The lncRNA OIP5-AS1/miR-181a-5p Axis Promotes TGF-β1-induced Fibrosis in HK2 Cells

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Introduction. This study was conducted to explore the role of OIP5-AS1 in a fibrosis cell model through its interaction with miR-181a-5p.
Methods. An in-vitro fibrosis model was established by inducing human renal tubular epithelial cells (HK2) with TGF-β1. The expression levels of OIP5-AS1 and miR-181a-5p in the control (Normal) and model (TGF-β1) groups were measured using Quantitative Real-time Polymerase Chain Reaction (qPCR).. qPCR and Western Blot (WB) were used to detect the expression of genes and proteins related to fibrosis and EMT in the two groups of cells. Subsequently, The effect of OIP5-AS1 on TGF-β1-induced fibrosis in HK2 cells was investigated by assessing cell proliferation using the CCK-8 assay and analyzing the expression of fibrosis- and EMT-related proteins through WB.. The targeting relationship between OIP5-AS1 and miR-181a-5p, as well as the influence of OIP5-AS1 on miR-181a-5p expression, was investigated using a dual-luciferase reporter assay. Subsequently, the impact of miR-181a-5p upregulation on the proliferation of TGF-β1-induced HK2 cells was examined through a CCK-8 assay.
Results. The study found that TGF-β1 treatment upregulated OIP5-AS1, α-SMA, Col-IV, and FN in HK2 cells while downregulating miR-181a-5p and E-cadherin. OIP5-AS1 downregulation promoted cell proliferation and inhibited fibrosis-related proteins. MiR-181a-5p was identified as a direct target of OIP5-AS1, and its upregulation enhanced cell proliferation.
Conclusion. The suppression of OIP5-AS1 attenuates TGF-β1-induced fibrosis in HK2 cells through the regulation of miR-181a-5p.

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INTRODUCTION

Diabetes mellitus (DM), with the incidence ranking third among all diseases, is a chronic noncommunicable disease that seriously endangers human life and health worldwide.[1] The situation is more serious in China, where there are approximately 144 million patients with DM, ranking China first in the world in terms of DM.[2] Diabetes mellitus is associated with various complications, among which diabetic nephropathy (DN) stands out as one of the most prevalent and severe chronic progressive microvascular complications.[3] With the increasing number of DM patients, the incidence of DN is also increasing rapidly. Although some achievements have been made in the prevention and treatment of DN, the

existing drugs and treatment methods for DN can only control the progression of DN to a certain extent but cannot completely reverse it. Therefore, investigating the pathogenesis of DN is highly important for the prevention and treatment.

Renal fibrosis typically represents the ultimate outcome of various kidney diseases, such as glomerulonephritis and diabetic nephropathy.[4] From a histological perspective, renal fibrosis is marked by an overabundance of extracellular matrix (ECM) deposition,[5] often associated with multiple pathological alterations in renal tubular epithelial cells. These changes include epithelial-to-mesenchymal transition (EMT), activation of fibroblasts, infiltration of immune cells, and apoptosis.[6,7] Despite extensive research into the pathogenesis and molecular mechanisms of renal fibrosis, effective treatments remain limited. Considering that renal fibrosis can result in scar formation and potentially progress to renal failure, it is imperative to investigate new mechanisms of renal fibrosis and identify novel therapeutic targets for CKD, which is highly important for developing effective treatment strategies and preventing kidney diseases.

Long noncoding RNAs (lncRNAs) are a type of RNA with transcriptional products exceeding 200 nucleotides in length and possess little to no protein-coding potential.[8,9] Growing evidence indicates that lncRNAs are involved in a wide range of regulatory functions in biological processes and disease development, and they significantly influence cell proliferation, migration, invasion, and apoptosis.[10-12] In recent years, researchers have demonstrated that lncRNAs play important regulatory roles in fibrosis. For example, silencing lnc-hser aggravated liver fibrosis by inducing epithelial–mesenchymal transition (EMT) and apoptosis.[13] LNC-PCF promotes the progression of pulmonary fibrosis by regulating Map3k11 through direct targeting of miR-344a-5p.[14] As part of the lncRNA family, the specific role and underlying mechanism of long non-coding RNA OPI5-AS1 in the progression of renal fibrosis require further exploration.

Therefore, this study focused on exploring the possible importance of OPI5-AS1 in the development of renal fibrosis and clarifying the complex mechanisms through evaluating the interaction between OPI5-AS1 and miR-181a-5p.

MATERIALS AND METHODS

Source of cells

HK-2 cells (CL-0109, Punosai) and 293T cells (GNHu17, Chinese Academy of Sciences) were used. The cells were maintained in DMEM complete medium (KGM12800S, KGI Bio) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin, and incubated at 37℃ in a 5% CO2 incubator.

