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Effect of microRNA-143-3p-mediated CTNND1 on the biological function of lung cancer cells

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Abstract: Lung cancer poses a serious threat to human life with high incidence and miRNA is an important biomarker in tumors. This study aimed to explore the effect of miR-143-3p on the biological function of lung cancer cells and the underlying mechanism. Eighty-seven samples of lung cancer tissues and 81 samples of tumor-adjacent tissues from patients undergoing radical lung cancer surgery in our hospital were collected. The lung cancer cells and lung fibroblast cells (HFL-1) were purchased, and then miR-143-3p-mimics, miR-NC, si-CTNND1, and NC were transfected into A549 and PC-9 cells to establish cell models. MiR-143-3p and CTNND1 expression levels were measured by the qRT-PCR, Bax, Bcl-2, and CTNND1 expression levels by the Western Blot (WB), and cell proliferation, invasion, and apoptosis by the MTT assay, Transwell assay, and flow cytometry. Dual luciferase report assay was used to determine the relationship between miR-143-3p and CTNND1. In this study, miR-143-3p was lowly expressed in lung cancer and CTNND1 was highly expressed in lung cancer. The overexpression of miR-143-3p inhibited cell proliferation and invasion, promoted cell apoptosis, significantly increased Bax protein expression, and decreased Bcl-2 protein expression. The inhibition of CTNND1 led to opposite biological characteristic in cells. The dual luciferase reporter assay demonstrated that miR-143-3p was a target region of CTNND1. Such results suggest that miR-143-3p can inhibit the proliferation and invasion of lung cancer cells by regulating the expression of CTNND1 and promote the apoptosis of lung cancer cells, sott is expected to be a potential target for lung cancer.

Introduction

Lung cancer, a common clinical respiratory malignant tumor, is one of the leading causes of cancer death (Wang and Jiang, 2018), with an increasing incidence in recent period due to the changes in social environment and people's living habits, which seriously threatens human life and health (Geng *et al.*, 2017). The high incidence and the absence of clear symptoms in early stage of lung cancer make its diagnosis and treatment a big challenge (Ahmed *et al.*, 2015). The advancement in molecular biology enlightens new directions for the diagnosis and treatment of lung cancer, but the pathogenesis of lung cancer is still not very clear (Zhou *et al.*, 2019). Therefore, the exploration of its pathogenesis and the search for new molecular biology therapeutic targets are very important for lung cancer patients.

MicroRNA (miR) is a highly conserved non-coding small RNA widely distributed in eukaryotic cells, 18-25 nucleotides long, being capable of affecting the biological functions of other genes by binding to the 3'UTR end of its target gene (Liu *et al.*, 2019, Zhou *et al.*, 2017). As a member of the miR-143 family, miR-143-3p was reported in a previous study (Javier *et al.*, 2019) to be lowly expressed in various tumors and to function as a tumor suppressor. A study (Xia *et al.*, 2018) found that miR-143-3p could inhibit the proliferation and invasion of human breast cancer cells by regulating MAPK7 expression. One other study (Guo *et al.*, 2019) stated that miR-143-3p could inhibit the metastasis of colorectal cancer cells by regulating ITGA6 and ASAP3. However, the expression and mechanism of miR-143-3p in lung cancer is vague. Recombinant Catenin Delta 1 (CTNND1) is a catenin and a signaling protein of various cells, and it is believed to be a key regulator of cancer development and metastasis (Shen *et al.*, 2019). A previous study (Tang *et al.*, 2016) believed that CTNND1 could boost the proliferation and metastasis of hepatoma cells by up regulating part of the activated Wnt/β-catenin signaling. A study (Schackmann *et al.*, 2013) suggested that CTNND1 contributed to the metastasis of breast cancer cells through the activation of growth factor receptor signaling. In this study, Targetscan, an online tool for prediction of miRNA targets, was employed and it discovered a targeted binding site between miR-143-3p and CTNND1, but this tool did not tell the influence of the two factors on lung cancer cells and if they have regulation effects.

Therefore, this study explored the role of miR-143-3p and CTNND1 in lung cancer and related mechanisms, so as

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to provide a new target for the diagnosis and treatment of clinical lung cancer.

