiR-130a-overexpressing cells led to decreased cell viability and cell migration detected by MTT assay and transwell migration assay, respectively (Figure 3B and 3C). On the other hand, miR-130a inhibitor pre-

vented significant inhibition effect on the level of miR-130a in H1299 cells (Figure 3D). The viability and migration of H1299 cells transfected with miR-130a inhibitor were greatly higher than that of H1299 cells transfected with NC (Figure 3E and 3F).

TGFA is a direct target of miR-130a

Based on the bioinformatics software, we found that miR-130a could potentially bind to the 3'-UTR of TGFA (Figure 4A). Then TGFA was tested for direct miR-130a targeting using a 3'-UTR luciferase-based reporter system, where the luciferase reporter vectors containing wild type 3'-UTR of TGFA (WT) or its mutant (MUT) were constructed. As shown in Figure 4B, the luciferase activity of WT UTR constructs showed remarkable down-regulation when it was co-transfected with miR-130a mimics in A549 cells. In contrast, WT UTR constructs co-transfected with miR-130a inhibitor greatly increased its luciferase activity. While the mutated 3'-UTR constructs showed no difference in luciferase activity when co-transfected with

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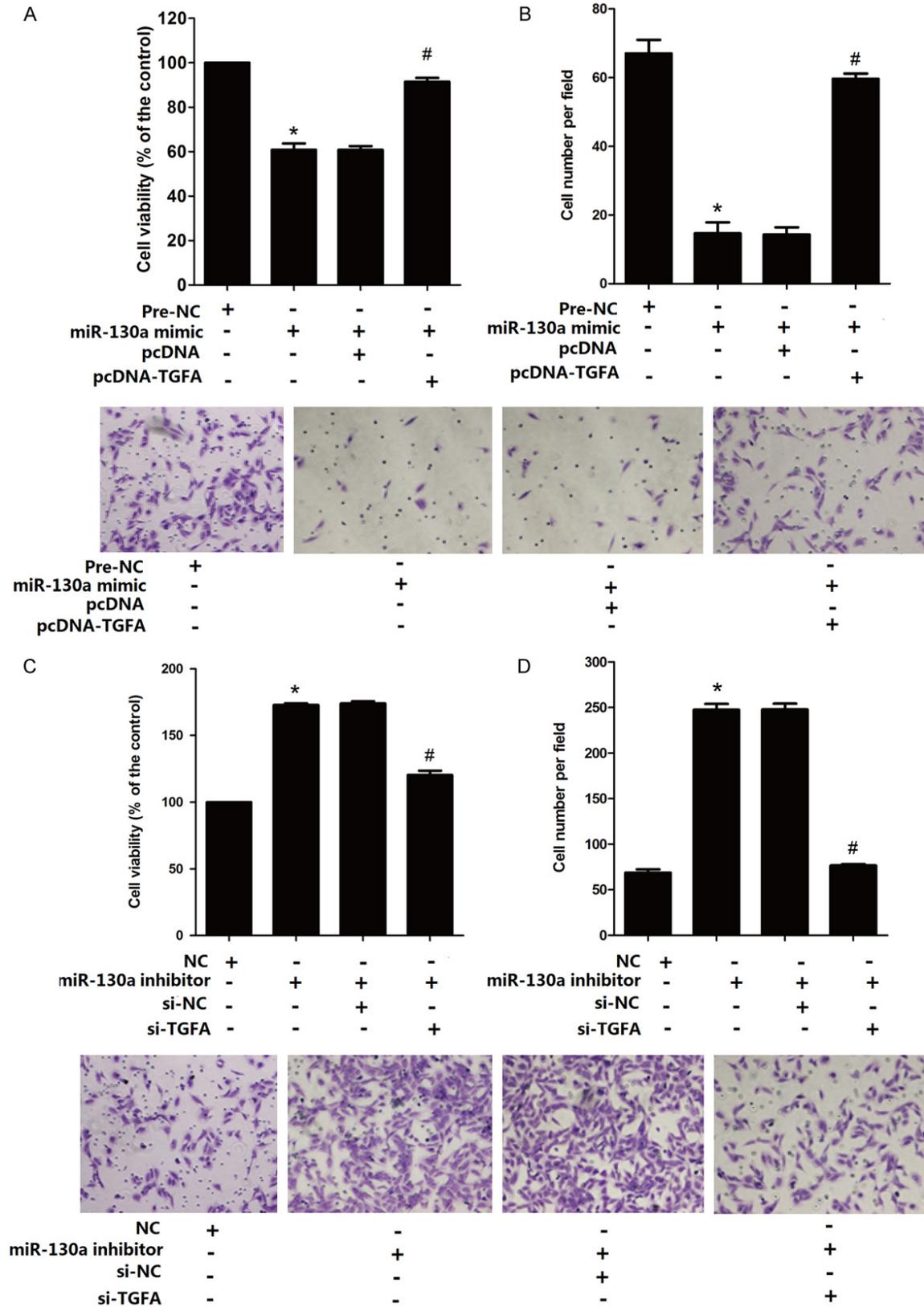


