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Original Article

MiR-193-3p suppresses phenotypic switching in vascular smooth muscle cells by regulating IGF2 during in-stent restenosis

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Abstract: Background: Dysregulated proliferation and migration of vascular smooth muscle cells (VSMCs) are central to the development of in-stent restenosis (ISR). Clinically, regulating VSMC phenotype during proliferation and migration presents a potential therapeutic approach to prevent IRS. However, the role of miR-193-3p in ISR pathogenesis remains largely uncharacterized. Objective: To investigate the role of miR-193-3p in ISR pathogenesis, focusing on the molecular mechanisms mediated by miR-193-3p, specifically the miR-193-3p/insulin-like growth factor-2 (IGF2) axis in regulating ISR. Methods: Serum levels of miR-193-3p were quantified in ISR patients and healthy controls using quantitative real-time polymerase chain reaction (qPCR). miR-193-3p mimic transfection in VSMCs was confirmed by qPCR. The phenotypic switching of VSMCs was assessed via qPCR and western blot. Proliferative and migratory activities were evaluated using CCK-8 and Transwell assays, respectively. IGF2 levels in VSMCs were assessed using qPCR and WB assays. Results: Serum levels of miR-193-3p were significantly reduced in ISR patients compared to healthy controls ($P < 0.05$). Overexpressing miR-193-3p markedly suppressed VSMC proliferation and migration ($P < 0.05$), while upregulating differentiation-associated VSMC markers at both mRNA and protein levels ($P < 0.05$). Mechanistically, IGF2 was identified as a direct target of miR-193-3p. Additionally, miR-193-3p expression was elevated in VSMCs following IGF2 stimulation ($P < 0.05$), and this upregulation counteracted IGF2-induced proliferative and migratory activity ($P < 0.05$). Conclusions: These findings suggest the miR-193-3p may serve as a potential biomarker for ISR and that targeting the miR-193-3p/IGF2 axis could be a promising strategy for managing ISR.

Keywords: miR-193-3p, IGF2, vascular smooth muscle cell, in-stent restenosis

Introduction

Coronary atherosclerotic heart disease (CAHD) remains the leading cause of mortality worldwide [1]. With the advancements in cardiovascular interventions, percutaneous coronary intervention (PCI) with stent implantation has become a primary treatment for CAHD [2]. Despite its clinical success, in-stent restenosis (ISR) continues to pose a significant challenge, compromising long-term outcomes in some patients [3-5]. As a result, there is growing interest in elucidating the mechanistic basis of ISR to inform the development of effective therapeutic strategies.

A hallmark of ISR is the phenotypic switching of vascular smooth muscle cells (VSMCs), characterized by excessive proliferation, migration, and extracellular matrix (ECM) synthesis, ultimately narrowing the vascular lumen [6]. This phenotypic transition involves a shift from a contractile to a synthetic state, with concomitant changes in gene expression and cellular behavior [7]. VSMC plasticity is influenced by various environmental signals, such as cytokines, growth factors, lipids, and interactions with ECM components, leading to a loss of contractility and enhanced proliferative capacity [8, 9]. Moreover, dedifferentiated VSMCs often exhibit mitochondrial hyperpolarization and an imbalance between proliferation and apoptosis, further contributing to neointimal hyperplasia [10]. Targeting this phenotypic transformation holds promise as a therapeutic

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strategy to mitigate ISR and other proliferative vascular disorders.

MicroRNAs (miRNAs) are short non-coding RNAs that bind to the 3' untranslated regions (3'-UTRs) of target mRNAs, degrading or repressing their translation [11]. Dysregulated miRNA expression has been linked to various cardiovascular conditions, including hypertension, atherosclerosis, vascular remodeling, and ISR [12, 13]. Importantly, miRNAs often exert cell type-specific effects, and modulating specific miRNAs has shown potential in suppressing neointimal growth in experimental models of ISR, potentially offering new therapeutic avenues for the management of vascular disease [14, 15].

MiR-193-3p has been demonstrated to regulate pulmonary artery smooth muscle cell behavior, inhibiting cell proliferation, migration, and apoptosis [16]. However, its role in regulating VSMC phenotypic modulation and its relevance to ISR remain largely unexplored. This study aims to investigate the expression of miR-193-3p in ISR patients, identify its downstream targets, and characterize its functional role in VSMC phenotype modulation. These findings may provide new insights into ISR pathogenesis and suggest the potential of miR-193-3p as both an indictor and a therapeutic target for treating ISR.

Materials and methods

Patient samples

Blood samples were collected from 20 ISR patients treated at Xi'an No. 3 Hospital (mean age: 62.7 ± 3.85 years; 16 males and 4 females) and 20 healthy individuals who underwent physical examination during the same time period (mean age: 63.2 ± 3.76 years; 16 males and 4 females) from April 2022 to April 2024. Inclusion criteria: 1) Age between 18 and 80 years; 2) Treatment with 75 mg/day clopidogrel and 100 mg/day aspirin; 3) A history of drug-eluting stent (DES) placement during the first PCI; 4) Cardiac function classified as I-III; and 5) Coronary angiography follow-up for 10-12 months. Patients with comorbid conditions such as malignancy, or hepatic or renal infections were excluded from the study. This study was approved by the Ethics Committee of Xi'an No. 3 Hospital.

Human aortic smooth muscle cell (HASMC) culture

HASMCs were cultured in smooth muscle cell medium (SMCM) containing 2% fetal bovine serum (FBS), 1% Smooth Muscle Cell Growth Supplement (SMCGS), and 1% penicillin-streptomycin, purchased from ScienCell Research Laboratories. Cells were maintained in a humidified incubator at 37°C with 5% CO_2.

Cellular transfection

MiR-193-3p mimics (5'-AACUGGCCUACAAAGUCCCAGU-3') and a corresponding negative control sequence (5'-CGCAGGUCAAGUGGCCGACUUA-3') were synthesized by GenePharma. A pcDNA3.1 vector encoding PAK4 was purchased from RiboBio (Guangzhou, China), while an empty pcDNA3.1 vector (V79020, Thermo Fisher Scientific, USA) was used as the negative control. Transfections were performed using Lipofectamine 3000 (L3000015, Thermo Fisher Scientific) according to the manufacturer's instructions.

