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RESEARCH ARTICLE

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MiR-630 suppresses non-small cell lung cancer by targeting vimentin

Bin Wang[1] | Jie Li[1] | Yulin Li[2] | Tao Liang[1] | Xiangyang Chu[1]

[1]Department of Thoracic Surgery, The First Medical Center of Chinese PLA General Hospital, Beijing, China

[2]Department of Respiratory and Critical Care Medicine, Aerospace Center Hospital, Beijing, China

Correspondence
Xiangyang Chu, Department of Thoracic Surgery, First Medical Center of Chinese PLA General Hospital, Beijing, China.
Email: drchu301@aliyun.com

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Abstract

Objective: This study aimed to clarify the function of miR-630 on non-small cell lung cancer (NSCLC) cells.

Methods: Quantitative real-time PCR was utilized to detect the mRNA expression of miR-630 and vimentin (VIM) in NSCLC tissues and cells. The protein expression of VIM, P53, Caspase-3, Bcl-2, Bax and JAK2/STAT3 was evaluated via Western blot. Dual-luciferase reporter assay was applied to evaluate whether VIM is the target gene of miR-630. The migration, invasion, proliferation and apoptosis of NSCLC cells were examined by wound-healing assay, transwell assay, CCK-8 assay, and flow cytometry, respectively.

Results: MiR-630 was lowly expressed in NSCLC tissues and cells, while VIM was highly expressed in NSCLC cells. Dual-luciferase reporter assay data validated that miR-630 directly targeted VIM. MiR-630 overexpression inhibited VIM expression, but the inhibition of miR-630 upregulated VIM expression. Besides, miR-630 mimics restrained cell migration, invasion, and proliferation, and promoted NSCLC cell apoptosis. Whereas, VIM overexpression partly attenuated the inhibitory effect of miR-630 on NSCLC cells. Moreover, miR-630 mimics impeded p-JAK2 and p-STAT3 protein expression; and miR-630 inhibitor upregulated p-STAT3 and VIM protein expression, which was reversed after the addition of STAT3 inhibitor C188-9.

Conclusion: MiR-630 constrained the progression of NSCLC by inhibiting JAK2/STAT3 pathway and downregulating VIM expression.

KEYWORDS
JAK2/STAT3 signaling pathway, miR-630, non-small cell lung cancer, vimentin

1 | INTRODUCTION

Lung cancer has been recognized as a common malignant tumor and is usually sub-divided into small cell lung cancer and non-small cell lung cancer (NSCLC) according to clinical pathological morphology, among which NSCLC accounts for 80%–85% of all lung cancer cases.[1,2] Targeted therapy has become the typical method to prolong the overall survival of lung cancer patients.[3,4] In spite of the improved clinical outcomes with targeted therapy, the 5-year survival rate of lung cancer patients remains lower than 20%.[1,2,5] Therefore,

Bin Wang and Jie Li contributed equally to this work.

in-depth exploration of abnormal expression of gene and protein related to targeted therapy for lung cancer, as well as the complex signal regulation system, helps to identify potential therapeutic targets and demonstrate the evolutionary mechanisms of NSCLC.

MicroRNAs (miRNAs) have been identified to be closely related to targeted therapy for various malignant tumors. Accumulated evidence suggests that miRNA dysfunction affects cell proliferation, metastasis, and apoptosis, as well as the role of oncogenes or tumor suppressor genes in different cancers. Chen et al. clarified that miR-193a-3p knockdown promoted ovarian cancer progression by targeting GRB7 and MAPK/ERK pathway.[6] MiR-378a-5p and miR-630 have been documented to induce cataract lens epithelial cell apoptosis by downregulating E2F3 expression.[7] Besides, miR-630 functions as a tumor oncogene in renal cell carcinoma.[8]

As an intermediate filament protein III in mesenchymal cells, vimentin (VIM) is implicated in the development of various malignancies with its complex biological functions.[9] Previous studies have found that VIM is highly expressed in NSCLC, breast, gastric, and colon cancers.[9–13] However, whether miR-630 interacts with VIM to modulate the development of NSCLC remains unclear.

Herein, the current research was designed to test the hypothesis that miR-630 functions as an anti-NCSLS microRNA by suppressing the activation of JAK2/STAT3 pathway and then inhibiting VIM expression, so as to provide a novel therapeutic target for NSCLC.

