Original Article

MiR-130 exerts tumor suppressive function on the tumorigenesis of human non-small cell lung cancer by targeting PTEN

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Abstract: MicroRNAs (miRNAs) have been involved in some human malignancies and correlated with tumor progression. The dysregulation of miR-130 is found in various cancers and correlated with tumor proliferation and apoptosis. However, its expression and function in non-small cell lung cancer (NSCLC) have not been investigated yet. In this study, we demonstrated that miR-130 is significantly down-regulated in NSCLC tissue samples and cell lines. Low miR-130 expression was closely associated with lymph node metastasis, late stages of disease progression and diminished survival in NSCLC patients. The up-regulation of miR-130 could significantly inhibit NSCLC cell growth and enhance cell apoptosis both in vitro and in vivo. Whereas inhibition of miR-130 exerted opposite effects. Furthermore, dual-luciferase reporter assay confirmed that PTEN was regulated by miR-130 directly, and the knock-down of PTEN markedly abrogated the anti-growth effect of miR-130. Additionally, miR-130 was found positively correlated with PTEN in NSCLC specimens. In conclusion, our results suggested that the expression of miR-130 is significantly associated with the growth and apoptosis of NSCLC cells by targeting PTEN, whilst miR-130 may be a potential therapeutic target for NSCLC treatment.

Keywords: Non-small cell lung cancer, miR-130, PTEN, proliferation, apoptosis

Introduction

Lung cancer is one of the most frequent and aggressive malignancies around the world, and more than 85% of lung cancers are classified histopathologically as NSCLC [1, 2]. Currently, despite significant progress made in surgery, radiotherapy as well as chemotherapy, the 5-year overall survival rate of lung cancer patients was just 16% for all stages [3, 4], and the underlying molecular mechanism of lung cancer has not been fully identified yet. Therefore, a better understanding of the processes and pathogenesis mechanisms involved in lung cancer at systemic, cellular, and molecular levels will help identify new diagnostic and therapeutic targets. Nowadays, along with the advance in the research on the molecular etiology and cellular immunology of lung cancer, novel anticancer strategies that focus on immunological therapy as well as genetic treatment may provide promising breakthroughs for lung cancer treatment [5-7].

MicroRNAs (miRNAs) are a class of endogenous and small non-coding RNAs with 21–23 ribonucleotides, which can induce mRNA degradation or act as repressors of translation through directly binding to a target site in the 3’-untranslated regions (UTRs) of their target genes. Existing studies found that dysregulation of miRNAs play a crucial role in a variety of cancers [8-12]. Numbers of publications have confirmed that miRNA-mediated gene involved in multiple pathological processes including cell proliferation, apoptosis, migration, survival as well as tumorigenesis [13, 14]. However, there are still numerous of undiscovered details about the role of miRNAs in the development and progression of cancers that still need to be explored.

MiR-130 was first found in regulating the respiratory syndrome virus replication and porcine reproductive [15]. A previous study demonstrated that the down-regulation of miR-130 contributed to the activation of lung fibroblasts by
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targeting IGF-1 [16]. A previous study demonstrated that miR-130 was served as a tumour promotive miRNA in most human cancer. In bladder cancer, Egawa et al. found that up-regulation of miR-130 promoted cell migration and invasion through FAK and Akt phosphorylation [17]. Duan et al. showed that the overexpression of miR-130 enhanced cell proliferation and migration by targeting TGFβR2 [18]. In addition, several studies have demonstrated the function of miR-130 in the progression of cancers [18, 19]. However, the comprehensive effect of the miR-130 on tumour progression including lung cancer has not been elucidated, and the relationship between miR-130 and tumorigenesis in NSCLC cells is currently unclear. This study was designed to investigate the functional role and the underlying molecular mechanism of miR-130 in NSCLC.