Luciferase reporter assay

HASMCs were inoculated in 6-well plates and incubated overnight. Wild-type (WT) or mutated (MUT) 3'UTR regions of IGF2, containing the miR-193-3p binding sites, were cloned into luciferase reporter constructs (GenePharma). These plasmids were co-transfected with miR-193-3p or negative control mimics into HASMCs. Following 48 hours, relative luciferase activity was measured using the Dual-Luciferase Reporter Assay System (Promega), using Renilla luciferase activity serving as the internal control for normalization.

Quantitative real-time polymerase chain reaction (qPCR)

Total RNA was isolated from transfected HASMCs using the Total RNA Extraction Kit (Solarbio) following the manufacturer's instruction. An All-in-One cDNA Synthesis SuperMix (Bimake) was used for preparing cDNA. qPCR was conducted using 2× SYBR Green PCR Master Mix (Solarbio) on a LightCycler 480 system (Roche). Gene expression was determined using the $2^{-\Delta\Delta Ct}$ method. The sequences of reverse and forward primers are shown in **Table 1**.

Table 1. Primer sequence

Gene	Forward primer (5'-3')	Reverse primer (5'-3')
miR-193-3p	ACACTCCAGCTGGGTGGGTCTTTGCGGGCG	TGGTGTCGTGGAGTCG
U6	CTCGCTTCGGCAGCACA	AACGCTTCACGAATTTGCGT
α-SMA	GTGACTACTGCCGAGCGTG	ATAGGTGGTTTCGTGGATGC
SMMHC	TGAACAAGGCCCTGGACAAGAC	TGCAGCTTCTCGTTGGTGTAGT
OPN	GTTGGTGGAGGATGTCTG	TACTTGGAAGGGTCTGTG
IGF2	AGACCCTTTGCGGTGGAGA	GGAAACATCTCGCTCGGACT
GAPDH	AACGGATTTGGTCGTATTG	GGAAGATGGTGATGGGATT

CCK-8 assay

HASMC proliferation was evaluated using CCK-8 assays. HASMCs were inoculated in 96-well plates and transfected for 48 hours. Subsequently, 10% CCK-8 reagent (Beyotime Biotechnology) was added, and cells were incubated for 2 hours. Absorbance at 450 nm was measured using a microplate reader.

Transwell migration assay

Transfected HASMCs were seeded in serum-free media (100 μL) into the upper chambers of Transwell inserts. The lower compartments contained 600 μL of complete media. After 24 hours, non-migrated cells on the upper membrane were removed, and migrated cells on the lower membrane were fixed with 4% paraformaldehyde, stained with 0.2% crystal violet, imaged, and quantified.

Western blotting

Following transfection, HASMCs were harvested, and total protein was extracted using RIPA buffer supplemented with protease inhibitors (Bimake). After protein quantification, samples were separated by 10% SDS-PAGE, after which Western blotting was conducted using primary antibodies specific to IGF2 and GAPDH (CST, USA).

Statistical analysis

Data were presented as mean ± SEM and were analyzed using GraphPad Prism version 7.0. Comparisons were made using unpaired two-tailed t-tests or one-way ANOVAs followed by Tukey's post hoc test. The correlation between miR-193-3p and IGF2 was analyzed utilizing Pearson correlation analysis. A P value of < 0.05 was considered statistically significant.

Results

Serum miR-193-3p expression in ISR patients

Previous studies identified several miRNAs with differential expression between the ISR and non-ISR groups, including miR-223 [17], miR-634 [18], miR-22-3p [19], and miR-193-3p [16]. Among these, miR-193-3p exhibited the most pronounced difference (**Figure 1A**) and was therefore selected for subsequent analysis. Further quantification confirmed that serum miR-193-3p levels were markedly reduced in ISR patients (n = 20) compared to non-ISR controls (n = 20) (**Figure 1B**). No significant differences in comorbidities or lipid profile indices were noted between the two groups (**Figure 1C-F**; **Table 2**). These findings indicate that miR-193-3p expression is markedly reduced in ISR and may be associated with disease pathogenesis.

miR-193-3p regulated phenotypic switching in VSMCs

To clarify whether miR-193-3p influences VSMC phenotype, the expression of contractile and synthetic marker proteins in VSMCs was evaluated following the transfection with miR-193-3p mimics. qPCR confirmed successful upregulation or downregulation of miR-193-3p (**Figure 2A**, **2B**). In cells with miR-193-3p overexpression, both mRNA and protein levels of the contractile markers α smooth muscle actin (α-SMA) and smooth muscle myosin heavy chain (SMMHC), were markedly increased compared to the negative controls (NC) (**Figure 2C**, **2D**, **2F-H**). In cells with miR-193-3p knockdown, the mRNA and protein levels α-SMA and SMMHC were markedly decreased compared to the NC (**Figure 2J**, **2K**, **2M-O**). Conversely, the levels of the synthetic marker osteopontin (OPN) were substantially lower in the miR-193-

