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MiR-124 changes the sensitivity of lung cancer cells to cisplatin through targeting STAT3

M.-M. QI[1], F. GE[2], X.-J. CHEN[3], C. TANG[4], J. MA[1]

[1]School of Basic Medicine, Nanjing University of Chinese Medicine, Nanjing, China
[2]Department of Gastroenterology, Haian Hospital of Traditional Chinese Medicine, Haian, China
[3]Hanlin College, Nanjing University of Chinese Medicine, Nanjing, China
[4]Department of Respiration, Jiangsu Province Hospital on Integration of Chinese and Western Medicine, Nanjing, China

Abstract. – OBJECTIVE: To investigate the role of micro ribonucleic acid (miR)-124 in drug resistance of non-small cell lung cancer (NSCLC), and to explore its underlying mechanism.

MATERIALS AND METHODS: The expression levels of miR-124 and signal transducer and activator of transcription 3 (STAT3) in maternal A549 cells and cisplatin-resistant A549/DDP cells were detected via quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and Western blotting. A549 and A549/DDP cells were transfected with miR-124 mimics and miR-124 negative control (NC), respectively. Changes in the expression of STAT3 were detected via qRT-PCR and Western blotting. Meanwhile, the sensitivity of cells transfected with miR-124 mimics to cisplatin was detected via methyl thiazolyl tetrazolium (MTT) assay. The effects of miR-124 on the apoptosis, invasion and metastasis of cells were detected via flow cytometry, wound healing assay and transwell assay, respectively. Moreover, wild-type and mutant-type STAT3 luciferase reporter plasmids were co-transfected with miR-124 mimics or miR-124 NC. Luciferase activity was analyzed using the dual-luciferase reporter gene assay.

RESULTS: QRT-PCR and Western blotting revealed that the expression level of miR-124 in A549/DDP cells was significantly lower than that of A549 cells. However, the expression level of STAT3 in A549/DDP cells was significantly higher than that of A549 cells. Overexpression of miR-124 remarkably reduced the expression level of STAT3 in A549/DDP cells, increased the sensitivity of A549/DDP cells to cisplatin, and inhibited the invasion and metastasis capacities of cells. In addition, luciferase reporter gene assay demonstrated that miR-124 could negatively regulate the protein expression of STAT3 by binding to its 3'-untranslated region (UTR).

CONCLUSIONS: MiR-124 regulates the sensitivity of NSCLC to cisplatin. Moreover, it inhibits the invasion and metastasis capacities through targeting STAT3, which can serve as a therapeutic target for cisplatin-based chemotherapy resistance of NSCLC.

Key Words:
MiR-124, STAT3, Non-small cell lung cancer (NSCLC), Cisplatin, Drug resistance.

Introduction

Lung cancer, as one of the most common malignant tumors, has become the malignancy with highest morbidity and mortality rates worldwide. It is estimated that there are more than 1.5 million deaths of lung cancer around the world every year, accounting for 1/4 of all tumor deaths[1]. Meanwhile, lung cancer is also the most prevalent in males, with a low 5-year survival rate and a high fatality rate. Chemotherapy is an important treatment for advanced non-small cell lung cancer (NSCLC). However, it often fails clinically due to drug resistance[2,3]. Cisplatin is a commonly-used chemotherapeutic drug in the treatment of lung cancer. The damage of cisplatin to lung cancer cells is caused by forming platinum-DNA deoxyribonucleic acid) complex and affecting DNA replication as well as transcription in cells. This may eventually activate the apoptotic pathway and lead to cell apoptosis[4]. However, drug resistance is inevitable in the application of cisplatin. Researches[5,6] have demonstrated that regulation of drug metabolism, changes in drug targets, as well as genetic or epigenetic abnormality of key genes in cell repair and apoptotic pathways, can lead to the formation of drug-resistant phenotype in tumors. McNally et al[7] have found that micro ribonucleic acid (miRNA) regulates these key genes through a variety of pathways, thus leading to drug resistance in tumors. MiRNA belongs to the endogenous, non-coding regulatory RNA family, which is derived from gene transcript of non-coding protein

Corresponding Author: Jian Ma, MD; e-mail: 718171345@qq.com

in the genome. MiRNA regulates gene expression at the post-transcriptional level. Furthermore, it inhibits the translation or causes the degradation of target genes mainly through incomplete complementary pairing with the 3'-untranslated region (3'-UTR) of target genes. This may eventually induce gene silencing[8]. As one of the most investigated miRNAs currently, miR-124 has been proved to regulate the sensitivity of various tumors to chemotherapeutic drugs[9]. However, no research has investigated the correlation between miR-124 and cisplatin resistance of NSCLC yet. Therefore, the aim of this study was to investigate the relationship between miR-124 and cisplatin resistance, and to explore its possible underlying mechanism. We might provide experimental basis and theoretical guidance for the treatment of patients with drug-resistant lung cancer.