2 | MATERIALS AND METHODS

2.1 | Patient samples and cell culture

Totally, 20 pairs of NSCLC tissues and adjacent normal tissues were collected from patients undergoing surgery in our hospital. We followed the principles expressed in the Declaration of Helsinki. Informed consents were obtained from all participants for the use of their tissue samples. Normal human lung epithelial cell line (BEAS-2B cells), NSCLC cell lines (H1975, H1299, A549 and H358 cells) were obtained from National Collection of Authenticated Cell Cultures. Cells in RPMI 1640 medium (Sigma Aldrich) were supplemented with 10% fetal bovine serum (FBS, Gibco BRL), penicillin 100 U/ml (Gibco) and streptomycin (Gibco) 100 mg/L at 37°C and 5% CO_2.

2.2 | Quantitative real time-PCR (qRT-PCR)

Trizol (Thermo Fisher Scientific) was utilized for total RNA extraction, followed by reverse transcription into cDNA via reverse transcriptase (TaKaRa) and oligonucleotide (dT). Real-time PCR was carried out by DNA fluorescent dye SYBR Green I at 60°C for 10 min, 95°C and 72°C for 30 s, and 95°C for 5 min. This experiment used specific primers of miR-630 (forward primer 5'-TTGAGCTGGATTGGCGGGAT-3' and reverse primer 5'-TTGACGGATGCGGAGGCT-3'). U6 specific primers (forward primer 5'-CATCACCATCAGGAGAGTCG-3' and reverse primer 5'-TGACGCTTGCCCACAGCCTT-3') were set as controls (GENEWIZ). All reactions were performed in triplicate, and the data were analyzed using comparative $2^{-\Delta\Delta CT}$ methods.

2.3 | Western blot

Protein samples were prepared from NSCLC cells using RIPA lysis (Thermo Fisher Scientific); the total protein concentration was extracted with extraction buffer (Thermo Fisher Scientific) and electrophored with 100 V SDS-PAGE. Then the protein samples were quantified by Bradford method before transferred to PVDF membrane. After being blocked with 10% goat serum for 0.5 h, the membrane was probed with primary antibodies against VIM, Bax, Bcl-2, Caspase-3, P53, p-JAK2, JAK2, p-STAT3, STAT3, β-actin, and GAPDH at 4°C. Then the membranes were subjected to secondary antibody (diluted at 1:5000) at room temperature for 2 h. Chemiluminesence Western blot reagents (Thermo Fisher Scientific) and ECL System (GE Healthcare) were applied to observe the protein band. The band intensity in protein imprinting was determined by ImageJ software.

2.4 | Cell transfection

H358 cells were inoculated in 12-well plates with cell suspension 2 ml in each well, and cultured in incubator for 24 h at 37°C and 5% CO_2. After that, H358 cells were respectively transfected with miR-630 mimics, vector, miR-630 inhibitor, NC, and miR-630 mimics + oe-VIM. The transfection method was referred to LipofectamineTM2000 transfection reagent instructions. The cells incubated for 24 h were collected for subsequent experiments.

2.5 | Dual-luciferase reporter assay

TargetScan (http://www.targetscan.org/vert_72/) indicated that there was a potential miR-630 binding site in the 3'UTR of VIM. The reporter plasmids (pmirGLO-VIM-WT and pmirGLO-VIM-Mut) were designed by Guangzhou RiboBio Co. Ltd. according to the manufacturer's instructions. HEK-293 cells were co-transfected with miR-630 mimics (or NC mimics) and pmirGLO-VIM-WT (or pmirGLO-VIM-Mut). After transfection for 48 h, luciferase activity was analyzed by using a standard luminometer.

2.6 | Wound-healing assay

Transfected H358 cells that seeded in 6-well plates grew to 80% confluence. The sterilized gun was employed to make scratches on the cell plate. Then, cultured cells were observed under a light microscope, followed by calculation of the scratches.

2.7 | Transwell assay

The cells at a density of 10^5 cells/ml were digested with trypsin–EDTA to prepare cell suspension (200 μl), which was seeded into the upper chamber of Matrigel-coated or -uncoated transwell chambers, while 10% FBS-cultured medium (500 μl) was added into the lower chamber. After an overnight culture, the residual cells on the upper layer were erased. The invasive/migrated cells were fixed with formaldehyde and stained with crystal violet. Lastly, the number of transmembrane cells was counted under a microscope.