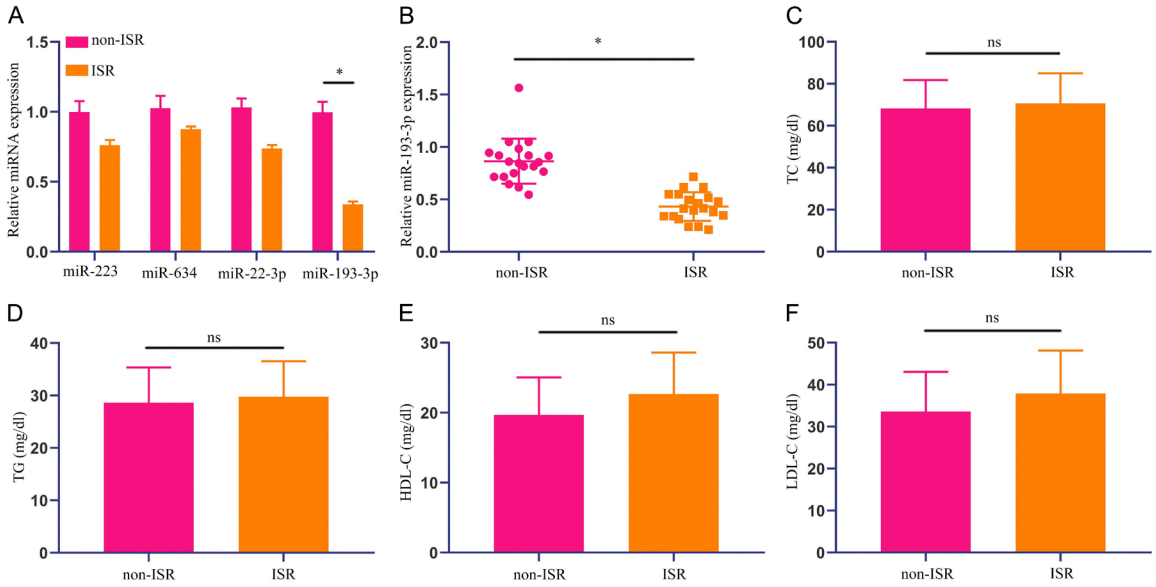


Figure 1. ISR patients exhibited a reduction in serum miR-193-3p levels. A: miR-223, miR-634, miR-22-3p, and miR-193-3p levels were detected via qPCR. B: ISR patients (n = 20) presented with a significant decline in miR-193-3p expression relative to non-ISR (n = 20). C: The TC (mg/dl) of ISR patients (n = 20) and non-ISR (n = 20) were detected. D: The TG (mg/dl) of ISR patients (n = 20) and non-ISR (n = 20) were detected. E: The HDL-C (mg/dl) of ISR patients (n = 20) and non-ISR (n = 20) were detected. F: The LDL-C (mg/dl) of ISR patients (n = 20) and non-ISR (n = 20) were detected. $^{ns}P > 0.05$; $^{*}P < 0.05$. Notes: TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol.

Table 2. Baseline participant characteristics

Characteristic	Non-ISR (n = 20)	ISR (n = 20)	*P*-value
Age, years	63.2 ± 3.76	62.7 ± 3.85	0.68
Sex (male), n	16	16	-
BMI, kg/m^2	24.5 ± 2.5	24.9 ± 2.5	0.58
History of smoking, n	11	12	-
Drinking history, n	8	9	-
Diabetes (type 2), n	7	8	-
Hypertension, n	10	11	-
Hyperlipidemia, n	4	5	-

Notes: BMI, body mass index.

3p overexpression group compared to NC group (**Figure 2E**, **2F**, **2I**), while OPN levels were substantially higher in the low-expressing miR-193-3p group compared to NC (**Figure 2L**, **2M**, **2P**).

In healthy blood vessels, VSMCs maintain a quiescent, contractile phenotype, characterized by high expression of α-SMA and SMMHC. However, during pathological processes, such as restenosis and atherosclerosis, VSMCs transition to a synthetic phenotype characterized by increased proliferative and migratory activities, diminished contractile markers, and upregulated OPN expression. These results suggest that miR-193-3p plays a crucial role in modulating the switching of VSMC phenotypes by promoting the contractile phenotype and inhibiting the synthetic phenotype.

miR-193-3p suppressed VSMC proliferative and migratory activity

To further investigate the functional role of miR-193-3p, VSMCs were transfected with miR-193-3p mimics, and proliferation and migration were assessed using CCK-8 and Transwell assays. Compared to the NC group, miR-193-3p overexpression resulted in a marked reduction in VSMC proliferation (**Figure 3A**). Additionally, the number of migrated cells was strikingly decreased in the miR-193-3p mimic group compared to the control group (**Figure 3B**, **3C**), indicating that miR-193-3p suppresses both proliferative and migratory activities in VSMCs.

miR-193-3p targets the IGF2 3'-UTR

To explore the molecular mechanism by which miR-193-3p exerts its effects, bioinformatic