Cell model construction and group intervention

Control group cells were cultured normally, and Model group was constructed by adding 10 ng/mL TGF-β1 (CA59, Novoprotein) to the cells and incubating them for 48 hours. OPI5-AS1 siRNA and its corresponding NC or miR-181a-5p and NC (all provided by Suzhou Zhongke Zhihui Biotechnology Co., LTD) were transfected into HK2 cells before the addition of TGF-β1. After successful transfection, TGF-β1 was added to the HK2 cells.

Cell transfection

When the cell density reached 70%, the cells were prepared for transfection. The medium of the cells was replaced with 1 ml of serum-free medium. Two EP tubes were sterilized, and 125 µl of Opti-MEM (31985-062, Gibco) was added to each tube. One tube was mixed with 5 µL of Lipofectamine 3000 (L3000015, Invitrogen), and the other one was mixed with 12.5 µl of RNA (the dry powder of the siRNA was dissolved in DEPC water; 125 µl/1OD) and incubated at room temperature for five minutes. The two EP tubes mentioned above were combined and incubated at room temperature for 15 minutes. Subsequently, the mixture was transferred to the corresponding wells of a six-well plate, and the cells were placed back into the incubator for further culturing. Six hours post-transfection, 1 ml of complete medium with 20% serum was added to the six-well plate. Forty-eight hours later, the corresponding experiments were carried out.

Dual luciferase assay

The cell density reached 50% for transfection, and the DMEM containing 5% serum was changed in advance. According to the experimental groups, the reagents of each group were prepared and added to the corresponding groups. Following mixing, the cells were maintained at room temperature for

15 minutes, after which 50 µl was dispensed into each well, and the reagents were added dropwise to the 12-well plate.

Forty-eight hours post-transfection, the cells were harvested, and 200 µl of lysis buffer was added to each well for cell lysis at 4℃ for 20 minutes. The lysed samples were subsequently stored at -80℃. For the detection process, 70 µl of cell lysate from each group was transferred to a black 96-well plate, followed by the addition of 100 µl of luciferase detection reagent to measure firefly luciferase activity. Next, 100 µl of Renilla luciferase assay reagent (prepared at a substrate:buffer ratio of 1:100) was added to each well to determine Renilla luciferase activity.

Real-time fluorescence quantitative PCR

The cells were collected in a culture dish, and the cell culture medium in the culture dish was removed. According to the amounts of cells, 1 mL of TRIzol Reagent (CW0580S, CWBIO) was added to each dish, and 0.2 mL of chloroform was added after each 1 mL aliquot of TRIzol reagent was added. The concentration and purity of the miRNAs and mRNAs (OD260/OD280) were determined by a UV–visible spectrophotometer. micDNA and cDNA were synthesized by a miRNA reverse transcription kit and an mRNA reverse transcription kit, respectively. The reaction procedure was conducted as follows: initial denaturation at 95℃ for 10 min, followed by 40 cycles of denaturation at 95℃ for 10 s, annealing at 58℃ for 30 s, and extension at 72℃ for 30 s. β-Actin served as the internal reference, and the relative gene expression levels were determined using the $2^{-\triangle\triangle Ct}$ method. The primer sequence information is shown in Table 1.

Western blot

The culture medium in the dishes was removed, and 100 µL of cell lysis buffer was added to each well, followed by incubation on ice for 20 min. Cells were scraped into one side using a cell scraper and transferred to labeled EP tubes. The supernatant was collected after centrifugation, transferred to a new EP tube for BCA protein quantification, and the total protein was stored at -20°C. Protein concentration was measured using a BCA kit (E-BC-K318-M, Elabscience). After denaturation, samples were subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS–PAGE) for 1.5 h, followed by transfer onto PVDF membranes at 300 mA for 1.5 h. The membranes were then incubated overnight at 4°C with the following primary antibodies: GAPDH (TA-08, Nakasuga Jinqiao, 1:2000), α-SMA (14395-1-AP, Proteintech, 1:1000), S100A4 (DF6516, Affinity, 1:1000), E-cadherin (GB11082, Servicebio, 1:1000), FN (66042-1-lg, Proteintech, 1:1000), Col-IV (AF0510, Affinity, 1:1000), and SIRT1 (DF6033, Affinity, 1:1000). The next day, the membranes were incubated with secondary antibodies, IgG (H+L) (ZB-2301, Zhongshan Jinqiao, 1:1000), at room temperature for 2 hours. After washing, the PVDF membranes (IPVH00010, Millipore) were treated with chemiluminescent substrate and imaged using an ultrahigh sensitivity chemiluminescence imaging system.