2.8 | CCK-8 assay

Cell suspension (100 μl per well) was injected into 96-well reaction plate. Next, 10 μl of CCK-8 solution (APE×BIO, USA) was added to each hole for an additional incubation for 1–4 h. Enzyme-labeled instrument was exploited to measure the optical density at 450 nm of each sample by using fluorescence microscope.

2.9 | Flow cytometry

The transfected cells were cultured in the orifice plate. The mass concentration was 2×10^6 cells/ml. Then, 0.25% trypsin was used for digestion, followed by 70% ethanol fixation for cells. The cells were placed in 4°C environment for 1 day. The centrifugal speed was 1500 rpm; the centrifugal radius was 15 cm. Discard the supernatant after centrifugation for 5 min. Then, the supernatant was rinsed with PBS for 5 min for three times at 37°C. Later, the cells were dyed without light for 30 min, and the degree of apoptosis was analyzed via flow cytometry.

2.10 | Statistical analysis

GraphPad Prism 8.0.2 (GraphPad Prism) was adopted for statistical analysis. Data were expressed as the mean ± standard error of the mean. One-way ANOVA was employed for the comparison between different experimental groups. The value $p<0.05$ was regarded as statistically significant.

3 | RESULTS

3.1 | MiR-630 expression is downregulated while VIM is upregulated in NSCLC tissues and cells

As shown in Figure 1A, miR-630 was found to exhibit significantly lower expression in NSCLC tissues than that in adjacent normal tissues ($p<0.001$). Subsequently, qRT-PCR was performed to figure out the relationship between miR-630 expression and human NSCLC cell lines. Results showed that miR-630 was lowly expressed in NSCLC cell lines (H1975, H1299, A549 and H358 cells) and its expression was the lowest in H358 cells (Figure 1B). On the contrary, the protein and mRNA expression of VIM in NSCLC cells were significantly higher than that in BEAS-2B cells, with the largest change in the expression multiple in H358 cell lines ($p<0.001$) (Figure 1C,D). Therefore, H358 cell lines were chosen for further analysis as the low-expression miR-630 cell line and high-expression VIM cell line.

3.2 | MiR-630 directly targets VIM

Dual-luciferase reporter gene assay was conducted to figure out whether VIM is the target gene of miR-630. As presented in

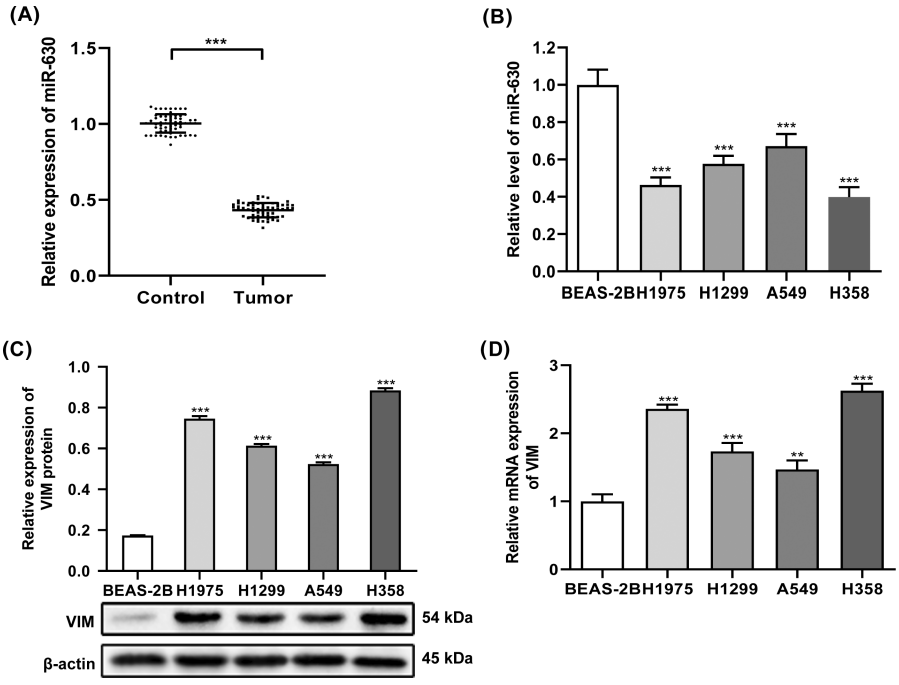

FIGURE 1 MiR-630 was highly expressed in NSCLC tissues and cells. (A) The mRNA level of miR-630 was detected in NSCLC tissues compared with that in adjacent normal tissues by qRT-PCR. ***$p<0.001$ vs. normal tissues. (B) MiR-630 expression in BEAS-2B cells and NSCLC cells was determined by qRT-PCR. VIM levels in these cells were evaluated by (C) Western blot and (D) qRT-PCR. **$p<0.01$ and ***$p<0.001$ vs. BEAS-2B cells

Figure 2A, miR-630 overexpression significantly decreased the luciferase activity of the reporter gene in pmirGLO-VIM-WT group ($p < 0.001$), whereas, it remained unchanged in pmirGLO-VIM-Mut group. This indicated that miR-630 had a targeted binding site to VIM.