Materials and Methods

Cell Culture

Maternal A549 cells were purchased from the Shanghai Cell Bank of the Chinese Academy of Sciences (Shanghai, China). Drug-resistant A549/DDP cells were produced *via* cisplatin concentration gradient induction. The specific induction method was as follows: after cell passage and adherence to the wall, cisplatin was added to incubate A549 cells until the final concentration of 0.5 nM. When cells covered 80% of the culture dish, they were passaged to make the final concentration of 1 nM. Through repeated culture and passage, A549/DDP cells that could grow in 100 nM cisplatin were finally obtained. A549 and A549/DDP cells were cultured in the medium containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA), 1% penicillin-streptomycin double-antibody solution and 1% non-essential amino acids in a 37°C, 5% CO_2 incubator.

Cell Transfection

MiR-124 mimics and miR-124 NC were purchased from GenePharma (Shanghai, China). A549 and A549/DDP cells were transfected with miR-124 mimics or miR-124 NC for 72 h according to the instructions of Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). Specific sequences were as follows: miR-124 mimics forward: 5'-CGUGUUCACAGCGGACCUUGAU-3', reverse: 5'-AUCAAGGUCCGCUGUGAACACG-3', miR-124 NC forward: 5'-UUCUCCGAACGUGUCAGU-3', reverse: 5'-ACGUGACACGUUCGGAGA A-3'.

Luciferase Reporter Gene Assay

A549/DDP cells were first inoculated into 12-well plates at a density of 1×10^5 cells per well. The corresponding transfection reagents were prepared according to specific instructions, including 50 ng wild-type or mutant-type 3'-UTR reporter plasmids, miR-124 mimics or miR-124 NC in a final concentration of 20 nM, and Lipofectamine 2000. When the confluence was up to 70%, A549/DDP cells were transfected with related mixtures. 48 h after transfection, luciferase activity was detected using the dual-luciferase reporter gene kit (Beyotime, Shanghai, China).

Fluorescence Quantitative Reverse Transcription-Polymerase Chain Reaction (qRT-PCR)

Total messenger RNA (mRNA) in cells was extracted in strict accordance with TRIzol reagent (Invitrogen, Carlsbad, CA, USA). Subsequently, extracted mRNAs were reversely transcribed into complementary deoxyribonucleic acid (cDNA) under the following conditions: 25°C for 10 min, 50°C for 30 min, and 85°C for 5 min. QRT-PCR was then performed using the fluorescence qRT-PCR kit (TaKaRa, Otsu, Shiga, Japan). Primers used in this study were as follows: miR-124 forward: 5'-CGGTAAGGCACGCGGTGA-3', reverse: 5'-AGTGCGAACTGTGGCGAT-3'. signal transducer and activator of transcription 3 (STAT3) forward: 5'-ATCACGCCTTCTACAGACTGC-3', reverse: 5'-CATCCTGGAGATTCTCTACCACT-3'. glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (internal reference) forward: 5'-GGTCTCCTCTGACTTCAACA-3', reverse: 5'-AGCCAAATTCGTTGTCATAC-3'. Specific qRT-PCR conditions were: 95°C for 5 min, 95°C for 15 s, 60°C for 1 min, for a total of 40 cycles. The temperature in melting curve was set as 60-95°C, and 3 replicates were set for each sample.

Cell Proliferation Assay

Cells in the logarithmic growth phase were digested and inoculated into 96-well plates at a density of 8×10^3 cells/well. The volume of complete medium was 200 μL. After treating with different concentrations of cisplatin for 48 h, the proliferation of A549 and A549/DDP cells was detected by methyl thiazolyl tetrazolium (MTT) kit (Sigma-Aldrich, St. Louis, MO, USA). Meanwhile, the proliferation of A549/DDP cells at 24 h, 48 h, 72 h and 96 h after transfection with miR-124 mimics or miR-124 NC was also detected,

respectively. Absorbance value at the wavelength of 450 nm was detected by a reader plate, and the cell growth curve was drawn.

Colony Formation Assay

Cells in the logarithmic growth phase were seeded into 6-well plates (500/well) and cultured for 24 h. When the cells adhered to the wall and well spread, the original culture medium was replaced with drug-free medium for 12-day culture. Subsequently, the cells were washed with phosphate-buffered saline (PBS) (Beyotime, Shanghai, China), and fixed with 10% formaldehyde. Finally, Giemsa staining was performed, and the cells were captured. Colony formed by more than 50 cells indicated 1 clone. The experiment was repeated for 3 times.

Flow Cytometry

After transfection with miR-124 mimics or miR-124 NC, A549/DDP cells were digested into single-cell suspension, and the cell concentration was adjusted to 5×10^3/mL. 1 mL cell suspension was centrifuged at 1000 rpm for 10 min at 10°C, and the supernatant was discarded. Next, 1 mL cold PBS was added and gently vibrated. After centrifugation at 1000 rpm for 10 min at 4°C, the supernatant was discarded, and the cells were re-suspended in the binding buffer. Subsequently, 10 μL Annexin V-fluorescein isothiocyanate (FITC) and 5 μL propidium iodide (PI) were added and mixed evenly, followed by incubation at room temperature for 10 min in dark. Finally, flow cytometry was performed. The experiment was repeated for 3 times, and the apoptotic rate was calculated.