Materials and methods

Patients and tissue specimens

The study protocol was approved by the ethics committee of The First Affiliated Hospital of Jinan University. A total of 89 fresh primary NSCLC tissues and matched adjacent noncancerous lung tissues were collected at the Department of Thoracic Surgery of The First Affiliated Hospital of Jinan University. The diagnosis of all specimens was histopathologically confirmed by two pathologists according to WHO criteria for lung cancer. The clinicopathological information of the patients is shown in Table 1. No patients had received chemotherapy or radiotherapy prior to surgery. Other exclusion criteria included acute or chronic infection, dysphagia, congestive heart failure, COPD, gastrectomy and cirrhosis. For living patients, the overall survival was defined as the amount of time from the day of primary surgery to the date of death or the end of follow-up.

Cell culture

Five NSCLS cell lines (A549, SPC-A1, NCI-H460, H1299 and PC9), HEK-293T cell line and the normal human bronchial epithelial cell line (16HBE) were all purchased from the Institute of Biochemistry and Cell Biology of the Chinese Academy of Sciences (Shanghai, China). The cells were routinely cultured in Dulbecco’s Modified Eagle Medium (Gibco, NY, USA) supplemented with 10% fetal bovine serum (Gibco, NY, USA), 0.5% penicillin-streptomycin, and 1% glutamine at 37°C in a humidified environment containing 5% CO₂.

Quantitative reverse transcription polymerase chain reaction (qRT-PCR)

The total RNA was extracted by Trizol Reagent (Life Technologies, Carlsbad, CA, USA). The cDNA was produced using 1 μg of total RNA according to the protocol for miScript II RT Kit (Qiagen, Hilden, Germany). Real-time PCR was performed on the 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA). GAPDH was used as endogenous controls for mRNAs expression. The relative expression of mRNA in each sample was calculated using the 2^(-ΔΔCt) method.

Western blot analysis

Cells were harvested with 1 × radioimmunoprecipitation assay lysis buffer (Thermo Scientific) with protease inhibitor cocktail (1 ×; Sigma-
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Aldrich). Homogenates were incubated on ice for 15 min and then centrifuged at 12,000 rpm for 10 min. The supernatant containing cell proteins was collected and stored at -80°C. Cell lysates were measured by Bradford assay and then were loaded on sodium dodecyl sulfate-polyacrylamide gel electrophoresis gels. Membranes were blocked overnight at 4°C using 5% non-fat dry milk in Tris-buffered saline for 1 h and incubated with primary antibodies (Sigma, Co, USA) overnight at 4°C. Afterwards, they were probed again with respective secondary antibodies (Sigma). Band signals were visualized using an enhanced chemiluminescence kit (Pierce, Minneapolis, MN, USA). The same membrane was reprobed with the anti-β-actin antibody, which was used as the internal control.

RNA transfection, plasmid construction and lentivirus transduction

Lentiviral constructs containing hsa-miR-130 (Lenti-miR-130) and anti-miR-130 (Lenti-anti-miR-130) along with their matched negative controls (Lenti-miR-NC or Lenti-anti-miR-NC) were synthesized by Ambion (TX, USA). Short interfering (siRNA) targeting PTEN was purchased from Thermo Scientific as specific oligo pools. Briefly, when cells were grown to 40~50% confluence in 6-well plates, the cells were transfected using lipofectamineTM 2000 (Invitrogen, CA, USA) according to the manufacturer’s protocol. Complete media was changed 5 h after transfection.

Cell viability assay

Cells were seeded in each well of 96-well plates (5 × 10³ cells/well). After overnight incubation, medium was removed and replaced with fresh culture medium. After 48 h incubation, 10 μL CCK-8 solution (Dojin Laboratory, Kumamoto, Japan) was added to each well 1 h before the end of culture, then the absorbance was measured at 490 nm using a microplate spectrophotometer (Bio-Tek, USA).

Annexin V/PI staining assay

Annexin V/PI staining assay was employed to further classify NSCLC cells in early apoptosis and late apoptosis/necrosis stages. NSCLC cells were labeled with Annexin V and PI by apoptosis detection kit (Becton Dickinson, CA, USA) according to the manufacturer’s protocol. In each analysis, at least 10,000 cells were recorded. The amount of early apoptosis and late apoptosis/necrosis were determined, respectively, as the percentage of Annexin V+/PI- or Annexin V+/PI+ cells.