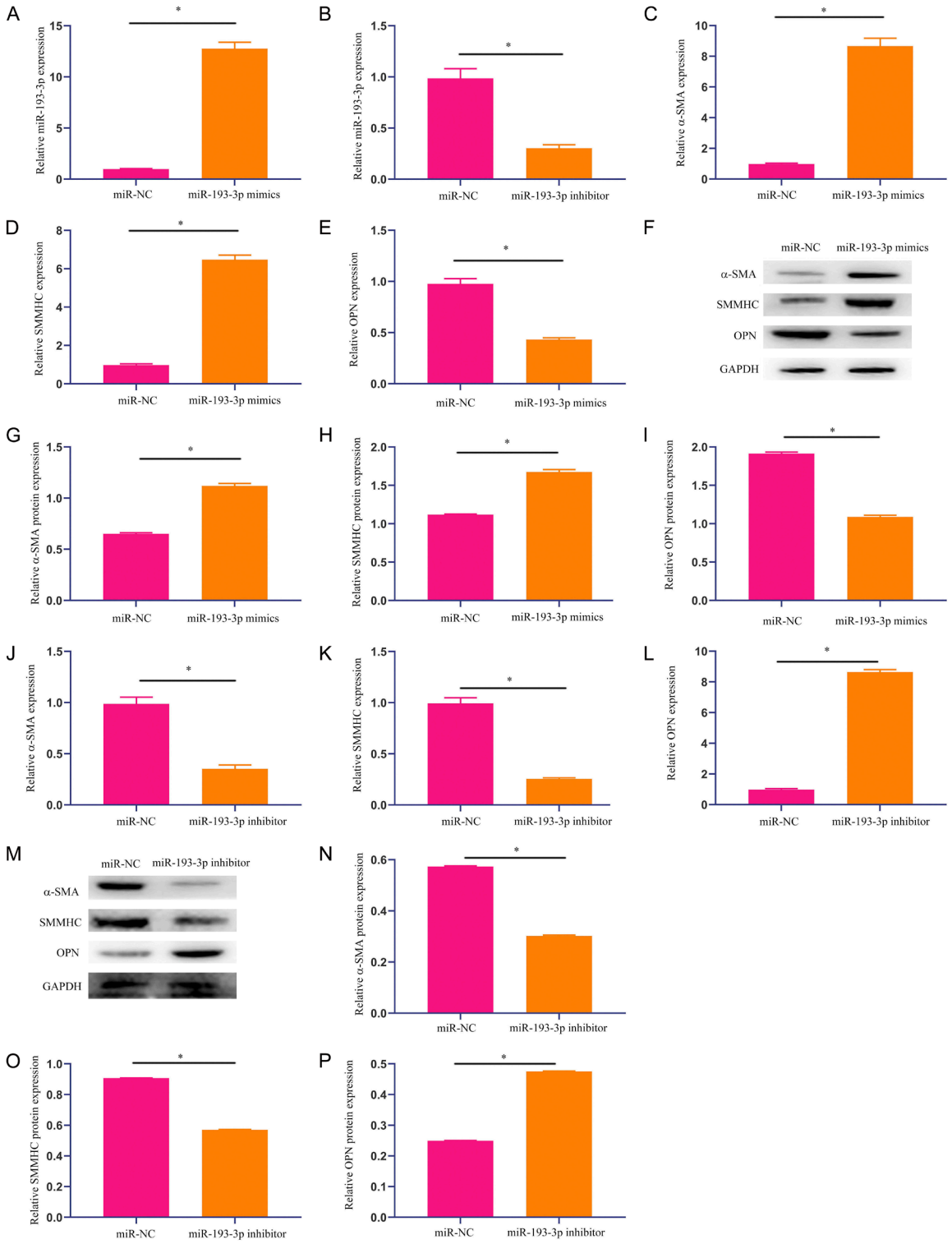


Figure 2. miR-193-3p regulated the phenotypic switching of VSMCs. (A, B) miR-193-3p expression following miR-193-3p mimic (A) or inhibitor (B) transfection (n = 3); (C-E) mRNA levels of contractile and synthetic marker α-SMA (C), SMMHC (D) and OPN (E) in VSMCs transfected miR-NC or miR-193-3p mimics (n = 3); (F-I) Protein levels of contractile and synthetic markers α-SMA, SMMHC and OPN in VSMCs transfected miR-NC or miR-193-3p mimics (n = 3); (J-L) mRNA levels of contractile and synthetic marker α-SMA (J), SMMHC (K) and OPN (L) in VSMCs transfected miR-NC or miR-193-3p inhibitors (n = 3); (M-P) Contractile and synthetic markers α-SMA, SMMHC and OPN protein levels were detected in VSMCs transfected miR-NC or miR-193-3p inhibitor (n = 3). *P < 0.05.

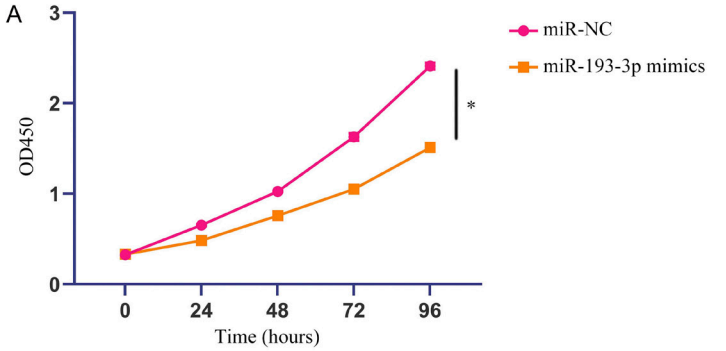
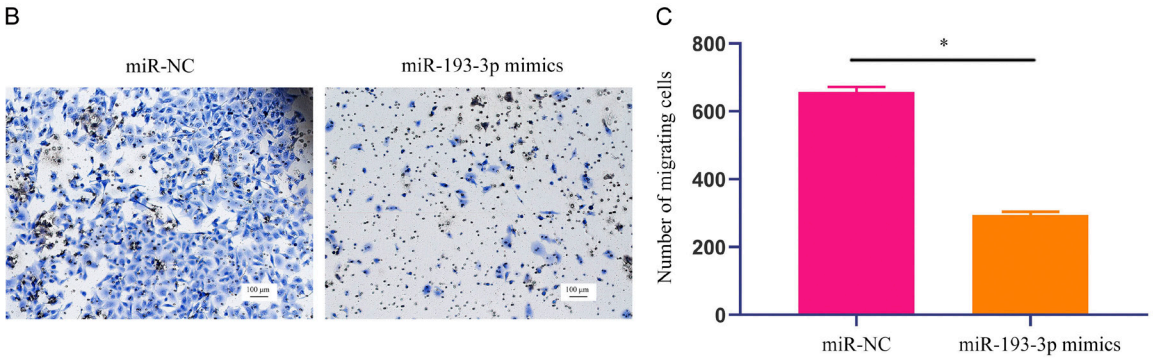


Figure 3. miR-193-3p suppressed the migratory and proliferative activity of VSMCs. A: CCK-8-based analysis of VSMC cell proliferation following miRNA mimic transfection (n = 3); B, C: Transwell assay-based analysis of VSMC migration following miRNA mimic transfection (n = 3). *P < 0.05.