Western Blotting

Total protein was extracted from cells using the lysis solution. 30 g/well protein sample was separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) under 350 mA, and transferred onto activated polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Then, the PVDF membranes were sealed with 5% skim milk powder for 1 h, and incubated with the primary antibody at 4°C for 10 h. After washing with Tris-buffered saline with Tween-20 (TBST) (Beyotime, Shanghai, China), the membranes were incubated with the horseradish peroxidase (HRP)-labeled secondary antibody at room temperature for 1 h. After washing with TBST, the image was developed, and the gray value was analyzed using Image J software. Relative expression of target protein = optical density $_{\text{target protein}}$/optical density $_{\beta\text{-actin}}$.

Wound Healing Assay

Cells were inoculated into 6-well plates and cultured under appropriate conditions. When 90-100% cells were fused, the 6-well plate was scratched uniformly using a 10 μL spearhead vertically to the bottom of plate. Floating cells were removed by PBS washing, and serum-free medium was added, followed by incubation. At 0 and 48 h after scratching, the migration distance in the cell scratch area was observed under a microscope. Several fields of each sample were randomly selected for photographing.

Transwell Migration and Invasion Assay

Transfected cells were collected, and serum-free medium was added into the upper chamber. Subsequently, 1×10^5 cells were added into the upper chamber, and the upper chamber was placed into the plate. 10% FBS medium in the plate was used for induction. Cell migration capacity (without Matrigel) was detected after culture for 24 h, and cell invasion capacity (Matrigel paved in the upper chamber) was detected after culture for 48 h. After culture, cells in the upper chamber were brushed off, and those in the lower chamber were treated with crystal violet staining and photographed. The number of cells was counted in each group.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 19.0 software (IBM, Armonk, NY, USA) was used for all statistical analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). *t*-test was used to compare the differences between two groups, and one-way analysis of variance was applied to compare the differences among groups, followed by LSD (Least Significant Difference) post-hoc test. $p<0.05$ was considered statistically significant.

Results

A549/DDP Cells Were More Resistant to Cisplatin, and miR-124 Expression Was Down-Regulated in A549/DDP Cells

To verify the successful induction of cisplatin resistance in A549/DDP cells, the inhibitory degree of different concentrations of cisplatin on maternal A549 cells and A549/DDP cells was

detected via MTT assay. Results revealed that the half maximal inhibitory concentration (IC50) of cisplatin on A549 cells and A549/DDP cells was 9 μM and 50 μM, respectively. Compared with A549 cells, A549/DDP cells displayed significant drug resistance. Meanwhile, drug resistance of A549 cells was 5.5 times as high as A549/DDP cells, showing a statistically significant difference ($p<0.05$) (Figure 1A). After confirming the resistance of A549/DDP cells to cisplatin, the expression level of miR-124 in A549/DDP and A549 cells was further detected via qRT-PCR. Results indicated that the expression of miR-124 in A549/DDP cells was significantly lower than that of A549 cells ($p<0.05$) (Figure 1B).

Up-Regulation of miR-124 Changed the Sensitivity of A549/DDP Cells to Cisplatin and Inhibited its Proliferation Capacity

The expression level of miR-124 in drug-resistant cells was significantly down-regulated. To verify the effect of miR-124 on drug resistance, we up-regulated miR-124 expression in A549/DDP cells to observe the sensitivity of cells to cisplatin. QRT-PCR results manifested that the expression level of miR-124 in cells transfected with miR-124 mimics was significantly up-regulated when compared with those transfected miR-124 NC (Figure 2A). Subsequently, transfected A549/DDP cells were co-incubated with different gradient concentrations of cisplatin, and its inhibitory rate on cells was observed. Results showed that the sensitivity of cells to cisplatin in the miR-124 mimics group was significantly higher than that of the control group. IC50 of cisplatin in the miR-124 mimic group was 15 μM, which was remarkably declined when compared with the control group. This indicated that up-regulation of miR-124 restored the sensitivity of A549/DDP cells to cisplatin (Figure 2B). Furthermore, the effect of miR-124 on cell proliferation was explored. Results of MTT assay revealed that after cell transfection, the proliferation of cells in the miR-124 mimic group was significantly lower than that of the control group. Colony formation assay also demonstrated that the number of proliferative cells in the miR-124 mimic group was significantly less than that of the control group after 12 d (Figure 2C-2D). The above results all indicated that up-regulation of miR-124 inhibited the proliferation capacity of A549/DDP cells.