Apoptotic cell determination

Cells were harvested and fixed for 20 min in PBS containing 1% glutaraldehyde. Then the cells were permeabilized with 0.1% Triton X-100 and stained with 1 mmol/L of Hoechst 33258, and the nuclei were observed under a fluorescence microscope (Olympus, Tokyo, Japan).

Dual luciferase reporter assay

A pmirGLO dual-luciferase miRNA target expression vector was used for the luciferase reporter assay (Promega, Madison, WI, USA) according to the manufacturer’s recommendations. After the NSCLC cells were plated in a 96-well plate for 24 h. Then, the cells were transfected with PTEN-3’UTR reporter plasmids and miR-130 or miR-NC. Forty-eight hours later, luciferase activity was determined using a luminometer (Turner Biosystems 20/20 luminometer; Promega).

In vivo tumorigenesis

To confirm the function of miR-130 in vivo, 1 × 10⁷ logarithmically growing A549 cells stably transfected with lenti-miR-NC or lenti-miR-130 were injected subcutaneously into the right armpit of 18–26 g male BALB/c nude mice. Four days after the implantation, the mice were randomly divided into two groups, 10 mice per group. At 56 days after inoculation, all mice were sacrificed whilst the tumor were excised, weighed, photographed and subjected to western blot. The survival of nude mice was evaluated up to day 120. All animal procedures were approved by the Ethics Animal Care and Use Committee of The First Affiliated Hospital of Soochow University.

Immunolocalization of PCNA in tumor samples

Xenograft tumor tissues of all mice from both the miR-NC and miR-130 groups were embedded in paraffin and fixed with formaldehyde. Such samples was sectioned and immunostaining was performed using specific antibody against PCNA with appropriate dilution and using normal host serum for negative control, followed by staining with appropriate HRP-
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The level of miR-130 is down-regulated in NSCLC specimens and cell lines

conjugated secondary antibody. The slides were developed in 3-3'-diaminobenzidine-tetrahydrochloride solution and counterstained with a weak haematoxylin solution stain. The stained sections were counted in 10 random views at 400 × magnification by two different pathologists who remained blind to the xenograft tumor groups. Staining intensity was semiquantitated in 20 randomly selected fields per tumor, and the proliferation index was expressed as PCNA-positive cells/total cells in the view × 100%.

**Terminal deoxyribonucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) labeling assay**

Apoptotic cells were detected by using the in situ cell death assay kit from Roche diagnostics as per manufacturer’s instructions. The apoptosis index was calculated as the percentage of TUNEL-labeled cells and was obtained by counting 20 randomly chosen visual fields of the most affected tumor areas under a microscope.

**Statistical analysis**

Data were expressed as mean ± standard deviation (SD) values or percent of controls. Statistical differences were evaluated by one-way analysis of variance (ANOVA) followed by dunnett-t multiple comparisons tests. Clinico-pathological findings were compared using unpaired t-tests or Pearson X² tests. Survival analysis was evaluated by Kaplan-Meier survival plot. All calculations were performed with the SPSS software (version 15.0, SPSS, Inc.). P-values < 0.05 were considered to be statistically significant.

**Results**

To elucidate the function of miR-130 in the initiation and development of NSCLC. The initial experiment was focused on the characterization of miR-130 in 89 NSCLC tissue samples and their matched adjacent noncancerous lung tissues. Our results showed that NSCLC tissues had a significantly decreased miR-130 expression in 75% (67/89) of NSCLC specimens cases (**Figure 1A**). Meanwhile, our data also demonstrated that the level of miR-130 in NSCLC tissues was markedly down-regulated compared to that in normal lung tissues (**Figure 1B**). Next, to determine whether the level of miR-130 was similarly down-regulated in NSCLC cell lines, the relative level of miR-130 in a panel of NSCLC cell lines was measured by qRT-PCR, namely A549, SPC-A1, NCI-H460, H1299 as well as PC9, along with 16HBE, which is a normal human bronchial epithelial cell line. The results demonstrated that the expression of miR-130 was decreased in all the five NSCLC cell lines compared to its expression in 16HBE cells (**Figure 1C**). The data above sug-
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gest that the level of miR-130 was decreased in both NSCLC tissues and cell lines. Since A549 and H1299 cell lines showed the lowest and highest expression of miR-130, respectively among the five NSCLC cells lines. Therefore, A549 and H1299 cell lines were chosen for the transfection of Lenti-miR-130 or Lenti-anti-miR-130, respectively.