Materials and Methods

Experimental materials and reagents

Eighty-one samples of lung cancer tissues and 81 samples of tumor-adjacent tissues from 81 patients undergoing radical lung cancer surgery in our hospital from January 2016 to September 2019 were collected and stored in a liquid nitrogen tank. More details about the patients are shown in Tab. 1. Inclusion criteria: Patients diagnosed with lung cancer by pathological diagnosis. Exclusion criteria: Patients with other malignant tumors, severe liver or kidney dysfunction, or severe infectious diseases; patients rejecting to offer specimens. All patients and their families gave written informed consent. The lung cancer cell lines PC-9, Calu-1, A549 and human lung fibroblast cells (HFL-1) were purchased from Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (CBP60078, CBP60085, CBP60058, CBP60185). qRT-PCR and reverse transcription kits were from TransGen Biotech Co., Ltd. (AQ201-01, AQ202-01, Beijing, China). MTT kit was from Sangon Biotech (Shanghai) Co., Ltd. (606334). Transwell kit, PBS, and fetal bovine serum (FBS) were purchased from Gibco™ (the USA, 1142802, 10010049, 10437028). Trizol reagent was from Invitrogen™. Dual luciferase reporter assay kit was from Beijing Solarbio Science & Technology Co., Ltd. RIPA and BCA protein kits Thermo Fisher Scientific (USA). Annexin V-FITC/PI Apoptosis kit was from Jiangsu Keygen Biotech Co., Ltd. Transwell Chamber was manufactured by Corning Inc (USA). Matrigel was provided by Beijing BioDee Biotechnology Co., Ltd. Bax, Bcl-2, and β-Actin antibodies were from Cell Signaling Technology. Goat Anti-Rabbit IgG secondary antibody was from Boster Biological Technology Co., Ltd. ECL developer was purchased from Thermo Fisher Scientific. PCR instrument was from Applied Biosystems (USA, 7500). All primers were designed and synthesized by Sangon Biotech (Shanghai) Co., Ltd.

TABLE 1

General information of patients

Factors	Lung cancer patients (n = 81)
Sex	
Male	49 (60.49)
Female	32 (39.51)
Age (year)	60.45 ± 8.16
BMI kg/m^2)	23.16 ± 1.02
Pathological type	
Adenocarcinoma	21 (25.93)
Squamous cell carcinoma	25 (30.86)
Adenosquamous carcinoma	11 (13.58)
Small cell carcinoma	24 (29.63)
Pathological stage	
Stage I	34 (41.98)
Stage II	36 (44.44)
Stage IIIa	11 (13.58)

RT-PCR detection of miR-143-3p and CTNND1 expression

The lung cancer tissue and the tumor-adjacent tissues were taken out from the liquid nitrogen tank and ground for the total RNA extraction using the Trizol reagent. The purity and concentration of the RNA were detected by ultraviolet spectrophotometer. Then 5 μg of total RNA was reversely transcribed into cDNA in accordance with the kit instruction. The reaction parameters were 37°C for 15 min, 42°C for 35 min, and 70°C for 5 min. The amplification system of miR-143-3p consisted of 20 μL of total volume including 1 μL of cDNA, 0.4 μL of forward primer, 0.4 μL of reverse primer, 10 μL of 2× TransTaq® Tip Green qPCR SuperMix, 0.4 μL of Passive Reference Dye (50×), and ddH_2O to adjust the volume. Amplification conditions: pre-denaturation at 94°C for 45 s, followed by 40 cycles of denaturation at 94°C for 10 s, annealing and extension at 60°C for 45 s. CTNND1 amplification system consisted of 20 μL of total volume including 1 μL of cDNA, 0.4 μL of forward primer, 0.4 μL of reverse primer, 10 μL of 2× TransTaq® Tip Green qPCR SuperMix, 0.4 μL of Passive Reference Dye (50×), and nuclease-free water to adjust the volume. Amplification conditions: pre-denaturation at 95°C for 30 s, followed by 40 cycles of denaturation at 95°C for 10 s, annealing and extension at 60°C for 35 s. Three replicate wells were set for each sample, and the experiment was carried out for three times. U6 was used as the internal reference of miR-143-3p, and β-actin was the internal reference of CTNND1. The data were analyzed using $2^{-\Delta\Delta Ct}$.