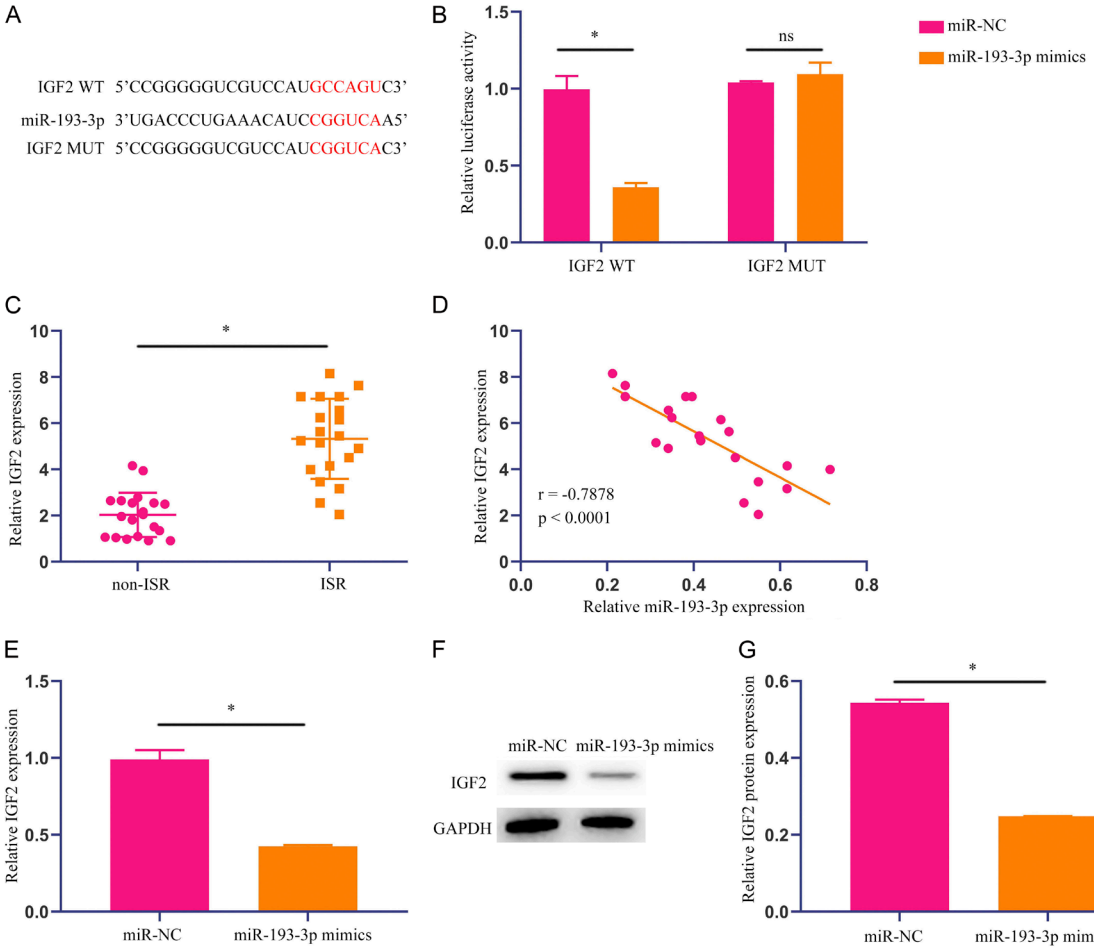


Figure 4. miR-193-3p interacted with the IGF2 3'-UTR, modulating IGF2 expression. (A) Binding site between the 3'-UTR of IGF2 and miR-193-3p; (B) Targeting relationship between miR-193-3p and IGF2 was assessed using a Dual-luciferase assay (n = 3); (C) IGF2 mRNA levels were elevated in ISR patients (n = 20) compared to controls (n = 20); (D) A negative association was noted between IGF2 and miR-193-3p in ISR patients (n = 20); (E-G) IGF2 mRNA (E) and protein (F and G) expression following miR-193-3p mimic transfection (n = 3). *P < 0.05.

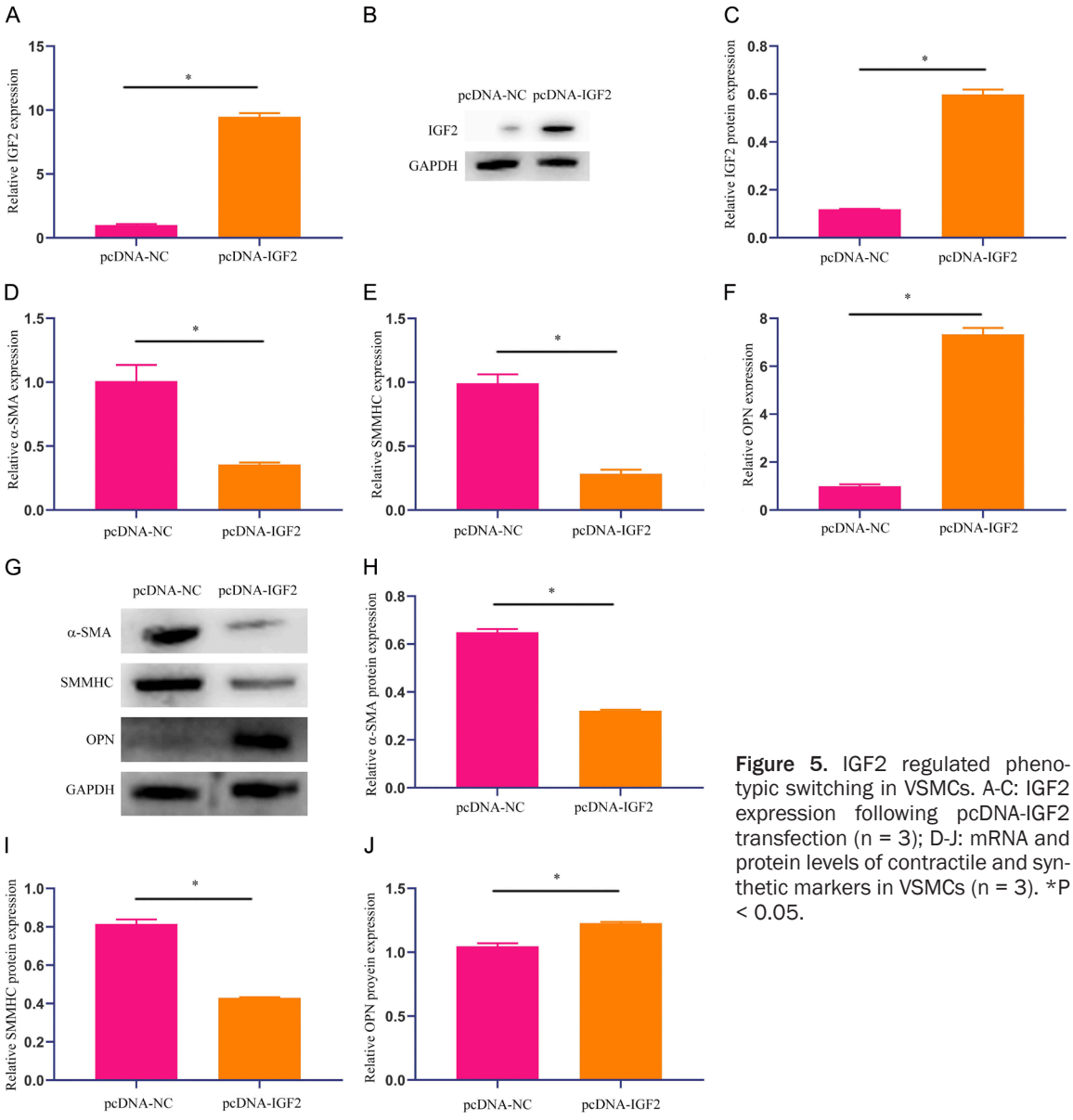


Figure 5. IGF2 regulated phenotypic switching in VSMCs. A-C: IGF2 expression following pcDNA-IGF2 transfection (n = 3); D-J: mRNA and protein levels of contractile and synthetic markers in VSMCs (n = 3). *P < 0.05.