Up-Regulation of miR-124 Promoted the Apoptosis of A549/DDP Cells

To investigate the mechanism of miR-124 up-regulation in inhibiting A549/DDP cell proliferation, we first explored the effect of miR-124 up-regulation on cell apoptosis. The apoptotic rate was detected *via* flow cytometry. Results revealed that the apoptotic rate of the miR-124-mimics group was 13.6%, which was significantly increased compared with that the control group (Figure 3A-3B). Furthermore, Western blotting found that after transfection with miR-124 mimics, the expression levels of Bcl-2 associated X protein (Bax), cleaved caspase-9 and cleaved poly-ADP-ribose polymerase (PARP) were significantly up-regulated, whereas the expression of Bcl-2 was remarkably down-regulated. The

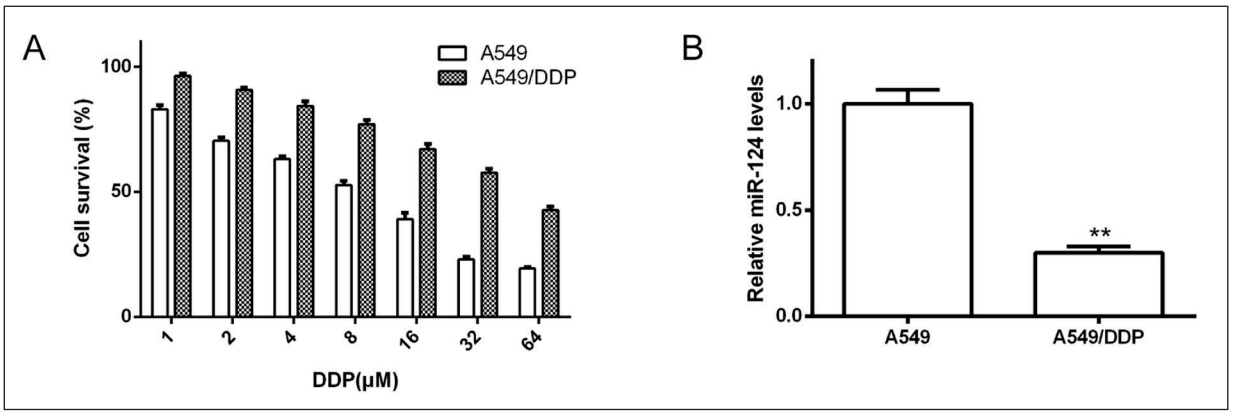

Figure 1. The expression of miR-124 in cisplatin (DDP)-resistant A549/DDP and A549 NSCLC cells. ***A,*** The proliferation curves of A549/DDP cells and parental cells were determined by MTT assay after treated with indicated concentrations of cisplatin for 48 h. ***B,*** The expression levels of miR-124 in A549/DDP and parental cells were detected. Data were presented as means ± SD (n = 3). $^{**}p<0.01$ *vs.* the control group.