Statistical analysis

All experiments were repeated three times, and the quantitative results were expressed as the mean ± standard deviation (X ± S). Independent sample t tests were used to compare the quantitative values between two groups; one-way analysis of variance was used to compare the quantitative values among multiple groups, and LSD method was used for pairwise comparisons. The test level was α = 0.05. SPSS 20.0 software was used for statistical analysis.

Table 1. Primer sequence information

Gene name	Forward Primer (5′→3′)	Reverse Primer (5′→3′)
OIP5-AS1	TGGGTCTTTTGCTGTTTGC	CTACTTCTTTAGTCTTCTTGCTTGG
miR-181a-5p	CGCGAACATTCAACGCTGTC	AGTGCAGGGTCCGAGGTATT
SIRT1	GGCGGCTTGATGGTAATCAG	TGGCATGTCCCACTATCACTG
α-SMA	GCGATCTCACCGACTACCTG	GCCGACTCCATACCGATGAA
FN	CATACCCGCCGAATGTAGGT	TCCAGGAACCCTGAACTGTAAGG
COL-IV	GACCATTTATTAGTAGGTGTGCTG	ACAAAAGAGTAGCCGATCCACA
E-cadherin	AATCTGAAAGCGGCTGATACTG	CCATTCGTTCAAGTAGTCATAGTCC
β-actin	TGGCACCCAGCACAATGAA	CTAAGTCATAGTCCGCCTAGAAGCA

RESULTS

Expression of the lncRNA OPI5-AS1/miR-181a-5p signaling axis in a fibrotic cell model

To explore the expression of the OPI5-AS1/miR-181a-5p signaling axis in a fibrotic cell model, we established a fibrotic cell model by treating HK-cells with TGF-β. After that, the protein expression of genes related to the OPI5-AS1/miR-181a-5p/SIRT1 signaling axis and EMT-related genes was measured by qRT–PCR and WB, and the results are shown in Figure 1. Figure 1-A shows that the levels of the OPI5-AS1 in the model group significantly increased compared with those in the control group ($P < .05$), while the levels of the miR-181a-5p and SIRT1 mRNAs significantly decreased ($P < .05$). Figure 1-B shows that the mRNA levels of the EMT-related