Cell culture and transfection

The lung cancer cell line was placed in a DMEM containing 10% PBS and cultured at 37°C under 5% CO_2. When the growth of adherent reached 85%, 25% trypsin was added for digestion. After digestion, the cell subculture was performed. Then the expression of miR-143-3p and CTNND1 mRNA was detected. The detection of miR-143-3p and CTNND1 mRNA expression demonstrated that the expression of miR-143-3p was lower in PC-9 and A549 cell lines than in the other two cell lines, so these two cell lines were selected for transfection and subsequent experiments. Lung cells were separately transfected with overexpressed miR-143-3p-mimics, miR negative control (miR-NC), targeted inhibited CTNND1 RNA (si-CTNND1), and negative control RNA (NC). The cells were transfected using Lipofectamin 2000 kit strictly in accordance with the kit instructions.

MTT assay for cell proliferation

After 48 h of transfection, the PC-9 and A549 cell lines were seeded into a 96-well plate, with 100 μL of cell solution in each well at a cell density of 3×10^4 cells/mL, and then incubated at 37°C. Then 20 μL of MTT solution was added to each well at the time of incubation for 24, 48, 72, and 96 h. Each time the MTT solution was added, the cell lines were incubated for 4 h before 150 μL of dimethyl sulfoxide was added and shaken for 10 min. Finally, the optical density was measured using a microplate reader at a wavelength of 490 nm to detect cell proliferation at each time points. The detection was repeated 3 times.

Detection of cell invasion by Transwell

Totally 3×10^5 of cell transfected for 24 h were collected and seeded on a 6-well plate, and then PBS washing was performed for 2 times. The cell suspension was seeded into the upper chamber and 200 μL of DMEM medium was added, 500 mL DMEM containing 20% FBS was added to the lower chamber. The whole system was cultured at 37°C for 48 h, and then the medium and cells in the upper chamber that did not pass through the surface of the membrane were wiped, followed by 3 times of washing with PBS, 10 min of fixation with paraformaldehyde, and 3 times of washing with double distilled water. The system was stained with 0.5% crystal violet when it got dried, and then the cell invasion was observed under a microscope.

Annexin V/PI detection

The transfected cells were digested with 0.25% trypsin and then washed twice with PBS. Next, 100 μL of binding buffer was added to prepare a suspension at a density of 1×10^6 cells/mL, followed by addition of annexin V-FITC and PI to perform the incubation at room temperature in the dark. Then the FC500MCL flow cytometry detection was performed three times to obtain the mean value.

Western blot detection

The RIPA lysis was perform on cells in each group to extract the total protein, and the protein concentration was determined by BCA method. The protein was adjusted to a concentration of 4 μg/μL and then separated by 12% SDS-PAGE and transferred to the PVDF membrane. The protein was stained by the Ponceau Sand blocked with 5% skim milk powder at 4°C overnight. After that, Bax (1:500), Bcl-2 (1:500), CTNND1 (1:500), and β-actin primary antibody (1:500) were added and the whole system was blocked at 4°C overnight. The primary antibody was washed and the horseradish peroxidase-labeled goat anti-rabbit secondary antibody (1:1000) was added to perform the incubation at 37°C for 1 h, followed by three times of PBS rinse, 5 min each time. The excess liquid on the film was dried with a filter paper, and the ECL was conducted to perform color development. Finally, the gray values were analyzed.

Detection of the target gene

The target gene of miR-143-3p was predicted using Targetscan7.2. CTNND1-3'UTR wild type (Wt), CTNND1-3'UTR mutant type (Mut), miR-143-3p-mimics, and miR-NC were transferred into PC-9 and A549 cells using Lipofectamine™ 2000 kit. After 48 h of transfection, the luciferase activity was determined using a dual luciferase reporter assay kit (Promega).

Statistical methods

The statistical analysis was performed using the SPSS20.0 and the data were visualized using the GraphPad 7. The independent t test was employed for comparison between two groups, the one-way ANOVA for comparison between multiple groups, and the LSD-t test for pairwise comparison. The expression at multiple time points was analyzed by the repeated measurement analysis of variance. The Bonferroni test was used for post-hoc test, and Pearson analysis was used to observe the correlation between miR-143-3p and CTNND1 in tissue samples. $p < 0.05$ indicated a statistical difference.

Results

Expression of miR-143-3p and CTNND1 in lung cancer tissues

The results of RT-PCR revealed that lung cancer tissues showed significantly lower miR-143-3p expression and significantly higher CTNND1 expression than tumor-adjacent tissues (both $p < 0.05$), and the expression of miR-143-3p was negatively correlated with CTNND1 expression ($r = -0.881$, $p < 0.05$; Fig. 1).