analyses were conducted to identify potential binding sites within the IGF2 3' untranslated region (3'UTR) (**Figure 4A**). Dual-luciferase reporter assays confirmed that miR-193-3p directly interacts with the IGF2 3'UTR, leading to suppression of IGF2 expression (**Figure 4B**). Notably, IGF2 expression was significantly elevated in ISR patient samples (**Figure 4C**). Furthermore, Pearson correlation analysis revealed a negative correlation between miR-193-3p and IGF2 mRNA expression in ISR patients (**Figure 4D**). Transfection with miR-193-3p mimics led to a significant reduction in IGF2 levels compared to controls (**Figure 4E-G**),

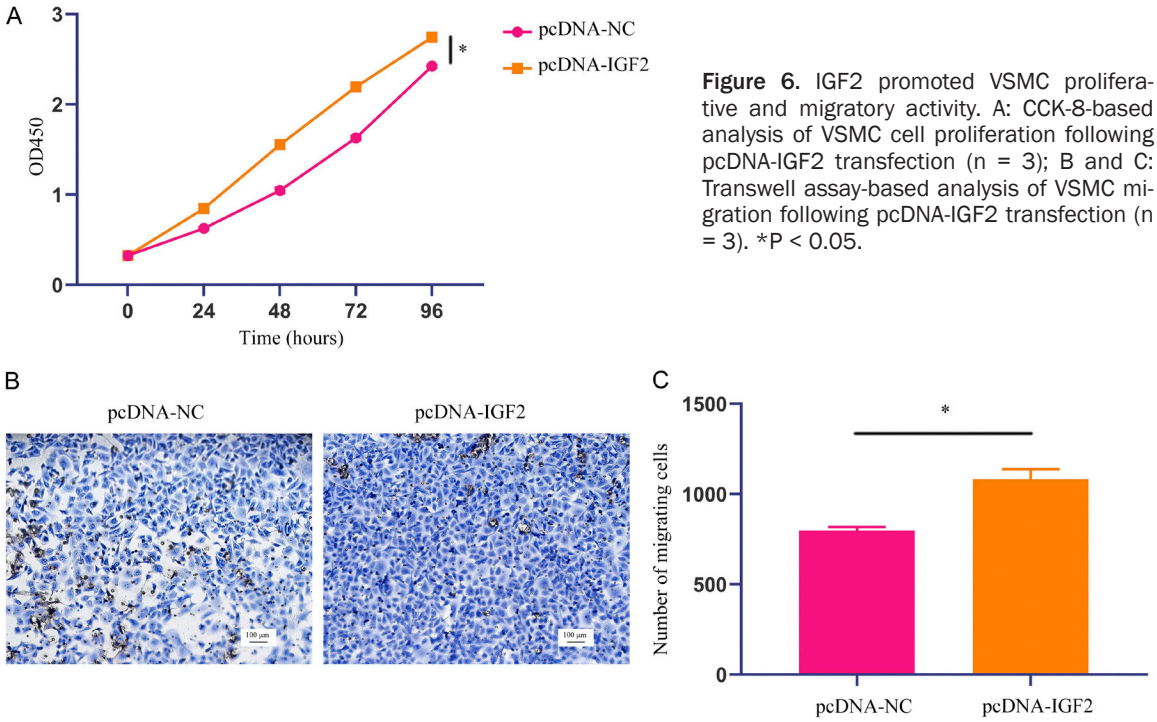


Figure 6. IGF2 promoted VSMC proliferative and migratory activity. A: CCK-8-based analysis of VSMC cell proliferation following pcDNA-IGF2 transfection (n = 3); B and C: Transwell assay-based analysis of VSMC migration following pcDNA-IGF2 transfection (n = 3). *P < 0.05.

suggesting that miR-193-3p negatively modulates IGF2 expression through direct post-transcriptional regulation.

IGF2 regulated phenotypic switching in VSMCs

To clarify the impact of IGF2 on VSMC phenotype, the expression of contractile and synthetic marker proteins in VSMCs was evaluated following transfection with the pcDNA-IGF2 vector. RT-qPCR and WB confirmed successful upregulation of IGF2 (**Figure 5A-C**). In VSMCs overexpressing IGF2, both mRNA and protein levels of the contractile markers α-SMA and SMMHC were markedly decreased compared to cells transfected with the pcDNA-NC (**Figure 5D**, **5E**, **5G-I**). Conversely, levels of the synthetic marker OPN were substantially upregulated (**Figure 5F**, **5G**, **5J**).

IGF2 promoted VSMC proliferative and migratory activity

To further investigate the role of IGF2, VSMCs were transfected with pcDNA-IGF2 plasmids, and proliferation and migration were assessed using CCK-8 and Transwell assays. Compared with the pcDNA-NC group, IGF2 overexpression significantly enhanced VSMC proliferation (**Figure 6A**). Additionally, the number of migrated cells was strikingly increased in the pcDNA-IGF2 group compared to controls (**Figure 6B**, **6C**), indicating that IGF2 promotes both proliferative and migratory activities in VSMCs.

miR-193-3p downregulated IGF2 to control phenotypic switching in VSMCs

To verify whether IGF2 mediates the effects of miR-193-3p on VSMC phenotypes, cells were co-transfected with miR-193-3p mimics and the pcDNA-IGF2 plasmids. Overexpression of IGF2 was confirmed by RT-qPCR and WB (**Figure 7A-C**). The miR-193-3p-induced upregulation of α-SMA and SMMHC expression was significantly reversed upon IGF2 overexpression (**Figure 7D**, **7E**, **7G-I**). Similarly, the inhibitory effects of miR-193-3p on OPN levels was also abrogated by IGF2 overexpression (**Figure 7F**, **7G** and **7J**). These findings collectively indicate that the regulation of VSMC phenotypic switching by miR-193-3p is, at least in part, mediated through the downregulation of IGF2.