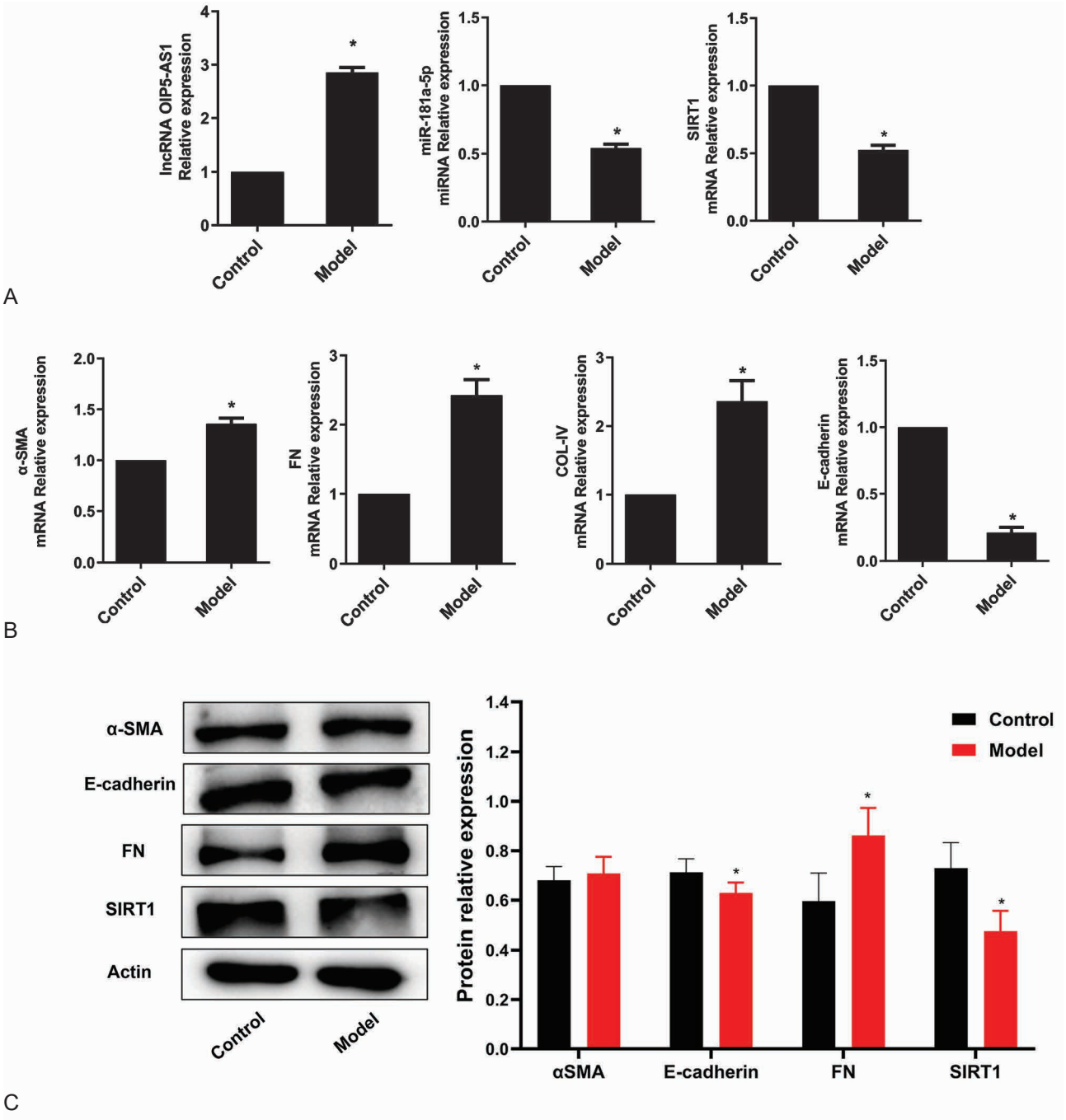


Figure 1. Expression of the lncRNA OPI5-AS1/miR-181a-5p signaling axis in a fibrotic cell model. (A) Expression of the lncRNA OPI5-AS1/miR-181a-5p. (B) Expression of fibrosis-related genes. (C) Expression of fibrosis-related proteins (*$P < .05$ vs. control).

genes α-SMA, FN, and Col-IV in the model group significantly increased compared with those in the control group ($P < .05$), while the mRNA level of E-cadherin significantly decreased ($P < .05$). Figure 1-C shows that compared with those in the control group, the α-SMA and FN protein levels in the model group were significantly higher, while the E-cadherin protein level was significantly lower ($P < .05$).

Effect of lncRNA OPI5-AS1 knockdown on TGF-β-induced HK2 cell proliferation

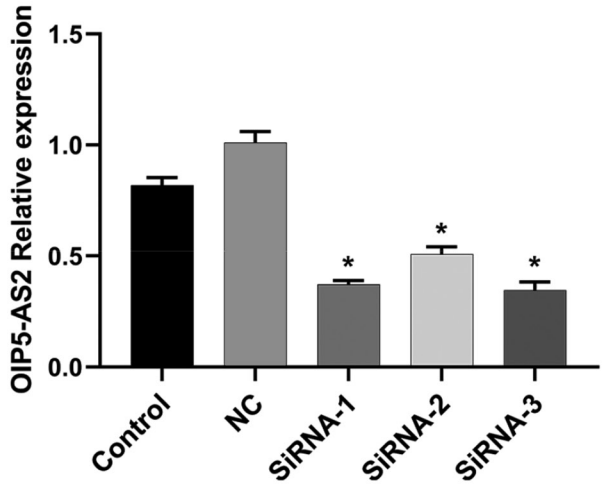
To investigate the effect of OPI5-AS1 knockdown on TGF-β-induced HK2 cell proliferation, first, three OPI5-AS1 siRNAs were constructed and transfected into HK2 cells, and the transfection effect was verified by qPCR. The results are shown in Figure 2-A. The expression of OPI5-AS1 was significantly downregulated ($P < .05$), among which siRNA-3 had the most significant effect, and siRNA-3 was selected for subsequent experiments. Next, the proliferation of cells in each group after OPI5-AS1 siRNA transfection was detected by a CCK-8 assay (Figure 2-B). Compared with that in the control group, cell proliferation in the model group and the NC group was significantly inhibited ($P < .05$). Compared with that in the model group, proliferation in the sh-OPI5-AS1 group was significantly greater ($P < .05$). These results suggest that the downregulation of OPI5-AS1 can promote the proliferation of HK2 cells induced by TGF-β.

Effect of lncRNA OPI5-AS1 downregulation on TGF-β-induced fibrosis and EMT-related protein expression in HK2 cells