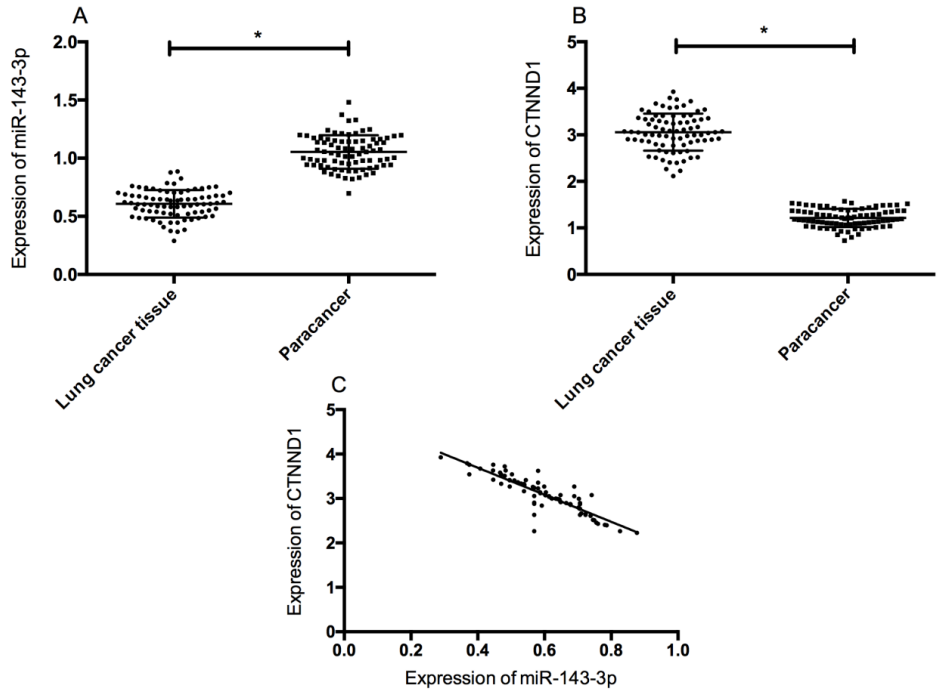

FIGURE 1. Expression of miR-143-3p and CTNND1 in lung cancer tissues. (A) MiR-143-3p expression was significantly lower in lung cancer tissues than in tumor-adjacent tissues. **(B)** CTNND1 expression was significantly higher in lung cancer tissues than in tumor-adjacent tissues. **(C)** The expression of miR-143-3p was negatively correlated with CTNND1 expression ($r = -0.881$, $p < 0.05$).

Effect of miR-143-3p on the biological function of lung cancer cells

According to the detection of miR-143-3p expression, the expression of miR-143-3p was significantly lower in PC-9, Calu-1, and A549 cells than in lung fibroblast cells (HFL-1) ($p < 0.05$). By transfecting PC-9 and A549 cells with miR-143-3p-mimics and miR-NC, it was found that the expression of miR-143-3p was notably higher in Calu-1 and A549 cells transfected with miR-143-3p-mimics than in Calu-1 and A549 cells transfected with miR-NC. The biological function of cells in the two groups was detected. Cells transfected with miR-143-3p-mimics had notably higher ability of proliferation and invasion, and notably lower apoptosis rate than cells transfected with miR-NC. Cells transfected with miR-143-3p-mimics had notably higher expression of Bax protein and lower Bcl-2 protein than cells transfected with miR-NC (Fig. 2).