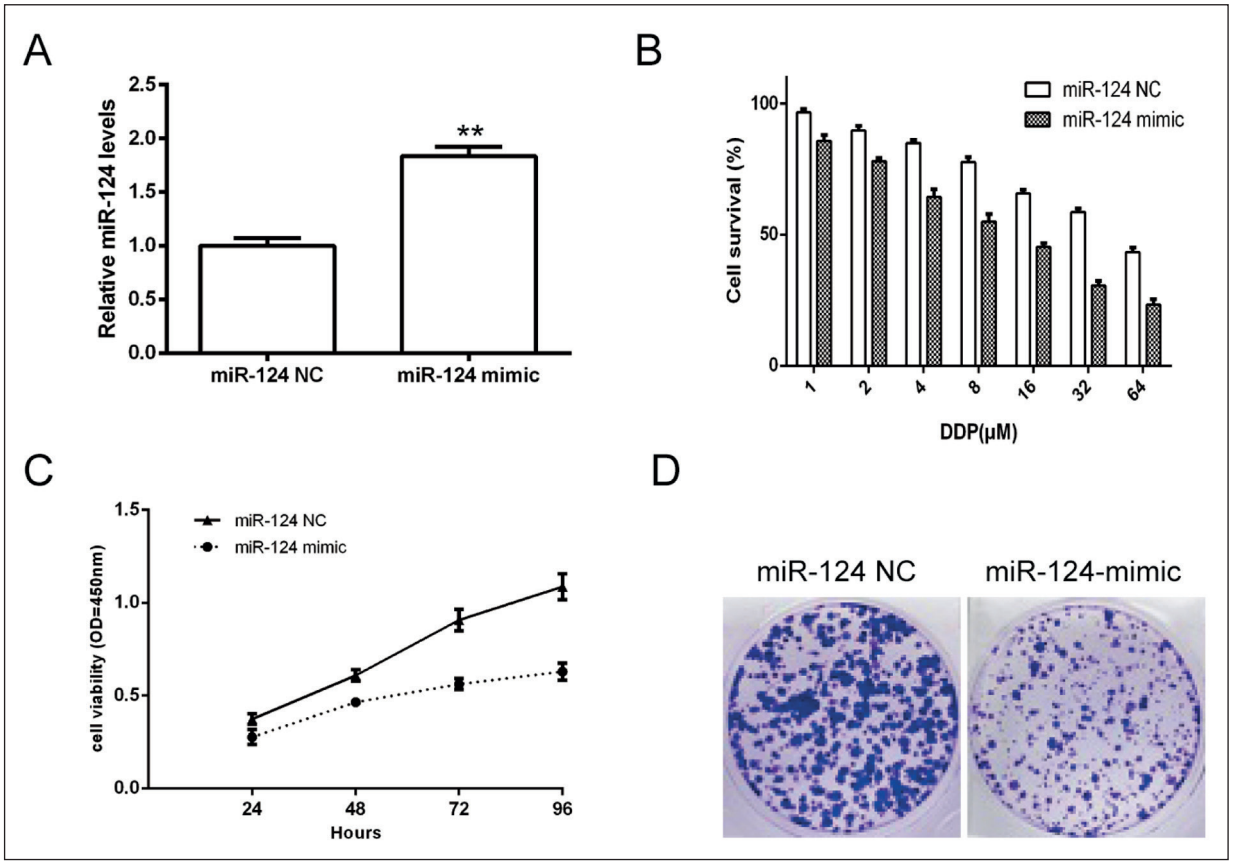

Figure 2. Overexpression of miR-124 reversed cisplatin resistance of A549/DDP cells. ***A,*** Expression of miR-124 in A549/DDP cells transfected with miR-124 mimics or miR-124 NC. ***B,*** A549/DDP cells were transfected with miR-124 mimics or miR-124 NC. The effect of miR-124 on cell proliferation was determined by MTT assay after treated with indicated concentrations of cisplatin for 48 h. ***C,*** MTT assay was performed to determine the proliferation of A549/DDP cells transfected with miR-124 mimics or miR-124 NC. ***D,*** Colony-forming assay was conducted to determine the proliferation of A549/DDP cells transfected with miR-124 mimics or miR-124 NC. Data were presented as means ± SD (n = 3). *p<0.05, **p<0.01 *vs.* the control group.

above results suggested that up-regulation of miR-124 could significantly up-regulate the expression levels of pro-apoptotic proteins (Bax, cleaved caspase-9 and cleaved PARP), initiate the mitochondrial apoptotic pathway and promote cells apoptosis, eventually inhibiting the tumor (Figure 3C-3D).

Up-Regulation of miR-124 Inhibited the Migration and Invasion of A549/DDP Cells

Invasion and migration capacity is one of the characteristics of malignant tumors, which is also an important cause of deaths in tumor patients. A large number of studies have demonstrated that the migration capacity of tumor is often enhanced after the occurrence of drug resistance. Therefore, the effect of miR-124 on the migration and invasion of A549/DDP cells was further explored. Wound healing assay showed that the migration distance of the miR-124 mimics group was significantly shorter than that of the control group (p<0.05, Figure 4A-B). Subsequently, transwell migration assay was performed. Interestingly, the number of cells passing through the filter membrane in the lower chamber in the miR-124 mimics group was significantly decreased, displaying a statistically significant difference (p<0.05, Figure 4C-4D). The above results indicated that up-regulation of miR-124 significantly inhibited the migration and invasion capacity of A549/DDP cells.

MiR-124 Targeted STAT3 and Regulated Its Expression in A549/DDP Cells

Rsearches have proved that miR-124 regulates the expression level of STAT3 in various tumor cells in a targeted manner, thus exerting