To further investigate the relationship between VIM and miR-630, qRT-PCR and western blot were performed. The transfection of miR-630 mimics significantly increased miR-630 mRNA expression and downregulated VIM mRNA and protein expression when compared with vector group (all $p < 0.001$) (Figure 2B–D). In addition, the inhibition of miR-630 expression obviously downregulated miR-630 mRNA expression and improved VIM mRNA and protein expression (all $p < 0.001$) (Figure 2E–G).

3.3 | MiR-630 regulates the migration and invasion of H358 cells by targeting VIM

To explore the impact of miR-630 on VIM modulation on the migration and invasion of H358 cells, wound-healing and transwell assays were carried out in this study (Figure 3A,B). Our data clarified that miR-630 overexpression dramatically impeded wound-healing rate, migration, and invasion of H358 cells ($p < 0.01$, $p < 0.001$ and $p < 0.001$, respectively). Nevertheless, VIM overexpression facilitated the wound-healing rate, invasion, and migration of H358 cells ($p < 0.01$, $p < 0.01$ and $p < 0.05$, respectively). Taken together, these findings suggested that miR-630 curbed H358 cell migration and invasion by downregulating VIM expression.

3.4 | MiR-630 modulates H358 cell proliferation and apoptosis by targeting VIM

To identify the efficacy of miR-630 on VIM regulation on viability and apoptosis of H358 cells in vitro, we performed CCK-8 assay and flow cytometry. CCK-8 assay data demonstrated that H358 cells transfected with miR-630 mimics grew slower than those cells in vector group ($p < 0.001$) (Figure 4A). From Figure 4B, transfection of miR-630 mimics resulted in accelerated apoptotic rates of H358 cell. Strikingly, VIM overexpression remarkably reversed the inhibited cell viability and promoted apoptosis (both $p < 0.001$; Figure 4A,B). Then, we speculated that miR-630 induces H358 cell apoptosis by modulating apoptosis-related factors, P53, Caspase-3, Bcl-2, and Bax levels. Figure 4C shows that miR-630 mimics significantly enhances the expression of P53, Caspase-3 and Bax, but lowered Bcl-2 expression (all $p < 0.001$), while VIM overexpression significantly abolished the function of miR-630 mimics.

3.5 | MiR-630 downregulates VIM expression through inhibition of JAK2/STAT3 pathway

Western blot was adopted to explore whether JAK2/STAT3 pathway is involved in the regulation of miR-630 on NSCLC cells. From Figure 5A, we noticed that miR-630 overexpression caused significant downregulation of p-STAT3 and p-JAK2 expression (both $p < 0.001$). Whereas, miR-630 inhibitor led to significant upregulation of p-STAT3 and p-JAK2 expression (both $p < 0.001$; Figure 5B).