miR-193-3p limited the migratory and proliferative activity of VSMCs through downregulation of IGF2

To further assess how the miR-193-3p/IGF2 axis regulates VSMC behaviors, cells were co-transfected with miR-193-3p mimics and pcDNA-IGF2 plasmids and subjected to prolifera-

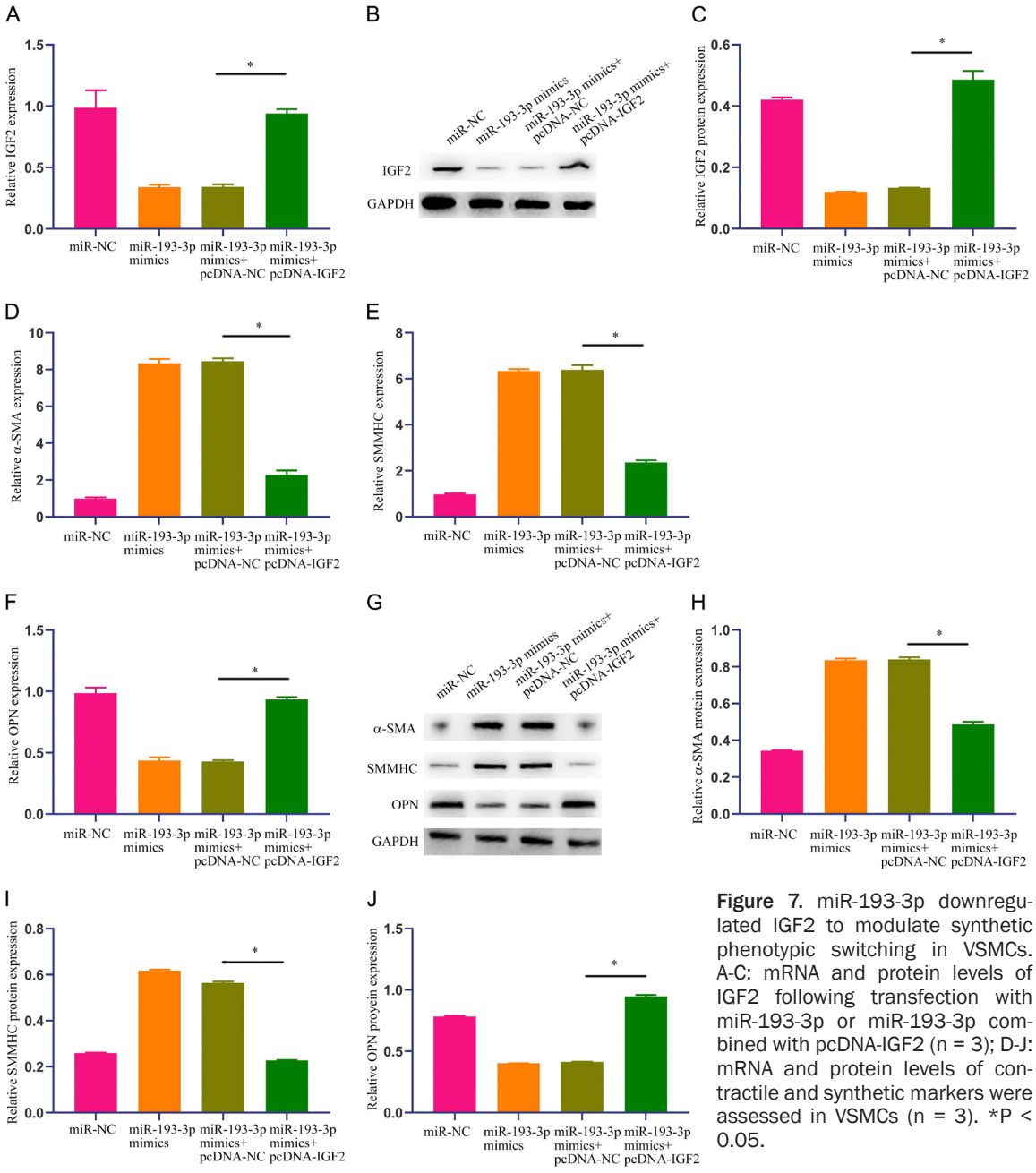


Figure 7. miR-193-3p downregulated IGF2 to modulate synthetic phenotypic switching in VSMCs. A-C: mRNA and protein levels of IGF2 following transfection with miR-193-3p or miR-193-3p combined with pcDNA-IGF2 (n = 3); D-J: mRNA and protein levels of contractile and synthetic markers were assessed in VSMCs (n = 3). *P < 0.05.

tion and migration assays. Overexpression of IGF2 significantly abrogated the suppressive effects of miR-193-3p on both proliferation (**Figure 8A**) and migration (**Figure 8B**, **8C**), supporting the conclusion that IGF2 is a key effector of miR-193-3p in regulating VSMC function.

Discussion

Despite advancements in interventional cardiology and drug therapy, treating patients with ISR remains a significant clinical challenge. Bare-metal stents, although widely used in PCI, are particularly prone to ISR, especially in cases involving complex lesions or anatomically difficult sites [20].