Association of miR-130 expression with clinicopathologic features and prognosis of NSCLC patients

To investigate whether the biological effects of miR-130 on the progression of NSCLC patients were clinically relevant. We subdivided the 89 NSCLC specimens into high miR-130 expression group (n = 44) and low miR-130 (n = 45) expression group according to the miR-130 median expression. Then the relationship between miR-130 expression and clinicopathologic features as well as prognosis of patients were statistically analyzed. As shown in Table 1, high miR-130 expression was closely correlated with higher incidence of lymph node status and advanced clinical stage. Furthermore, Kaplan-Meier analysis was carried out to evaluate the correlation of miR-130 level with the overall survival of NSCLC patients. Survival analysis revealed that the median overall survival was longer in patients with higher miR-130 level than in those with lower miR-130 expression (Figure 1D). Our data demonstrated that miR-130 is a positive prognostic factor in NSCLC patients.

Effect of miR-130 on the cell growth and apoptosis of NSCLC cells in vitro

To elucidate the potential effect of miR-130 on the tumorigenicity of NSCLC cells. The expression of miR-130 in H1299 cells with high endogenous miR-130 level was down-regulated by the transfection of anti-miR-130 or anti-miR-NC. We also promoted the expression of miR-130 in A549 cells after transfection of miR-130 or miR-NC. As a result, the expression of miR-130 was decreased significantly after the NSCLC cells were transfected with anti-miR-130. Moreover, transfection of miR-130 led to a significant increase in its expression (Figure 2A). Additionally, the effects of miR-130 or anti-miR-130 on the growth of NSCLC cells were investigated. As shown in Figure 2B, the down-regulation of miR-130 markedly accelerated the cell growth of H1299 cells. By contrast, transfected with the miR-130 in A549 cells caused a significant decrease in cell growth compared with the negative control. We further examined the cellular apoptosis by annexin V assay in miR-130-depleted H1299 and miR-130-overexpressed A549 cells. Our data showed clearly that the inhibition of miR-130 reduced cell apoptosis in H1299 cell. However, the ectopic expression of miR-130 increased the percentage of apoptotic cells in A549 cells (Figure 2C). To investigate the molecular mechanisms of miR-130 on the cell growth and apoptosis of NSCLC cells, we tested the levels of growth-related protein PCNA and apoptotic indicator PARP in NSCLC cells. Western blot analysis showed the overexpression of miR-130 in A549 cells resulted in decreased PCNA protein level and increased PARP cleavage. In contrast, a higher expression of PCNA as well as a lower expression of PARP cleavage were detected in H1299 cells after transfected with anti-miR-130 (Figure 2D). These data suggest that miR-130 plays a crucial role in the cell growth and apoptosis of NSCLC cells in vitro.

MiR-130 directly targets PTEN

To understand the molecular mechanisms by which miR-130 inhibits tumor cell growth and increases cell apoptosis in NSCLC cells. Three well-developed bioinformatics algorithms (RNAhybrid 2.1, TargetScan and PicTar) predicted that miR-130 target PTEN (Figure 3A). Next, the dual-luciferase activity assay was used to reveal whether miR-130 regulates the level of PTEN directly or indirectly. MiR-130 promoted the relative luciferase activity of the wt 3'-UTR of PTEN. However, the regulatory effect of miR-130 on luciferase activity was abolished following the co-transfection of PTEN 3'-UTR-mut in A549 cells (Figure 3B). Furthermore, the protein expression level of PTEN was assessed in NSCLC cells transfected with miR-130, anti-miR-130 and their matched controls. The down-regulation of miR-130 decreased the protein level of PTEN. Whereas the level of endogenous PTEN was increased when A549 cells were transfected with miR-130 (Figure 3C). Furthermore, we performed PTEN loss-of function experiments in A549 cells to
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investigate whether the silencing of PTEN could regulate the cell growth and apoptosis of NSCLC cells in vitro. Our results showed that the transfection with miR-130 markedly inhibited cell growth and promoted the apoptosis rate in A549 cells. Whereas the effects of miR-130 were attenuated by cotransfection with siPTEN (Figure 3D, 3E).