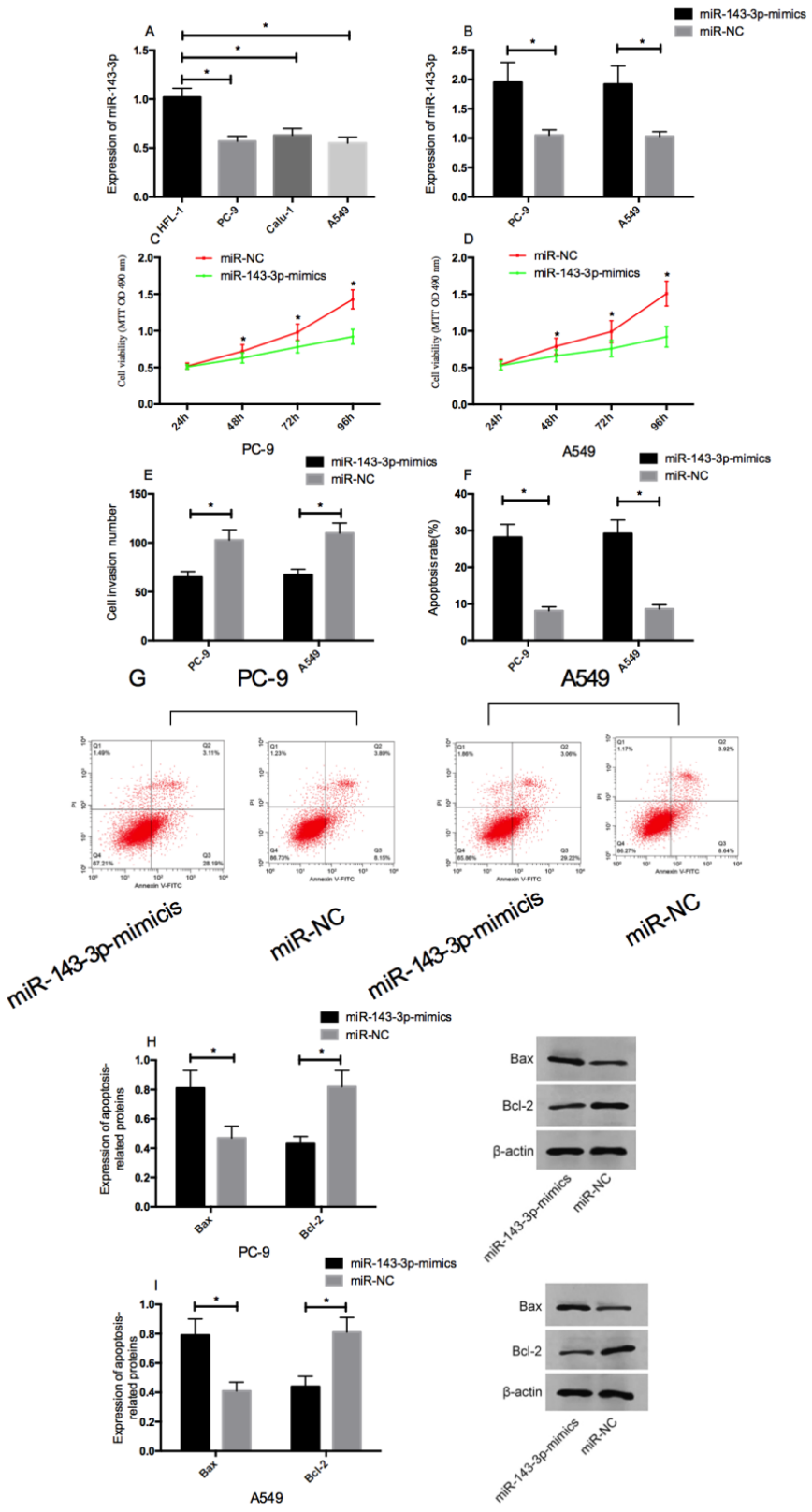

FIGURE 2. Effect of miR-143-3p on the biological function of lung cancer cells. **(A)** miR-143-3p expression in lung cancer cell lines. **(B)** MiR-143-3p expression in lung cancer cells after transfection. **(C, D)** The proliferation of lung cancer cells transfected with miR-143-3p-mimics. **(E)** The invasion of lung cancer cells transfected with miR-143-3p-mimics. **(F)** The apoptosis rate of lung cancer cells transfected with miR-143-3p-mimics. **(G)** Diagram of flow cytometry apoptosis. **(H, I)** Cells transfected with miR-143-3p-mimics had notably higher expression of Bax protein and lower Bcl-2 protein than cells transfected with miR-NC. * $p < 0.05$.

Effect of CTNND1 on the biological function of lung cancer cells

According to the detection of CTNND1 expression, the expression of CTNND1 was significantly higher in PC-9, Calu-1, and A549 cells than in lung fibroblast cells (HFL-1) ($p < 0.05$). By transfecting PC-9 and A549 cells with si-CTNND1 and Si-NC, it was found that the expression of CTNND1 was notably lower in PC-9 and Calu-1 cells transfected with si-CTNND1 than in PC-9 and Calu-1 cells transfected with Si-NC. The biological function of cells in the two groups was detected. Cells transfected with si-CTNND1 had notably lower ability of proliferation and invasion, and notably higher apoptosis rate than cells transfected with Si--NC. Cells transfected with si-CTNND1 had notably higher expression of Bax protein and lower Bcl-2 protein than cells transfected with Si-NC (Fig. 3).