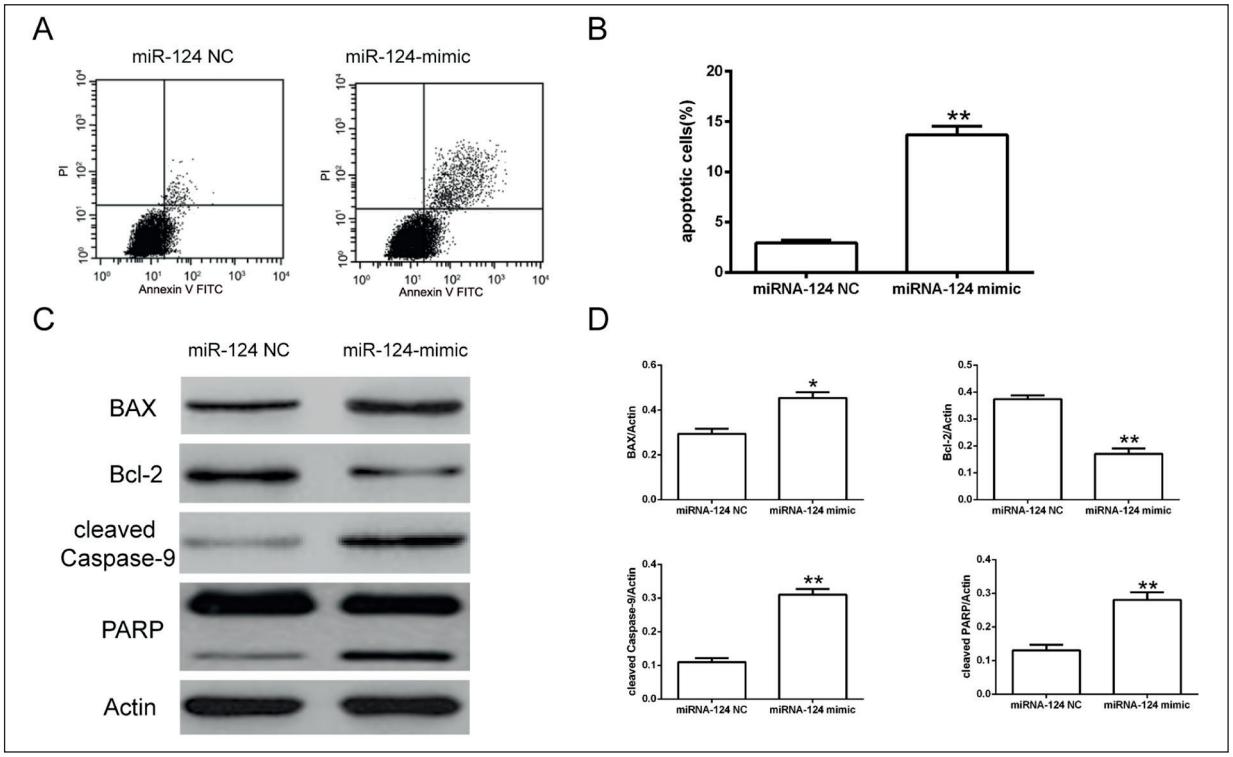

Figure 3. Overexpression of miR-124 induced the apoptosis of A549/DDP cells. ***A, B,*** Representative data of FACS and statistical graph analysis of cell apoptosis in A549/DDP cells transfected with miR-124 mimics or miR-124 NC. ***C, D,*** The proteins levels of BAX, Bcl-2, cleaved caspase-9 and PARP in A549/DDP cells were determined by Western blotting after transfection with miR-124 mimics or miR-124 NC for 48 h. Data were presented as means ± SD (n = 3). *p<0.05, **p<0.01 *vs.* the control group.

relevant biological effects. Therefore, we speculated that miR-124 could target to STAT3 and regulate its expression in A549/DDP cells. To verify this hypothesis, the expression of STAT3 in A549 cells and A549/DDP cells was detected *via* qRT-PCR and Western blotting, respectively. Results revealed that STAT3 expression was significantly up-regulated in A549/DDP cells. Then the mRNA expression of STAT3 in A549/DDP cells after miR-124 overexpression was detected. QRT-PCR results found that the mRNA expression level of STAT3 was significantly declined in A549/DDP cells after transfection with miR-124 mimics (*p<0.05, **p<0.05) (Figure 5A). The effect of miR-124 overexpression on the protein expression of STAT3 was further analyzed. Western blotting demonstrated that the protein expression level of STAT3 was significantly decreased after transfection with miR-124 mimics (p<0.05) (Figure 5B). This suggested that miR-124 could bind to STAT3 in a targeted manner, promote the degradation of STAT3 mRNA and further decrease the protein expression of STAT3. Further, dual-luciferase reporter gene assay was performed to investigate whether miR-124 negatively regulated STAT3 expression through binding to its 3'-UTR (Figure 5C). Constructed pMIR-STAT3-3'-UTR reporter gene vector was transfected into A549/DDP cells with stable expression of miR-124. It was found that after these cells were transfected with pMIR-STAT3-MUT-3'-UTR reporter gene vector, the luciferase activity was significantly decreased when compared with that of cells transfected with pMIR-STAT3-3'-UTR (p<0.05). The reporter gene vector cloned with pMIR-STAT3-MUT-3'-UTR was transfected into A549/DDP cells with stable expression of miR-124 and its control miRNA. Results manifested that after transfection with pMIR-STAT3-MUT-3'-UTR, no significant changes were found in the luciferase activity (p>0.05) (Figure 5D). The above experimental results indicated that miR-124 targeted STAT3 and suppressed its expression in A549/DDP cells.