Recent research has identified several miRNAs with aberrant expression profiles in ISR patients [13, 21]. For example, miR-93-5p has been proposed as a potential biomarker for ISR [22], and dysregulation of miR-17 has also

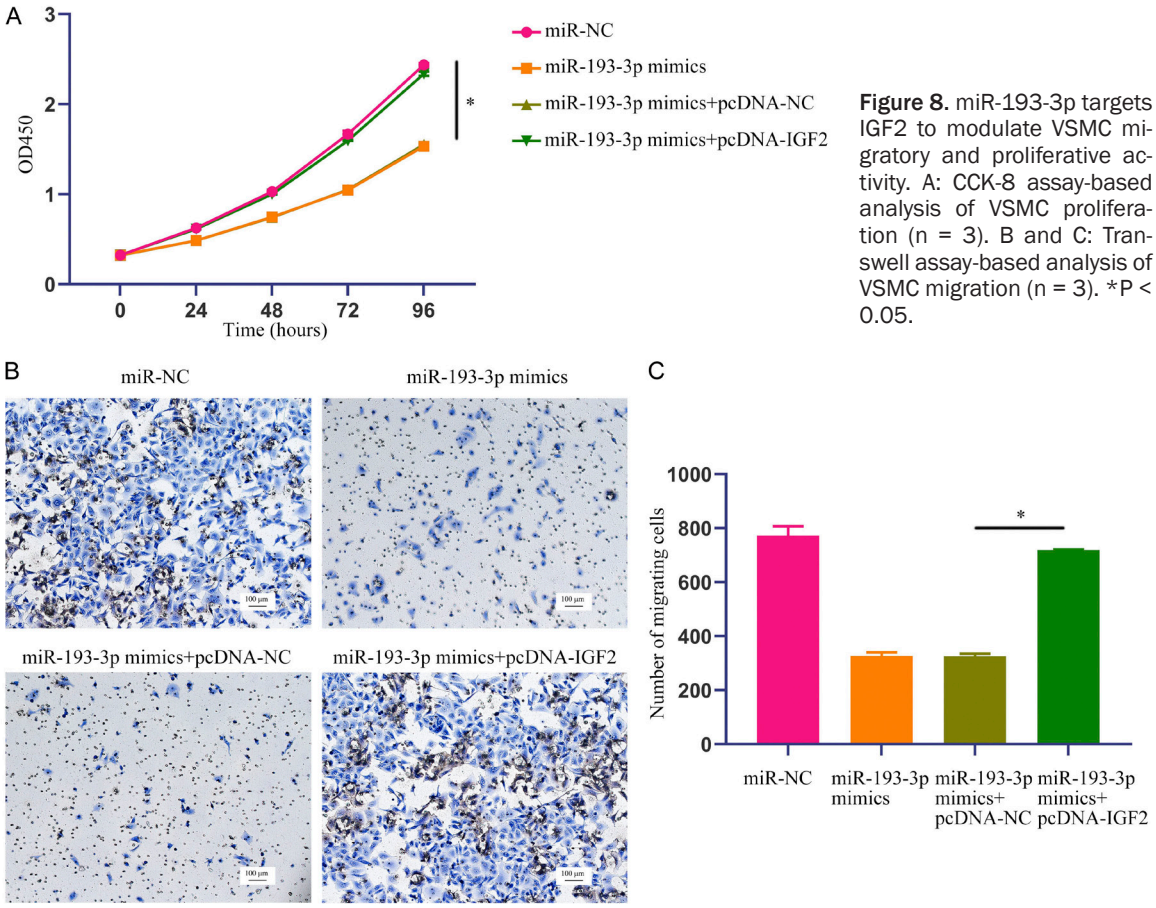


Figure 8. miR-193-3p targets IGF2 to modulate VSMC migratory and proliferative activity. A: CCK-8 assay-based analysis of VSMC proliferation (n = 3). B and C: Transwell assay-based analysis of VSMC migration (n = 3). *P < 0.05.

been reported in ISR [23]. However, the role of miR-193-3p in ISR remains poorly understood. The present findings show that miR-193-3p is significantly downregulated in the sera of ISR cases compared to non-ISR controls. Functional studies have indicated that miR-193-3p upregulates the contractile proteins α SMA and SMMHC while suppressing the synthetic indicator OPN in VSMCs. Moreover, miR-193-3p inhibits proliferative and migratory activities in VSMCs. Mechanistically, these effects are mediated through the direct suppression of IGF2, which was confirmed as a downstream target of miR-193-3p. Rescue experiments confirmed that overexpression of IGF2 reversed the phenotypic and functional effects of miR-193-3p overexpression.

In this study, bioinformatics analysis was conducted to identify potential interaction sites for miR-193-3p in the 3'-UTR of IGF2 mRNA. The expression of IGF2 was found to be elevated in the ISR group, while miR-193-3p level was significantly reduced. Pearson's correlation analysis revealed a strong inverse relationship between miR-193-3p and IGF2 mRNA levels in ISR patients. IGF2 plays a crucial role in the pathogenesis of various vascular disorders and is produced by multiple vascular cell types, including VSMCs [24-26]. Previous studies have shown that downregulation of miR-637 promotes VSMC proliferation and migration via regulating IGF2 expression [26]. Moreover, overexpression of miR-193-3p markedly increased mRNA and protein levels of α-SMA and SMMHC, markers of contractile activity, in VSMCs. However, these effects were markedly attenuated by simultaneous overexpression of IGF2, suggesting a direct antagonistic interaction. Similarly, the inhibitory effects of miR-193-3p on OPN, a marker of the synthetic VSMC phenotype, were also significantly reversed by IGF2 overexpression. In functional assays, miR-193-3p-mediated suppression of VSMC proliferation and migration in VSMC was notably mitigated when IGF2 was concurrently overexpressed, further supporting the regulatory axis between miR-193-3p and IGF2.

This study still has several limitations. First, the precise molecular mechanisms through which IGF2 influences VSMC behavior remain to be fully elucidated. Second, no pharmacological agents targeting miR-193-3p or IGF2 were identified or evaluated in this investigation. Third, the sample size of ISR cases included in this study was relatively small, necessitating validation in larger patient cohorts. Future research will focus on dissecting the downstream signaling pathways involved and exploring the translational potential of targeting the miR-193-3p-IGF2 axis as a therapeutic intervention for ISR.

Conclusion

In summary, this study identifies the miR-193-3p-IGF2 axis as a key regulatory pathway influencing VSMC phenotypic modulation in ISR. The downregulation of miR-193-3p observed in ISR facilitates VSMC dedifferentiation via upregulation IGF2, thereby promoting a synthetic, proliferative, and migratory phenotype. Conversely, overexpression of miR-193-3p enhances contractile protein expression while inhibiting cellular proliferation and migration, effects that are counteracted by IGF2 overexpression. These results offer novel mechanistic insights into the molecular basis of ISR and suggest that IGF2 may serve as a potential therapeutic target. Strategies aimed at restoring miR-193-3p expression or inhibiting IGF2 may hold promise for the treatment of ISR.

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Disclosure of conflict of interest

None.

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