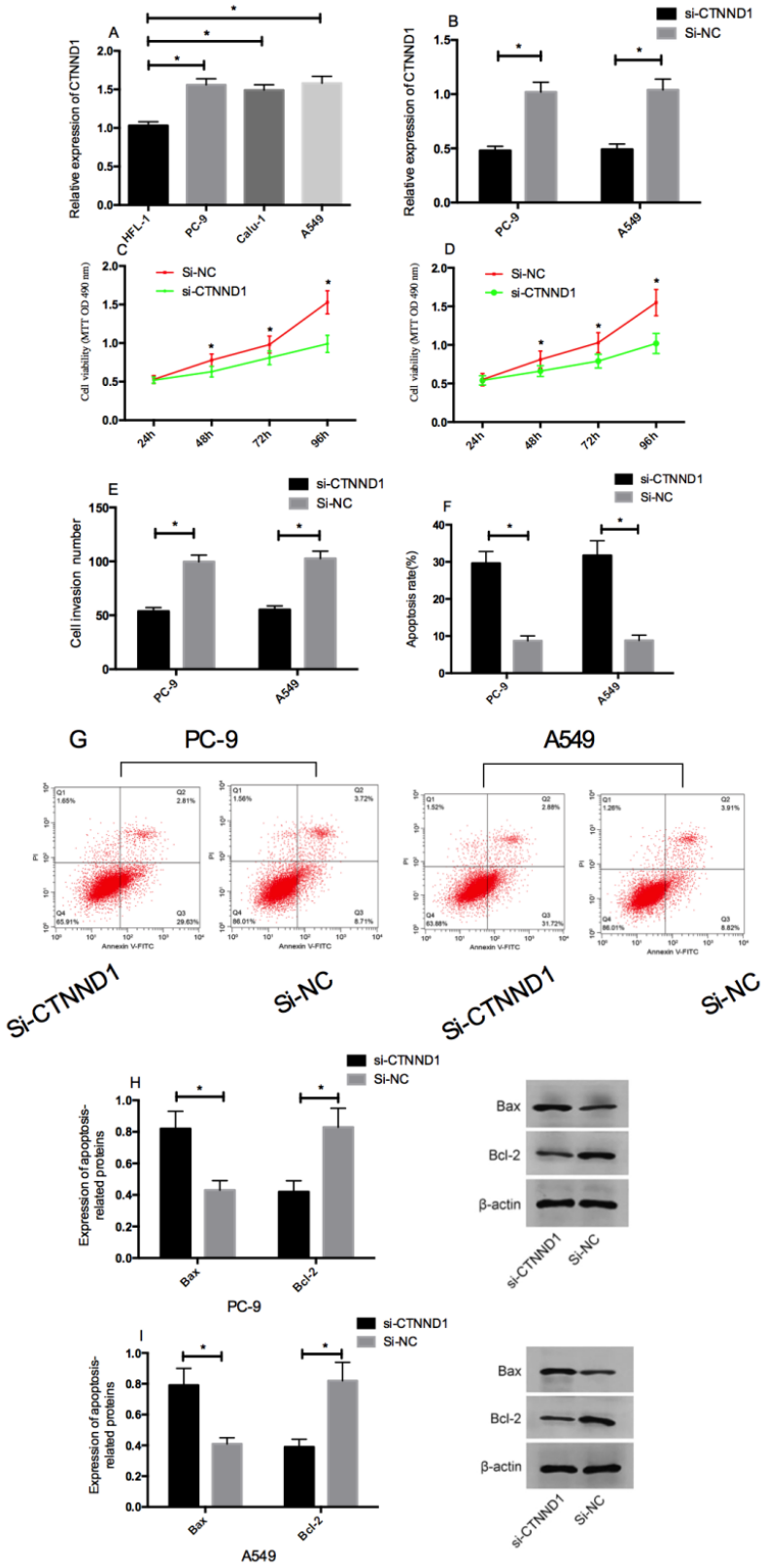

FIGURE 3. Effect of CTNND1 on the biological function of lung cancer cells. **(A)** CTNND1 expression in lung cancer cell lines. **(B)** CTNND1 expression in lung cancer cells after transfection of si-CTNND1. **(C, D)** The proliferation of lung cancer cells with down-regulated CTNND1 expression. **(E)** The invasion of lung cancer cells with down-regulated CTNND1 expression. **(F)** The apoptosis rate of lung cancer cells with down-regulated CTNND1 expression. **(G)** Diagram of flow cytometry apoptosis. **(H, I)** Expression of Bax and Bcl-2 proteinsin lung cancer cells with down-regulated CTNND1 expression. * $p < 0.05$.

MiR-143-3p gene identification

To further verify the relationship between miR-143-3p and CTNND1, Targetscan7.2 was employed to predict the downstream target gene of miR-143-3p and it discovered the presence of a targeted binding site between CTNND1 and miR-143-3p. Then the double luciferase reporter assay was performed, finding that the miR-143-3p overexpression greatly decreased the luciferase activity of CTND1-3'UT Wt ($p < 0.05$), but had no effect on the luciferase activity of CTNND1-3'UTR Mut ($p > 0.05$). WB assay showed that the expression of CTNND1 protein in PC-9 and A549 cells transfected with miR-143-3p-mimics was significantly decreased ($p < 0.05$) (Fig. 4).

Discussion

As a common respiratory malignant tumor, lung cancer shows an increasingly high morbidity and mortality in recent years (Chetty *et al.*, 2010). About two-thirds of patients are already with advanced tumors or tumor metastasis at the time of diagnosis due to the absence of clear symptoms in the early stage, which deprives most patients of chances of surgery and effective treatment (Xu *et al.*, 2016; Göke *et al.*, 2012). With recent development of molecular biology, miRNA, a regulatory gene, has been discovered to play an important role in the occurrence and development of a variety of tumor diseases (Sun *et al.*, 2019). MiR-143-3p is found to be down-regulated in various tumors such as laryngeal carcinoma (Wang *et al.*, 2017) and endometrial cancer (Chen *et al.*, 2019), but its mechanism of action in lung cancer has not been clarified.