**MiR-130 overexpression in A549 cells provokes a decreases in NSCLC growth in vivo and an increases in mouse survival**

On account of that miR-130 plays an important role in suppressing cell growth in vitro, the next step was to investigate the effects of miR-130 on tumor growth in vivo. In order to make tumor growth easier to monitor, the subcutaneous xenograft tumor model in nude mice was developed to assess the tumor formation ability of A549/miR-NC and A549/miR-130 cells. At the end of experiment, the subcutaneous xenograft tumors were excised and weighed. As shown in Figure 4A, consistent with the results obtained from the in vitro assays, the xenograft tumor weights were indicative of a significant decrease in the A549/miR-130 group in comparison with A549/miR-NC group. Elevated level of miR-130 in A549/miR-130 tumors was observed by qRT-PCR (Figure 4B). Furthermore,
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Survival analysis showed that median survival was significantly prolonged in the A549/miR-130 group than A549/miR-NC group (Figure 4C). This prolonged survival was caused by the slower growth of tumor in the mice inoculated with miR-130-overexpressed A549 cells. Taken together, our results demonstrated that the up-regulation of miR-130 can effectively inhibit tumor growth as well as improve the prognosis of NSCLC in vivo.

Immunohistochemical (IHC) staining in vivo

Then, the immunohistochemical detection of cell proliferation marker PCNA expression in the tumor tissues was performed. As indicated in Figure 4D, the percentage of PCNA positive stained cells was significantly higher in the tumor derived from A549/miR-NC group than its expression in the A549/miR-130 group. In addition, quantitative data showed that TUNEL staining of these tissue sections indicated significant differences in the percentage of TUNEL-positive cells in the tumors derived from the A549/miR-NC group compared with the A549/miR-130 group (Figure 4E). Subsequently, the level of PTEN in the xenograft tumors of both groups was examined by western blot. Our results demonstrated the expression of PTEN was markedly increased in A549/miR-130 cells formed tumors compared with that in A549/miR-NC cells formed tumors at the translational level (Figure 4F).

The level of miR-130 is positively correlated with PTEN expression in NSCLC specimens

To address the putative relationship between miR-130 and PTEN in NSCLC tissues, both the expressions of miR-130 and PTEN mRNA were examined in the 89 cases of NSCLC specimens by qRT-PCR. As shown in Figure 5A, the expression of PTEN mRNA was down-regulated in NSCLC tissues in comparison with normal tissues. Interestingly, the abundance of miR-130 was positively correlated with that of PTEN in NSCLC specimens (Figure 5B). Investigations into such information indicated that miR-130 was closely associated with PTEN in NSCLC.

Discussion

Over the past decades, there has been no significant improvement of therapeutic agents for NSCLC treatment. Nowadays, accumulating evidences demonstrated that miRNAs are up-regulated or down-regulated in NSCLC samples, and associated with histological subtypes, tumor stages, recurrent tumors and
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Figure 4. Overexpression of miR-130 significantly suppressed the growth of NSCLC subcutaneous tumor. A: Necropsy photographs of tumor-bearing mice showing therapeutic benefit of miR-130 overexpression. B: The relative level of miR-130 was analyzed in tumor tissues by qRT-PCR. C: Survival of mice from miR-130 group was significantly prolonged in comparison with those of the miR-NC group. D: Up-regulation of miR-130 remarkably reduced PCNA positive expression in xenograft tumors. E: Apoptosis of NSCLC cells in vivo was detected by TUNEL assay. F: Western blot showing that the expression of PTEN was decreased in the subcutaneous tumors of miR-130 group. ***P < 0.001, **P < 0.01.