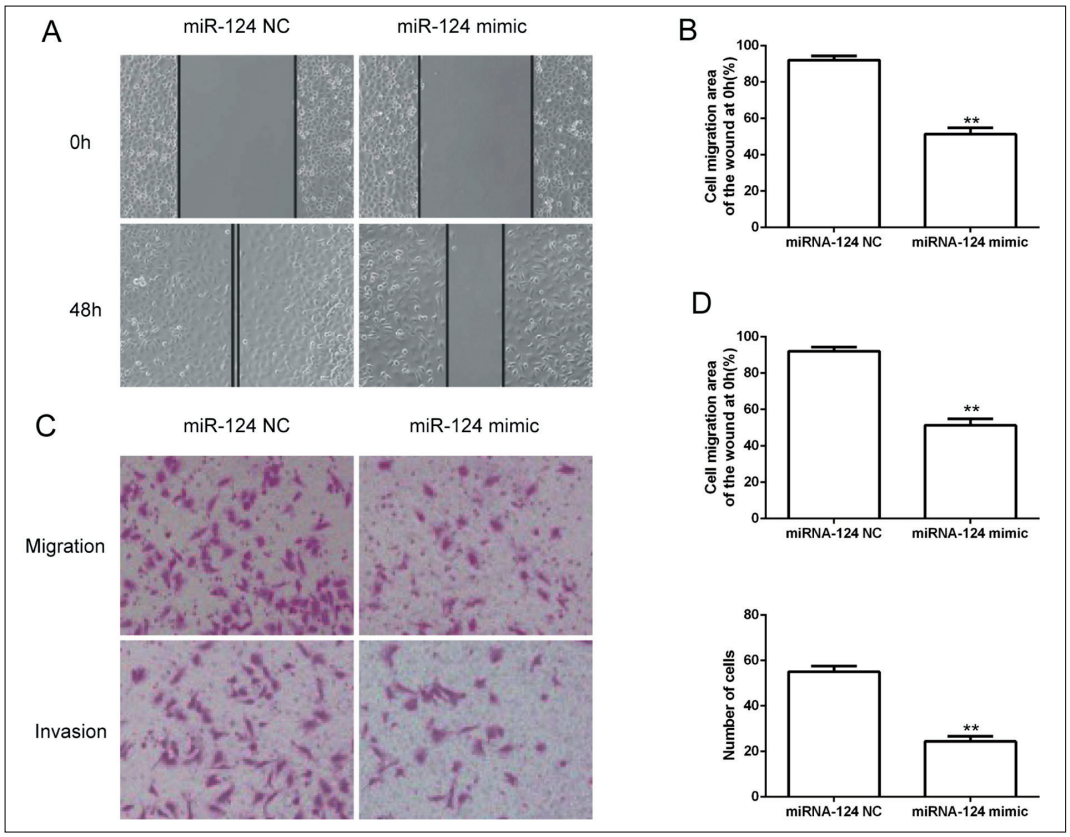

Figure 4. Overexpression of miR-124 suppressed the migration and invasion of A549/DDP cells. ***A, B,*** A549/DDP cells were transfected with miR-124 mimics or miR-124 NC for 48 h. The effect of miR-124 on cell migration was determined by cell scratch test. ***C, D,*** The effect of miR-124 on cell migration and invasion was determined by transwell test. Data were presented as means ± SD (n = 3). ***p*<0.01 *vs.* the control group.