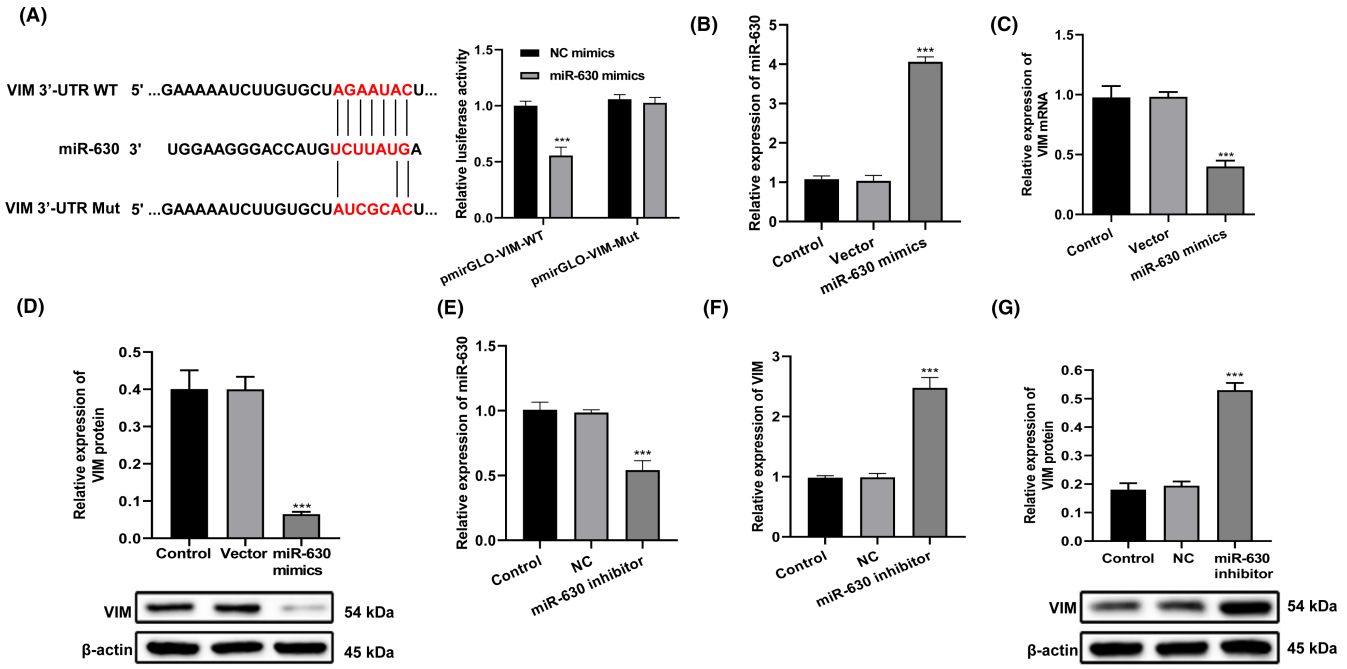

FIGURE 2 MiR-630 directly targeted VIM. (A) Bioinformatics software predicted the binding site of miR-630 in the 3'-UTR of VIM. Luciferase activity of HEK293T cells transfected with miR-630 mimics in the presence of pmirGLO-VIM-WT or pmirGLO-VIM-Mut was determined. (B) MiR-630 mRNA expression, (C) VIM mRNA expression and (D) VIM protein expression in H358 cells transfected with vector or miR-630 mimics were measured by qRT-PCR and Western blot. (E) MiR-630 mRNA expression, (F) VIM mRNA expression and (G) VIM protein expression in H358 cells transfected with NC or miR-630 inhibitor were measured by qRT-PCR and Western blot. ***$p < 0.001$ vs. vector or NC group