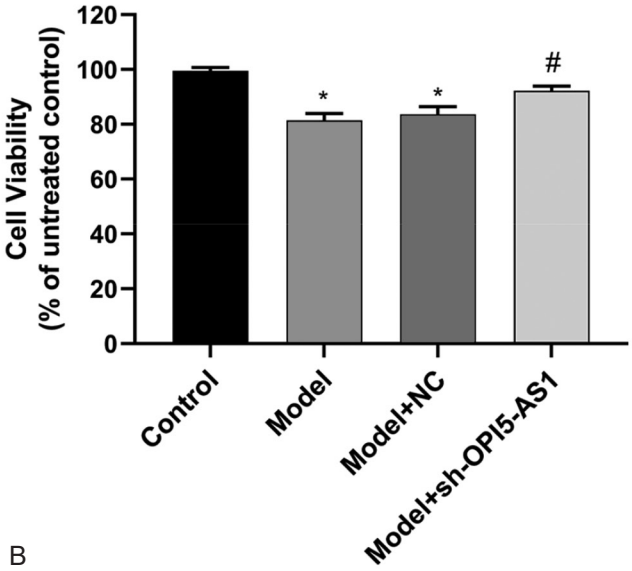
To investigate the effect of OPI5-AS1 knockdown on TGF-β-induced EMT-related gene and protein expression, fibrosis and EMT-related gene and protein expression were detected by WB (Figure 3 and Figure 3-B and 3-C). Compared with the control group, the expression of the fibrosis-related proteins α-SMA and col IV was significantly upregulated in the model group ($P < .05$). Compared with the model group, the expression of α-SMA and col IV was significantly downregulated in the sh-OPI5-AS1 group ($P < .05$). (Figure 3-B and 3-C) Compared with those in the control group, the expression levels of the EMT-related proteins FN and S100A4 were significantly upregulated in the model group ($P < .05$). Compared with those in the model group, the expression levels of FN and S100A4 were significantly downregulated in the sh-OPI5-AS1 group ($P < .05$). OPI5-AS1 inhibited TGF-β-induced fibrosis and EMT in HK2 cells.

miR-181a-5p is a direct target of OIP5-AS1 in renal tubular epithelial cell fibrosis

It is well known that lncRNAs act on a variety of miRNAs through sponges and have a variety of biological functions. To investigate the potential target genes of OIP5-AS1 involved in the development and progression of renal fibrosis



A



B

Figure 2. Effect of lncRNA OPI5-AS1 knockdown on TGF-β-induced HK2 cell proliferation. (A) Transfection verification. (B) CCK-8 detection of cell proliferation in each group (*$P < .05$ vs. control, #$P < .05$ vs. model).