In this present study, the expression of miR-143-3p was lower in lung cancer tissues than in tumor-adjacent tissues. We also detected the expression of miR-143-3p in lung cancer cells and normal lung cells, and the results were similar to the expression in tissues. One previous study (Zhang *et al.*, 2016) found that miR-143 had a low expression in non-small cell lung cancer tissues, which is similar to our findings. We speculated that miR-143-3p may play a role as a tumor suppressor gene in lung cancer, so we made miR-143-3p over-expressed in PC-9 and A549 cells. The results demonstrated that the over-expression of miR-143-3p led to inhibited proliferation and invasion of PC-9 and A549 cells and a higher apoptosis rate. Such results suggest that miR-143-3p functions as a tumor suppressor in lung cancer. It may inhibit the further development of lung cancer by suppressing the proliferation and invasion of lung cancer cells and promoting apoptosis of lung cancer cells. Such results also indicate that the low expression of miR-143-3p may induce the occurrence and development of tumors. A study reported (Yang *et al.*, 2015) that miR-143-3p could inhibit the proliferation of tumor cells and promote the apoptosis, which is consistent with the results of this study. However, the specific mechanism of miR-143-3p in lung cancer remains unclear.

In general, miRNAs regulate tumor cells by acting on their target genes (Jin *et al.*, 2018). We found a targeting relationship between miR-143-3p and CTNND1 through the TargetScan database analysis. CTNND1 is also known as p120-catenin, and a study (Kourtidis *et al.*, 2013) stated that CTNND1 could work as a cancer-promoting gene by regulating various signaling pathways. A former study (Greco *et al.*, 2010) found that CTNND1 was highly expressed in