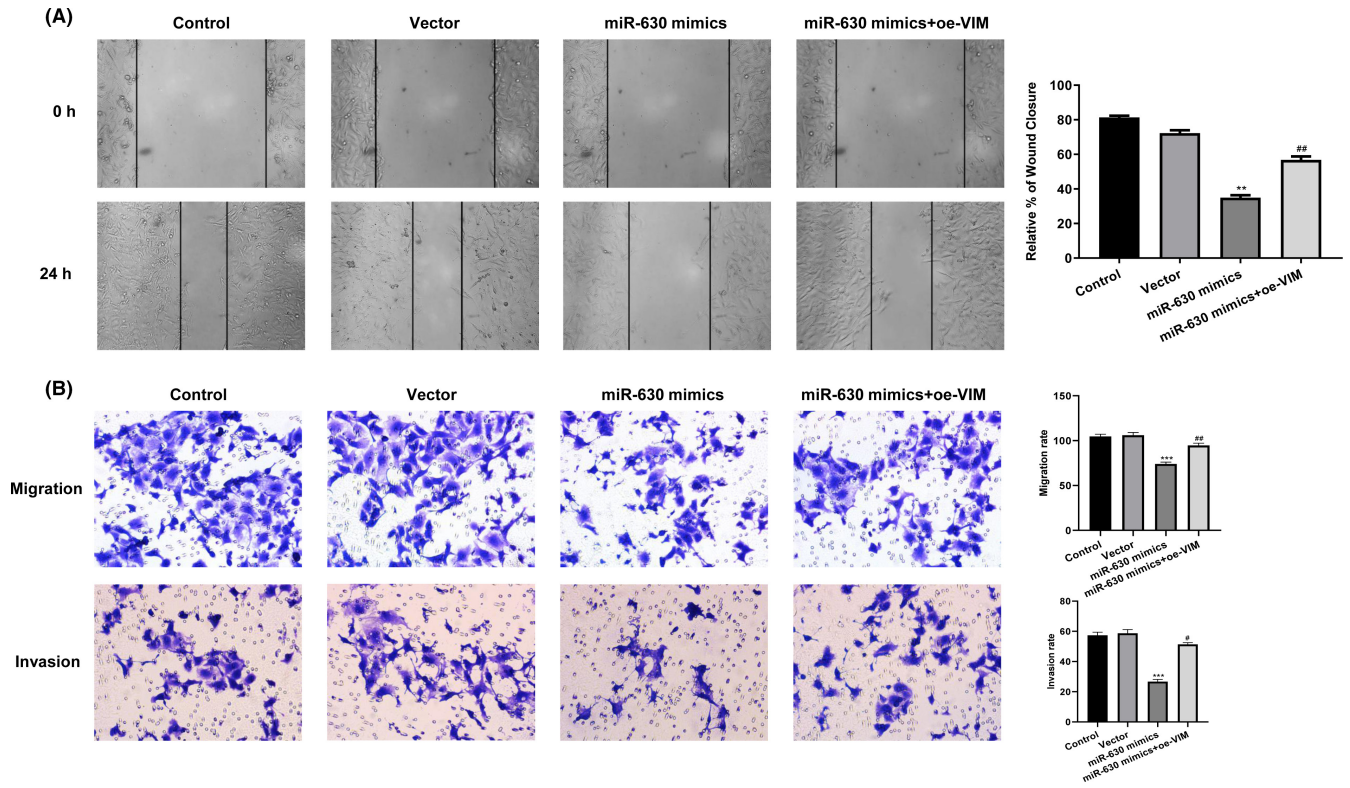

FIGURE 3 MiR-630-mediated VIM expression inhibited NSCLC cell migration and invasion. (A) Wound-healing assay was used to detect the ability of H358 cell migration. $^{**}p<0.01$ vs. vector group. $\#\#p<0.01$ vs. miR-630 mimics + oe-VIM group. (B) Transwell assay was employed to examine abilities of H358 cell migration and invasion. $^{***}p<0.001$ vs. vector group. $\#p<0.05$, $\#\#p<0.01$ vs. miR-630 mimics group