Figure 5. Effect of TGFA on the cell proliferation and migration of lung cancer cells. A: The effect of TGFA overexpression on the cell viability of A549 cells transfected with miR-130a mimic or pcDNA-TGFA. B: The effect of TGFA overexpression on the cell number per field of A549 cells transfected with miR-130a mimic or pcDNA-TGFA. C: The effect of TGFA overexpression on the cell viability of A549 cells transfected with miR-130a inhibitor or si-NC. D: The effect of TGFA overexpression on the cell number per field of A549 cells transfected with miR-130a inhibitor or si-NC.

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expression on the cell migration of A549 cells transfected with miR-130a mimic or pcDNA-TGFA. C: The cell viability was detected in H1299 cells transfected with miR-130a inhibitor or si-TGFA. D: The cell migration was examined in H1299 cells transfected with miR-130a inhibitor or si-TGFA. The data are represented as mean \pm SD. *vs Pre-NC or NC, $P < 0.05$; #vs miR-130a mimic + pcDNA or miR-130a inhibitor + si-NC, $P < 0.05$.

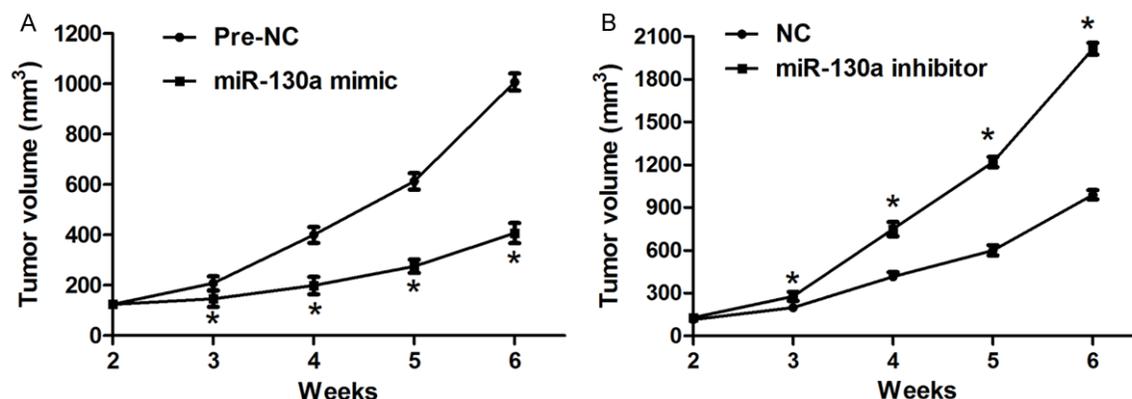


Figure 6. Effect of miR-130a on tumor growth in xenotransplanted tumor model of lung cancer cells. The tumor volume was measured in mice subcutaneously infected with A549 cells transfected with Len-miR-130a mimic (A) or infected with H1299 cells transfected with Len-miR-130a inhibitor (B). The data are represented as mean \pm SD. *vs control, $P < 0.05$.

miR-130a mimics or inhibitor (**Figure 4B**). In addition, the effect of miR-130a was also tested at the mRNA and protein level of TGFA, which displayed miR-130a overexpression-induced reductions in mRNA and protein levels for TGFA (**Figure 4C-E**). These findings indicated that TGFA was a direct target of miR-130a, negatively regulated by miR-130a at the mRNA and protein levels.

MiR-130a inhibits cell proliferation and migration via targeting TGFA in lung cancer cells

To test whether the anti-proliferative and anti-migratory effect of miR-130a overexpression was associated with down-regulation of TGFA, pcDNA-TGFA or the control pcDNA was transfected into the miR-130a-overexpressing A549 cells. TGFA overexpression significantly restored the decreased cell proliferation and migration induced by miR-130a overexpression (**Figure 5A** and **5B**). To further examine the effect of TGFA knockdown on the function of miR-130a, H1299 cells were transfected with miR-130a inhibitors or si-TGFA. As shown in **Figure 5C** and **5D**, TGFA knockdown led to the decreased cell proliferation and migration which was increased by miR-130a inhibitors. These data indicated that miR-130a inhibited cell proliferation and migration via targeting TGFA in lung cancer cells.