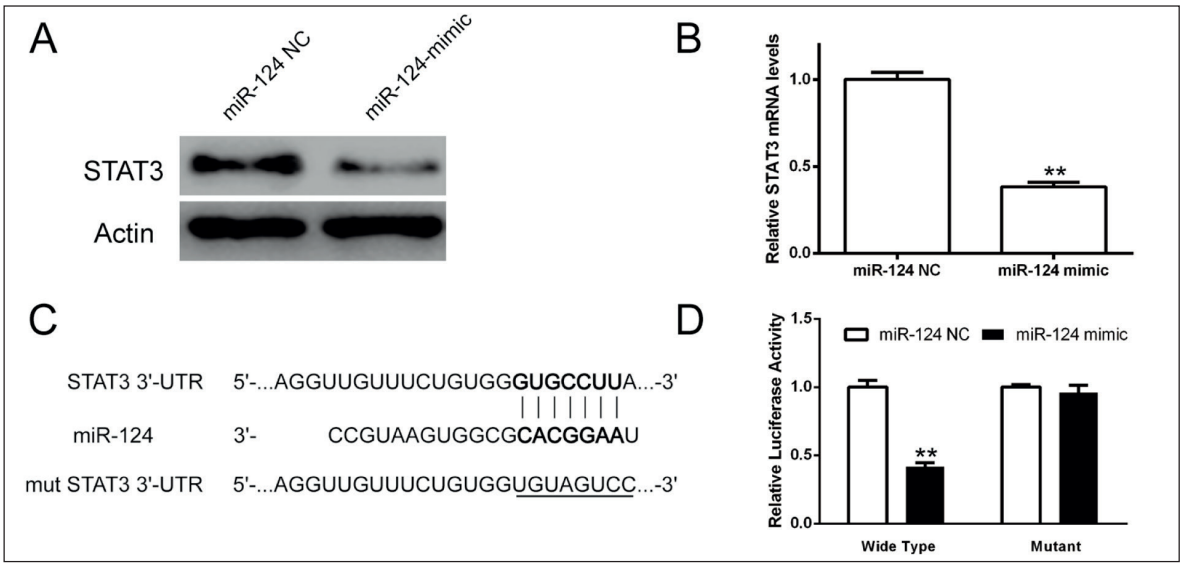

Figure 5. STAT3 was a direct target of miR-124. ***A,*** The protein level of STAT3 in miR-124 overexpressing A549/DDP cells and control cells was measured by Western blotting. ***B,*** The relative mRNA expression of STAT3 in miR-124 overexpressing A549/DDP cells and control cells was measured by qRT-PCR. ***C,*** The predicted binding sites of miR-124 in the 3'-UTR of STAT3. ***D,*** Dual-luciferase reporter assay was used to determine the binding site. A549/DDP cells treated with miR-124 mimics or miR-124 NC were transfected with pMIR construct containing WT or mutant STAT3 3'-UTR site. Data were presented as means ± SD (n = 3). ***p*<0.01 *vs.* the control group.

Discussion

MiRNA is a kind of endogenous, non-coding RNA with about 20-25 bp in length. MiRNA can exert a variety of biological functions through regulating its target genes, which is highly conservative in genetics[10]. According to previous researches, miRNA participates in the regulation of malignant tumors through a variety of pathways. As oncogenes and tumor suppressor genes, they may regulate the apoptosis, growth, proliferation, migration and invasion of tumor cells[11-13]. In addition to the direct regulation of tumor, miRNA can also influence the drug resistance of tumor[14].

Researches have demonstrated that changes of miR-124 expression can alter the sensitivity of malignant tumor cells to chemotherapy. Liang et al[15] have found that highly expressed miR-124 promotes the resistance of acute lymphoblastic leukemia to dexamethasone. Hu et al[9] have demonstrated that low expression of miR-124 promotes the resistance of NSCLC to gefitinib. They have also indicated that the underlying mechanism is related to the role of miR-124 in targeted regulation of SNAI2 and STAT3 molecules, as well as the epithelial-mesenchymal transition (EMT) pathway. According to Chen et al[16], overexpression of miR-124 leads to declined DNA repair capacity of cancer cells, thereby increasing the sensitivity of cells to anti-tumor drugs. However, the correlation between miR-124 and cisplatin resistance of lung cancer has not been studied yet. Kamran et al[17] have found that activated STAT3 can promote the progression of malignant tumors through a variety of ways, such as promoting the proliferation, invasion, metastasis, drug resistance and EMT of tumor cells, regulating tumor microenvironment, and facilitating the renewal and differentiation of tumor stem cells. The activation of STAT3 is regulated by traditional cytokine and growth factor signaling pathways. Meanwhile, plenty of evidence[18-20] has shown that miRNA also plays an important role in regulating the STAT3 signaling pathway. In breast cancer, miR-519d exerts an anti-tumor effect via inhibiting STAT3 expression[21]. The low expression of miR-20a in liver cancer cells, which is a negative regulatory factor of STAT3, can relieve the inhibition of STAT3, promote the expression of STAT3, enhance the activity of STAT3 and accelerate cell proliferation[22]. Continuous activation of STAT3 in tumor up-regulates the expression of apoptosis-inhibiting factors and cell cycle regulatory factors, stimulates cell proliferation, hinders cell apoptosis and mediate drug resistance to various chemotherapeutic drugs. Moreover, the same authors[17] have proved that STAT3 can regulate the invasion and metastasis of multiple malignant tumors. A number of studies have shown that miR-124 inhibits STAT3 expression in a targeted way, thereby inhibiting tumor proliferation and promoting chemotherapy sensitivity[23,24]. Based on the above research results, we explored the role of miR-124 in cisplatin resistance of NSCLC and its related mechanism. Interestingly, the expression level of miR-124 in cisplatin-resistant A549/DDP cells and A549 cells was detected *via* qRT-PCR, respectively. Results found that the expression level of miR-124 in A549/DDP cells was significantly lower than that of maternal A549 cells. This indicated that down-regulation of miR-124 might be involved in the drug resistance of lung cancer cells. To verify this hypothesis, A549/DDP cells were transfected with miR-124 mimics. Subsequent experiments demonstrated that the sensitivity of A549/DDP cells to cisplatin was enhanced, the apoptotic rate was increased, and the invasion and metastasis capacity was inhibited. Considering that miR-124 has been found to inhibit STAT3 expression in a targeted manner in a variety of tumors, we hypothesized that miR-124 might also promote cisplatin resistance through regulating STAT3. In the present study, qRT-PCR and Western blotting results confirmed our hypothesis. Meanwhile, the up-regulation of miR-124 in A549/DDP cells could inhibit the expression of STAT3. Luciferase reporter gene assay verified the binding site of miR-124 and STAT3, and results confirmed that miR-124 could indeed negatively regulate STAT3 expression through predicted site.

Conclusions

We showed that the low expression of miR-124 promoted the resistance of lung cancer to cisplatin by targeting STAT3, thereby inhibiting cell apoptosis. Our findings may provide certain theoretical basis for reversing the cisplatin resistance of lung cancer based on targeted regulation of miR-124.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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