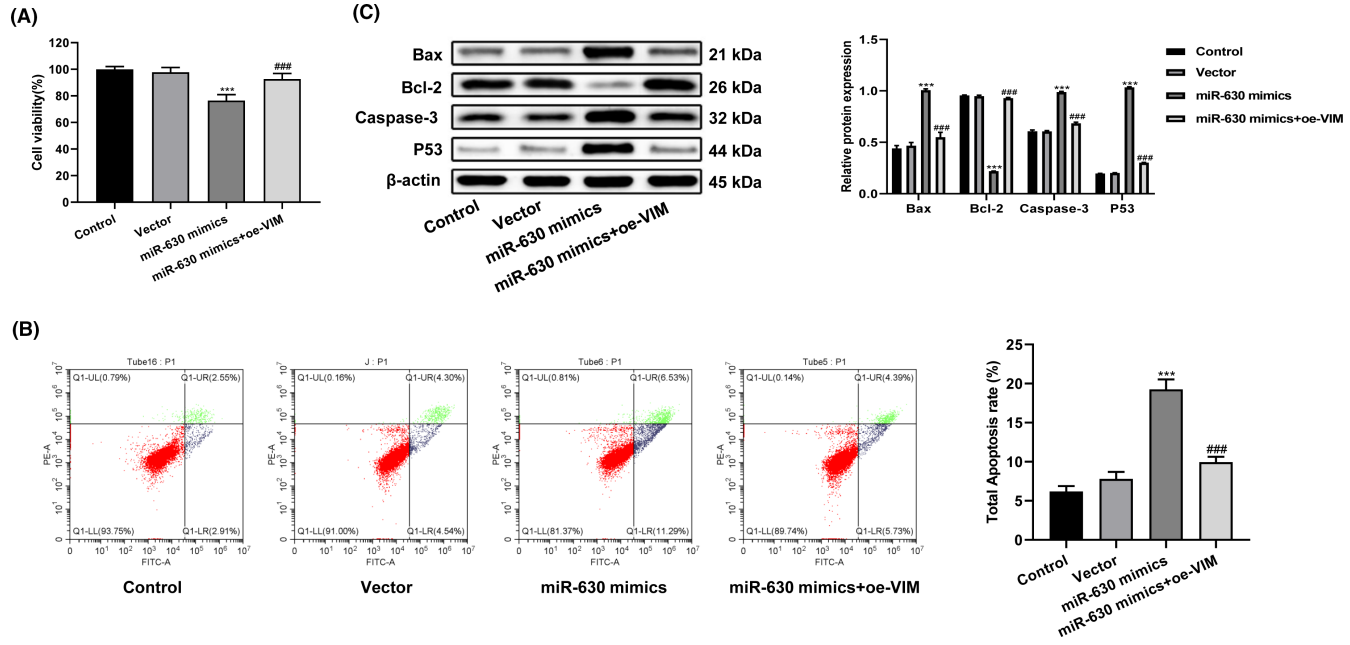

FIGURE 4 MiR-630-mediated VIM expression affected proliferation and apoptosis of NSCLC cells. (A) CCK-8 assay was carried out for the detection of cell viability. (B) The function of miR-630-mediated VIM expression on NSCLC cell apoptosis was evaluated using flow cytometry. (C) The expression of apoptosis-related proteins (P53, Caspase-3, Bcl-2 and Bax) was detected by Western blot. $^{***}p<0.001$ vs. vector group. $\#\#p<0.01$, $\#\#\#p<0.001$ vs. miR-630 mimics group

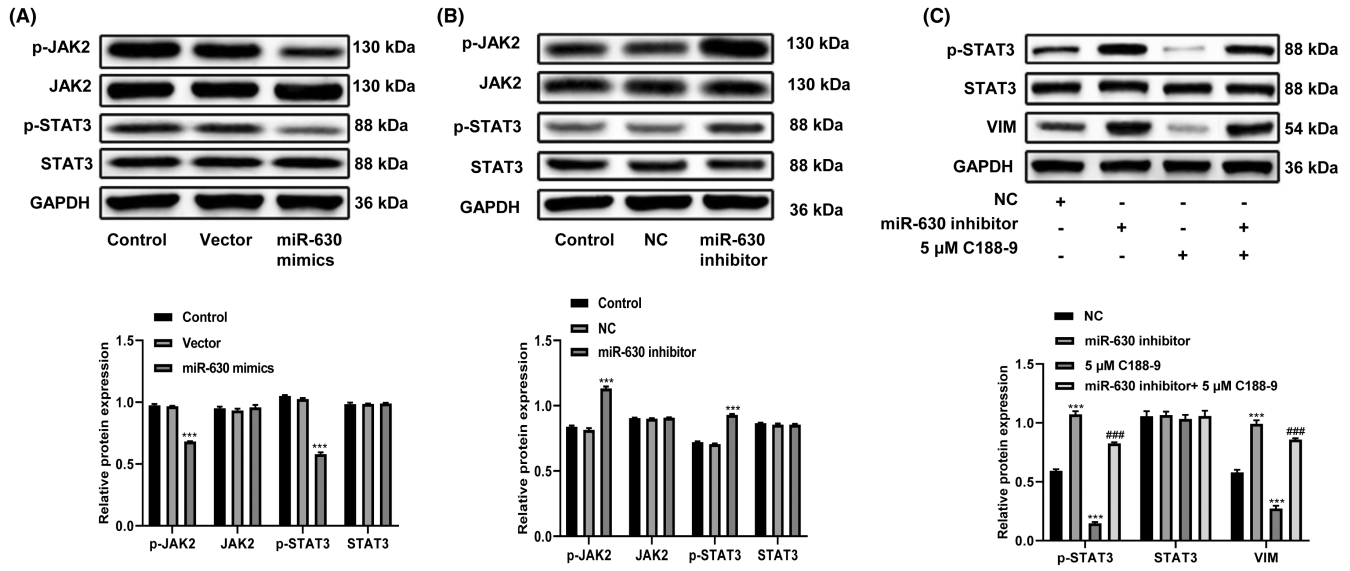

FIGURE 5 Ectopic miR-630 expression affected VIM expression through JAK2/STAT3 signaling pathway. (A) Western blot was adopted to measure p-JAK2 and p-STAT3 protein expression. ***$p < 0.001$ vs. vector group. (B, C) Western blot was used to detected the protein expression of p-JAK2, p-STAT3 and VIM. ***$p < 0.001$ vs. NC group. ###$p < 0.001$ vs. 5 μM C188-9 group

These data indicated that miR-630 overexpression blocked the activity of JAK/STAT3 signaling in H358 cells. Considering the key role of STAT3 in cell apoptosis, STAT3 inhibitor C188-9 (5 μM) was utilized in this study. As shown in Figure 5C, C188-9 alone treatment significantly constrained the protein expression of VIM and p-STAT3, while co-treatment with miR-630 inhibitor upregulated VIM and p-STAT3 expression (all $p < 0.001$).