MiR-130a functions as a tumor suppressor in xenotransplanted tumor model of lung cancer cells

To confirm the function of miR-130a in lung cancer *in vivo*, the xenotransplanted tumor model of lung cancer cells was established through subcutaneously infected with A549 cells transfected with Len-miR-130a mimic or infected with H1299 cells transfected with Len-miR-130a inhibitor. The tumor growth was significantly suppressed in mice infected with A549 cells overexpressing miR-130a (**Figure 6A**). In addition, miR-130a knockdown greatly promoted the tumor growth in mice infected with H1299 cells (**Figure 6B**). These data show that miR-130a functioned as a tumor suppressor in xenotransplanted tumor model of lung cancer cells.

Discussion

In the present study, lower expression of miR-130a was observed in lung cancer tissues and cells compared to that in the corresponding controls. In addition, low expression of miR-130a correlates with aggressive lung cancer. MiR-130a overexpression suppressed the cell proliferation and migration of lung cancer cells. A dual luciferase reporter assay indicated that miR-130a directly negatively regulated the

expression of TGFA, which was upregulated in lung cancer tissues and cells. TGFA knockdown reversed the effect of miR-130a inhibitors on cell proliferation and migration. In xenotransplanted tumor model of lung cancer in nude mice, miR-130a overexpression significantly suppressed the tumor growth. Taken together, our results suggest that miR-130a plays an important role in the proliferation and migration of NSCLC.

Despite the great advances in understanding the function of miRNAs on cancer pathogenesis, invasion and metastasis, few miRNAs were applied in clinic for disease diagnosis and therapy, which implied an urgent need to clarify the clinical significance and function of an individual miRNA. Accumulating evidences have revealed that miR-130a played an important role in multiple kinds of tumors [19, 20]. For example, Pan et al. found that miR-130a inhibited cell proliferation, invasion and migration in human breast cancer by targeting the RAB5A [17]. MiR-130a down-regulation was associated with poor prognosis for hepatocellular carcinoma [21]. In gefitinib-sensitive NSCLC cell lines, miR-130a was overexpressed and negatively correlated with Met expression [22]. Similarly, miR-130a was found to induce TNF-related apoptosis-inducing ligand (TRAIL)-sensitivity in NSCLC by downregulating miR-221&222 [23]. In our study, we found the low expression of miR-130a in NSCLC tissues and cells, which was consistent with the results of previous studies [18, 24]. Our gain- and loss-of-function experiments further demonstrated that upregulation of miR-130a significantly reduced the viability and migration of lung cancer cells, and downregulation of miR-130a increased the number of migrated cells.

To investigate the regulatory effect of miR-130a on its target, a dual luciferase reporter assay was performed to explore the effect of miR-130a on the expression of TGFA. Our data showed that TGFA was a direct target of miR-130a. A negative correlation between miR-130a and TGFA expression was observed in lung cancer tissues. In addition, TGFA overexpression significantly restored the decreased cell proliferation and migration induced by miR-130a overexpression, which indicated that miR-130a inhibited proliferation and migration via targeting TGFA in lung cancer cells.

As an EGFR-specific ligand, TGF- α has been well known as a crucial mediator of oncogenesis and malignant progression. Accumulating evidence reveals that an abnormally high expression of TGF- α occurs in several cancers, including lung cancer [9, 25]. Chen et al. reported that miR-505 functioned as a tumor suppressor in endometrial cancer by targeting TGF- α [9]. TGF- α was also a target of miR-376c which inhibited cell proliferation and invasion in osteosarcoma [25]. In patients with advanced non-small cell lung cancer, overexpression of TGF- α related closely to the metastasis of lymph nodes and poor prognosis [26]. Wu et al. found that TGF- α neutralizing antibody could inhibit proliferation of lung adenocarcinoma cells [11]. In addition to being a target gene of miRNA, TGF- α could regulate cell proliferation and cancer progression through multiple signaling pathways. For example, TGF- α promotes osteosarcoma metastasis by ICAM-1 and PI3K/Akt signaling pathway [27]. It promoted carcinogenesis through TGF- α -EGFR-RAS-MAPK signaling pathway in liver cancer [28, 29]. Collectively, these studies provide robust evidence of a critical role for TGF- α in cancer development.

In summary, we demonstrate that miR-130a suppresses cell proliferation and metastasis in NSCLC by targeting TGFA. The newly-identified miR-130a-mediated TGFA gene silencing may facilitate a better understanding of the molecular mechanisms of lung cancer progression and provide the basis for exploring a new strategy for treatment of patients with NSCLC.

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Disclosure of conflict of interest

None.

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