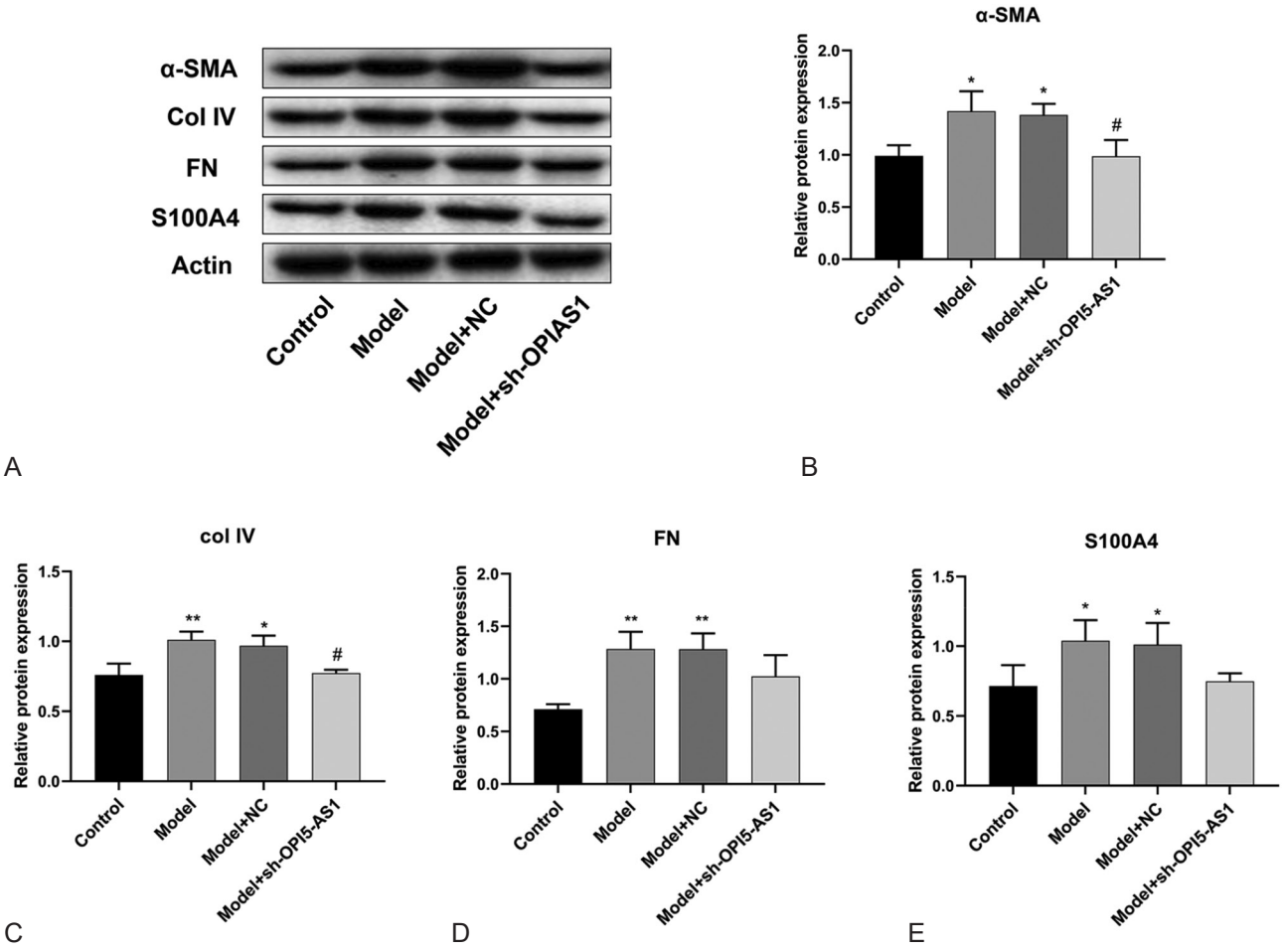


Figure 3. Effect of lncRNA OPI5-AS1 knockdown on TGF-β-induced fibrosis and EMT-related protein expression in HK2 cells. (A) Representative WB band plots and (B-E) bar graphs of relevant protein expression in each group (*P < .05 vs. control, **P < .01 vs. control, #P < .05 vs. model).

and to evaluate OIP5-AS1-related miRNAs, we used bioinformatics analysis (from the starBase database) to identify genes directly regulated by OIP5-AS1. Among all the targets, miR-181a-5p was selected for further study because it is an important regulator of the occurrence and progression of renal fibrosis in DN. The binding site of OIP5-AS1 for miR-181a-5p is shown in Figure 4A. miR-181a-5p expression was significantly downregulated in HK2 cells treated with TGF-β. In addition, we found that miR-181a-5p was negatively regulated by OIP5-AS1. Compared with that in the NC group, the expression level of miR-181a-5p in the sh-OIP5-AS1 group was significantly greater (Figure 4-B).

To further verify whether OIP5-AS1 directly binds to miR-181a-5p, a dual luciferase reporter assay was performed. The 3′ untranslated region of wild-type (WT) or mutant (Mut) OIP5-AS1 was amplified with a luciferase reporter plasmid. As shown in Figure 4-C, cotransfection of OIP5-AS1-WT cells with the miR-181a-5p mimic resulted in a significant decrease in luciferase activity, while the miR-181a-5p binding site in the 3′ untranslated region of OIP5-AS1-Mut cells was not significantly mutated. These results indicated that OIP5-AS1 could directly bind to miR-181a-5p.

Effect of miR-181a-5p upregulation on TGF-β-induced HK2 cell proliferation

To investigate the effect of miR-181a-5p upregulation on TGF-β-induced HK2 cell proliferation, a miR-181a-5p mimic was constructed and transfected into HK2 cells, and the effect of transfection was verified by qPCR. The results are shown in Figure 5-A. After miR-181a-5p mimic transfection, the level of miR-181a-5p increased significantly (P < .05). Next, the cell proliferation of each group after miR-181a-5p mimic transfection

miRNA	GeneID	GeneName	GeneType	TargetSite	Alignment
hsa-miR-181a-5p	ENSG00000247556	OIP5-AS1	processed_transcript	chr15:41594753-41594774[+]	Target: 5' cuuuuagaACAGU-AUGAAUGUa 3' miRNA : 3' ugaguggcUGUCGCAACUUACAa 5'
hsa-miR-181a-5p	ENSG00000247556	OIP5-AS1	processed_transcript	chr15:41581240-41581265[+]	Target: 5' gaUGGUUGCACAGCAGUAUGAAUGUa 3' miRNA : 3' ugAGUGGC-UGUCG-CA-ACUUACAa 5'