4 | DISCUSSION

The most notable finding in the current research was that miR-630 targeted VIM through JAK2/STAT3 signaling pathway, thereby inhibiting the development of NSCLC. Many evidences have shown that downregulation of miR-630 contributes to tumors progression, revealing that miR-630 might be a biomarker and therapeutic target for cancers. One prior research pointed out that downregulated miR-630 expression increased proliferation, migration, and invasion of osteosarcoma cells through targeting PSMC2.[14] Besides, miR-630 can inhibit the growth and metastasis of papillary thyroid carcinoma cells.[15] Moreover, miR-630 has been proved to be downregulated in lung cancer cells.[16] Although miR-630 has been studied to be implicated in the progression of NSCLC, the mechanism of its action remains unclear.

In the present study, we first analyzed miR-630 expression in NSCLC tissues and adjacent normal tissues, and found that miR-630 expression was decreased in NSCLC tissues. Then, the expression of miR-630 and VIM in four NSCLC cell lines and BEAS-2B cells were evaluated to identify their correlation. We noticed that miR-630 had different degrees of low expression in NSCLC cells with relatively lowest in H358 cells, while VIM was highly expressed in four NSCLC cell lines, indicating that miR-630 was negatively correlated with VIM in different NSCLC cell lines.

Vimentin is a multifunctional protein with 466 amino acids, which is highly evolutionary conservation in vertebrates. Battaglia et al. have proved that VIM intermediate filaments are essential for the plasticity of mesenchymal cells under normal physiological conditions and cancer cell migration during epithelial–mesenchymal transition.[17] Additionally, several researches stated that VIM expression was downregulated in well-differentiated endometrial cancer cells and giant cell tumor of bone.[18,19] Overexpression of VIM promotes migration, invasion, and metastasis of CRC cells.[20] To our knowledge, miRNA play its biological function by suppressing target gene expression. Thus, TargetScan was adopted to find possible miR-630 binding site in the 3'UTR of VIM. Dual-luciferase reporter assay results showed that pmirGLO-VIM-Mut luciferase activity was unchanged after transfection with miR-630 mimics, suggesting that miR-630 had a targeted binding site to VIM. Meanwhile, miR-630 mimics impeded H358 cell proliferation, migration, and invasion and enhanced cell apoptosis. However, overexpressed VIM weakened these effects of miR-630 on H358 cells, which indirectly indicated that miR-630 affected NSCLC cells by modulating VIM expression.

JAK2/STAT3 is a vital cell signaling pathway, resulting in the progression of various cancers. Pan et al.[15] have shown that miR-630 restrained the growth, metastasis and epithelial–mesenchymal transition of papillary thyroid carcinoma cells by inhibiting JAK2/STAT3 signaling pathway. Xu et al.[21] have also put forward that JAK2/STAT3/VIM pathway is implicated in the regulation of the human colon cancer cell viability and migration. Biodegradable nanoparticles-mediated combination of erlotinib and metrintinib to treat ELTN-resistant NSCLC by inhibiting JAK2/STAT3 pathway.[22]

In this study, miR-630 mimics downregulated the expression of p-JAK2 and p-STAT3, which was reversed after miR-630 inhibitor treatment. Additionally, after the addition of STAT3 inhibitor C188-9 (5 μM), decreased VIM level was synchronized with the declined p-STAT3 expression modulated by miR-630. In other words, upregulated miR-630 expression impeded VIM expression by inhibiting the phosphorylation of JAK2 and STAT3.

5 | CONCLUSION

Our study finds that miR-630 inhibits VIM expression by impeding the phosphorylation of JAK2 and STAT3, thereby curbing the progression of NSCLC. In summary, miR-630 plays a tumor suppressor role in NSCLC by targeting VIM. This study is the first to illustrate the suppressing effect and mechanism of miR-630 targeting VIM on NSCLC, which provides a new direction for NSCLC treatment.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Xiangyang Chu https://orcid.org/0000-0003-0117-7097

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