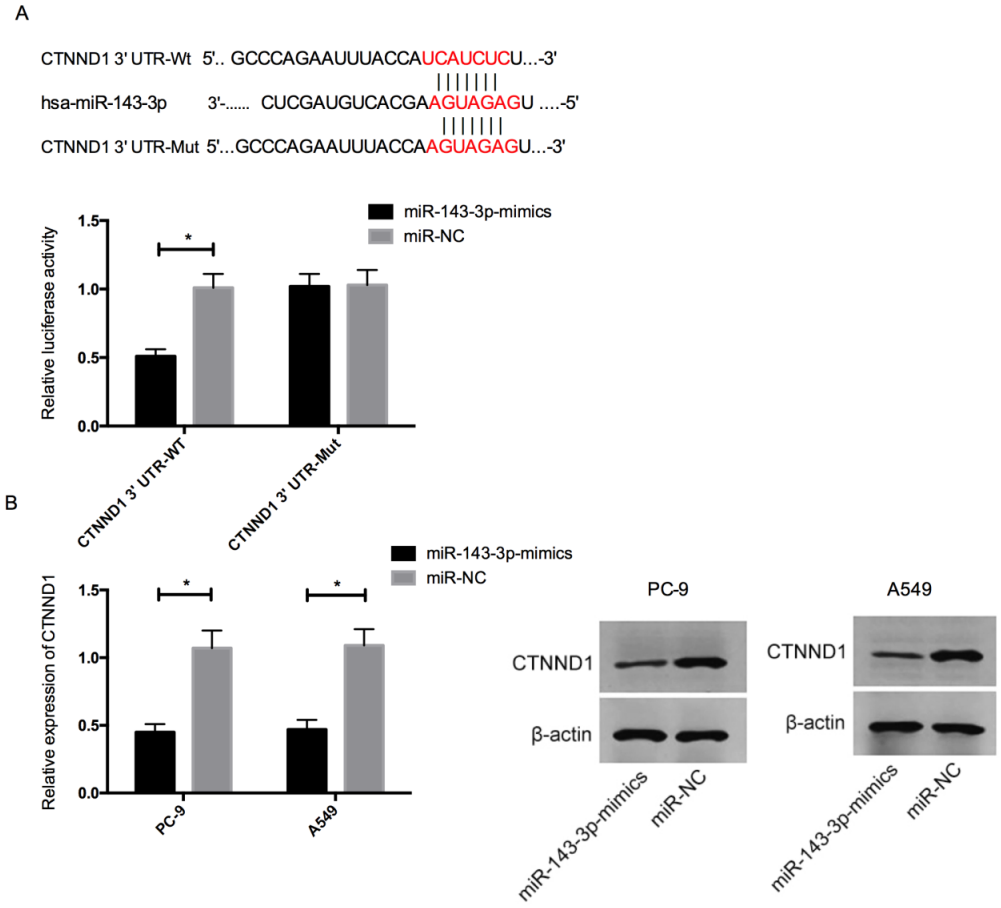

FIGURE 4. Dual luciferase report. (A) There is a binding site between miR-143-3p and CTNND1 according to the relative luciferase activity-double luciferase reporter assay. **(B)** CTNND1 protein expression was significantly down-regulated in lung cancer cells after transfection ($p < 0.05$).

colorectal cancer cells and may play its role by regulating the Wht pathway. This study also observed a high expression of CTNND1 in lung cancer tissues, suggesting that CTNND1 may also function as a cancer-promoting gene in lung cancer. We transfected Si-CTNND1 into PC-9 and A549 cells and discovered that inhibition of CTNND1 expression in lung cancer cells can suppress the proliferation and invasion of lung cancer cells and promote the apoptosis of lung cancer cells. Such results suggest the role of CTNND1 as a cancer-promoting gene in lung cancer. One study (Wu *et al.*, 2016) proved that the inhibition of CTNND1 expression in osteosarcoma cells could control cell invasion and migration. A previous study (Kantidze *et al.*, 2009) identified the transcription factor Kaiso as a specific binding partner of CTNND1 and believed that the influences of CTNND1 on the tumor occurrence and development were achieved by regulating the classical Wnt/β-catenin signaling pathway through binding to Kaiso. But the certain signaling pathway through which CTNND1 performs its function in lung cancer is still under investigation.

In summary, lowly expressed in lung cancer, miR-143-3p can control the proliferation and invasion of lung cancer cells by inhibiting the expression of CTNND1 and promote cell apoptosis. This study has some limitations. For example, we failed to figure out the way how miR-143-3p-mediated CTNND1 affects lung cancer cells. Besides, we did not explore the clinical value of miR-143-3p in lung cancer. Such problems will be addressed in-depth in future experiments.

Conflicts of Interest

The authors declare that they have no conflicts of interest to report regarding the present study.

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