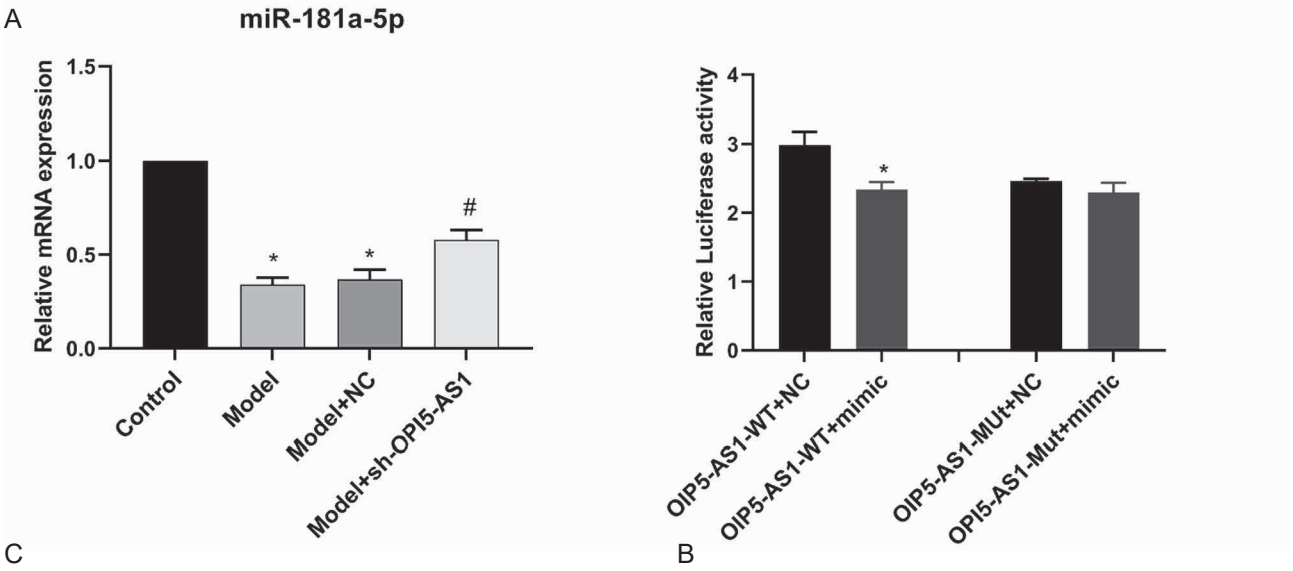


Figure 4. miR-181a-5p is a downstream target of OPI5-AS1. (A) The binding sites of OPI5-AS1 and miR-181a-5p are shown. (B) The expression of miR-181a-5p was detected by RT–PCR. (C) The targeting relationship between OPI5-AS1 and miR-181a-5p was verified by dual-luciferase reporter assays (*P < .05 vs. control or OPI5-AS1-WT+NC, #P < .05 vs. model).

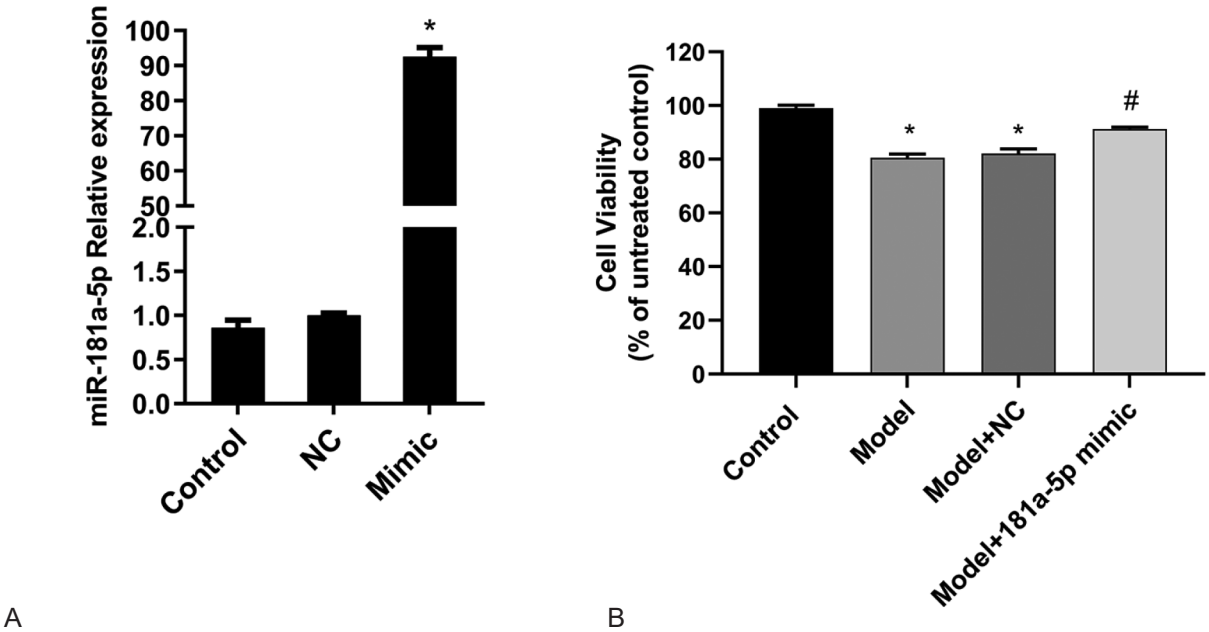


Figure 5. Effect of miR-181a-5p upregulation on TGF-β-induced HK2 cell proliferation. (A) Transfection verification. (B) CCK-8 detection of cell proliferation in each group (*P < .05 vs. control, #P < .05 vs. model).

was detected by a CCK-8 assay, and the results are shown in Figure 5-B. Compared with the control group, cell proliferation in the model group and the NC group was significantly inhibited (P < .05).