Figure 5. The level of PTEN is positively correlated with miR-130 expression in NSCLC specimens. A: Examination of PTEN expression in the NSCLC tissues and non-cancer tissues. B: An inversely correlation between miR-130 and PTEN expression in NSCLC tissues.

Phosphatase and tensin homologue (PTEN) is an important tumor suppressor gene in a variety of cancers [23-25]. Deletions and inactivating mutations of PTEN have been found in several solid cancers, including NSCLC [26, 27]. Additionally, trials have shown that PTEN inhibits the phosphorylation of Akt, which plays a vital role in many pathophysiological processes [28]. Recent studies have reported that PTEN gene was regulated directly by several miRNAs [26, 27]. In our model, the level of PTEN was down-regulated in NSCLC specimens, which

overall survival [20-22]. MiR-130 is found as an oncogene in most human cancer. Such function is exerted partly by its pro-proliferative and pro-growth potential [17-19]. However, to the best of our knowledge, there is no information regarding the contribution that miR-130 makes to the tumorigenesis of NSCLC. This paper utilized the genetic gain and loss of function techniques to explore the functional role of miR-130 in the tumorigenesis of NSCLC. The current study showed that the expression of miR-130 is down-regulated in NSCLC tissues and cell lines, indicating that miR-130 may not behave as a tumor promotive miRNA in all cases. In addition, lower expression of miR-130 was associated with aggressive clinicopathological features and poor prognosis in NSCLC patients. The differential expression of miR-130 was indicative of the fact that miR-130 might be involved in the carcinogenesis of NSCLC. Thus, we hypothesized that the induction of miR-130 may lead to an inhibition of cell growth in NSCLC cells.

In this study, the expression of miR-130 in NSCLC cells was interfered with an effort to investigate the effect of miR-130 on the malignant biological behaviors of NSCLC cells. Functional studies showed that the ectopic expression of miR-130 inhibited the NSCLC cell growth and enhanced cell apoptosis in vitro, whereas the cell growth and apoptosis were significantly promoted and inhibited respectively in miR-130-depleted NSCLC cells. Further trials were employed to validate the hypothesis that the function of miR-130 on the inhibition of NSCLC cell growth is sustained in vivo. In vivo results showed that the up-regulation of miR-130 in NSCLC cells significantly increases TUNEL staining and decreases PCNA immunoreactivity, which is indicative of the apoptosis and cellular proliferation within tumors. In vivo results supported our hypothesis that miR-130 functions as a tumor inhibitor in NSCLC. These in vitro results along with in vivo findings provide promising evidence that supports miR-130 as a valuable future agent for NSCLC treatment.
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was in consistent with a published report [26]. Moreover, there is a significantly positive correlation between PTEN and miR-130 in NSCLC tissues. In addition, our results showed that the anti-proliferative effect of miR-130 was almost completely abrogated by the reduced expression of PTEN. Furthermore, our current finding showed that PTEN was regulated by miR-130 directly. All in all, our data conclusively demonstrated that miR-130 inhibit cell growth and promoted cell apoptosis in NSCLC cells by targeting PTEN.

Conclusion

In summary, our findings are consistent with the hypothesis that miR-130 inhibits tumorigenesis in NSCLC cells by targeting PTEN, thereby inhibiting cell growth and promoting apoptosis of NSCLC cells both in vitro and in vivo. This work provides further evidence for the role of miR-130 in the functional regulation of NSCLC cells. In this way, promotion of miR-130 is a potential therapeutic target for NSCLC prevention and treatment in the future.

Disclosure of conflict of interest

None.

Abbreviations

miRNAs, microRNAs; NSCLC, non-small cell lung cancer; PTEN, Phosphatase and tensin homologue; UTRs, untranslated regions; qRT-PCR, quantitative reverse transcription polymerase chain reaction; siRNA, Short interfering RNA; CCK-8, cell counting kit-8; NC, negative control; PCNA, proliferating cell nuclear antigen; TUNEL, terminal deoxyribonucleotidyl transferase mediated dUTP nick end labeling; SD, standard deviation; ANOVA, analysis of variance.

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