Compared with the model group, cell proliferation in the miR-181a-5p mimic group was significantly promoted ($P < .05$). These results suggest that upregulation of miR-181a-5p can promote the proliferation of HK2 cells induced by TGF-β.

DISCUSSION

Renal fibrosis is increasingly becoming a major public health problem and is recognized as a common terminal stage of diabetic nephropathy.[15] The pathogenesis of renal fibrosis is a progressive process that reduces the capacity for tissue repair and ultimately leads to end-stage kidney disease.[16]

Increasing evidence highlights that aberrant expression levels of lncRNAs and miRNAs are associated with renal diseases such as renal fibrosis.[17] For example, Wang *et al.* demonstrated that knockdown of lncRNA Gas5 contributes to anti-fibrosis effects by competitively binding to miR-96-5p.[18] In addition, the lncRNA NR_038323 inhibited HG-induced renal fibrosis through the miR-324-3p/DUSP1 axis.[19]

As a typical multifunctional lncRNA, OPI5-AS1 is widely expressed in a variety of diseases and plays a crucial role in a variety of molecular and cellular processes. For example, OPI5-AS1 overexpression promotes tumorigenesis and the development of gastric cancer by competitively binding to miR-106a-5p.[20] In lung adenocarcinoma cells, the lncRNA OIP5-AS1 regulates the expression of Bcl-2 by targeting miR-448 to affect the progression of lung adenocarcinoma.[21] OIP5-AS1 induces the LPAATβ/PI3K/AKT/mTOR signaling pathway by adsorbing miR-340-5p, leading to cisplatin resistance in osteosarcoma.[22] However, the underlying mechanism of OIP5-AS1 in renal fibrosis remains unclear. Our results showed that OIP5-AS1 was significantly upregulated in a TGF-β-induced HK2 fibrosis cell model, and inhibition of OIP5-AS1 restored TGF-β-induced HK2 cell proliferation. In addition, inhibition of OIP5-AS1 significantly inhibited fibrosis and EMT-related protein expression.

Transforming growth factor-β-1 is an important factor leading to renal fibrosis.[23] In this study, HK-2 cells induced by transforming growth factor-β-1 were used to establish an in vitro renal tubular fibrosis model. We focused on the potential function of OIP5-AS1 and further explored its underlying molecular mechanism in the progression of renal fibrosis. We found that the expression of miR-181a-5p was significantly downregulated in HK-2 cells treated with Tgf-β.

miRNAs are a group of small, noncoding RNAs of approximately 22 nucleotides that have been proposed to act as negative regulators.[24] Studies have shown that miRNAs have inhibitory or oncogenic roles in tumorigenesis, while the expression of lncRNAs can regulate the activity of miRNAs.[25] LncRNAs typically bind to miRNAs as competing endogenous RNAs and subsequently exert their functions. Therefore, we hypothesized that OPI5-AS1 affects the renal fibrosis process by sponging specific miRNAs. We used bioinformatics analysis to identify genes directly regulated by OPI5-AS1. In this study, we identified miR-181a-5p as a target miRNA of OPI5-AS1. Correspondingly, the expression level of miR-181a-5p was negatively regulated by OPI5-AS1. In addition, luciferase assays showed that miR-181a-5p could bind to OPI5-AS1 3′UTR and reduce its luciferase activity in HK-2 cells. In addition, we found that upregulation of miR-181a-5p promoted TGF-β-induced HK2 cell proliferation.

CONCLUSIONS

Overall, to the best of our knowledge, this study demonstrates that OPI5-AS1 knockdown plays an antifibrotic role by directly targeting miR-181a-5p to promote cell proliferation and downregulate the expression of EMT-related proteins. Overall, these findings provide insight into the mechanisms of renal fibrosis and offer new predictive biomarkers for renal disease patients' progression.

ETHICAL COMPLIANCE

Not Aapplicable.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

Conceptualization-XY.L, G.Y; Methodology-XY.L, HX.P; Software-Q.F; Validation-XY.L, SM.Z; Formal Analysis-Y.L; Investigation-XY.L, YL.Z; Resources-G.Y, HX.P; Data Curation-Q.F; Writing-Original Draft-XY.L; Writing-Review & Editing-XY.L, G.Y; Visualization-HX.P; Supervision-G.Y; Project Administration-XY.L; Funding Acquisition-XY.L.

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