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Original Article

miR-183 modulates renal fibrosis via targeting *SFTPA2* genes

Jun Li, Chunli Cha, Liuling Dai, Guoshu Chen, Jingjuan Li, Lisha Pu, Simin Pan

Department of Nephrology, The First Affiliated Hospital of Kunming Medical University, Kunming, P.R. China

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Abstract: The aim of this study was to investigate whether miR-183 could modulate progression of renal fibrosis via targeting *SFTPA2* genes. C57BL/6 mice were submitted to unilateral ureteral obstruction (UUO) for inducing renal interstitial fibrosis. Transforming growth factor (TGF)-β1-treated HK-2 cells were used as *in vitro* models of renal fibrosis. miR-183 levels in the cells was monitored by transfecting miR-183 mimic. Expression of miR-183 and SP-A was detected by RT-PCR and Western blotting. Levels of interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α in serum and media were measured by ELISA. Compared with the sham group and negative group, expression of SP-A increased while expression of miR-183 decreased in renal tissues of UUO mice. Elevated serum levels of IL-6, IL-1β, and TNF-α indicated increased inflammation responses *in vivo*. In TGF-β1-treated HK-2 cells, there was also a negative correlation between expression levels of miR-183 and *SFTPA2*. Over expression of miR-183 in the cells could inhibit SP-A2 expression and reduce levels of inflammatory factors in the culture supernatant. In conclusion, dysregulation of miR-183 and SP-A2 was related with renal fibrosis. The regulatory role of miR-183 was mediated by targeting *SFTPA2* genes and affecting inflammation response.

Keywords: Renal fibrosis, surfactant protein A, miR-183, inflammation

Introduction

Chronic kidney diseases (CKD) result from over-accumulation and deposition of extracellular matrix (ECM), as responses to injuries [1]. Eventually all CKD will progress to renal fibrosis, characterized by glomerulosclerosis and tubulointerstitial fibrosis. Renal fibrosis is a common symptom of end-point CKD and indicates deterioration of renal function. The exact etiology of renal fibrosis is not yet fully understood. Identification of endogenous anti-fibrotic factors should provide us with new insight for therapeutic interventions.

Surfactant protein A (SP-A) is a lipoprotein complex essential for the innate immune system. Human SP-A is encoded by two highly homologous genes, *SFTPA1* and *SFTPA2*, which encode SP-A1 and SP-A2, respectively [2]. Alveolar epithelial cells secrete a variety of surfactant proteins to reduce surface tension and to maintain the integrity of alveolar structure. SP-A is the most abundant surfactant protein on the alveolar surface [3]. SP-A is also detected in kidney epithelium [4, 5]. SP-A has a well-defined role in innate immunity and inflammation regulation [6]. Recent studies have suggested that SP-A might also play a role in CKD. One previous study reported that polymorphisms in SP-A genes were related with susceptibility to recurrent urinary tract infections [7]. Later, a genome-wide association study (GWAS) discovered that *SFTPA2* gene is a pulmonary fibrosis-related gene [8]. In our previous studies, we found that abnormal increase of *SFTPA2* activity in clinical renal samples was associated with chronic obstructive nephropathy [9].

Currently, it is widely accepted that microRNAs (miRNAs) are important molecules of post-transcriptional regulation. miRNAs are a group of small non-coding RNAs that negatively regulate gene expression by binding to the 3'-untranslated region (3'-UTR) of target genes [10]. More and more studies have demonstrated that miRNAs are involved in the homeostasis of kidneys and development of kidney disease. Some com-

Table 1. Primers used for reverse transcription and quantitative PCR

Name	Primer sequence
Primers used for reverse transcription	
miR-183	5'-GCGAGCACAGAATTAATACGACTCACTATAGGT-3'
U6	5'-GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAAAATATGGAAC-3'
Primers used for quantitative PCR	
U6	Forward: 5'-CTCGCTTCGGCAGCACA-3' Reverse: 5'-AACGCTTCACGAATTTGCGT-3'
miR-183	Forward: 5'-TATGGCACTGGTAGAATTCACT-3' Reverse: 5'-GCGAGCACAGAATTAATACGAC-3'
Mouse SP-A	Forward: 5'-CGTCCACTTTACATCACTG-3' Reverse: 5'-GGTCGCATTCCACATAG-3'
Human SFTPA2	Forward: 5'-GGAAGCCCTGGTATCCCCGC-3' Reverse: 5'-TAATGGTATCAAAGTTGACTG-3'
Human collagen I	Forward: 5'-TGTTCAGCTTTGTGGACCTC-3' Reverse: 5'-CTTGGTCTCGTCACAGATCA-3'
Mouse GAPDH	Forward: 5'-GGATTTGGTCGTATTGGG-3' Reverse: 5'-GGAAGATGGTGATGGGAT-3'
Human GAPDH	Forward: 5'-ATGGGTGTGAACCATGAGAAGTATG-3' Reverse: 5'-GGTGCAGGAGGCATTGCT-3'

prehensive reviews have summarized advances in this topic [11-13]. A previous study reported that transfecting miR-183 into lung adenocarcinoma cell line NCI-H441 could significantly reduce expression of *SFTPA1* and *SFTPA2* genes [14].

Renal fibrogenesis and pulmonary fibrogenesis share similar features. Both are related with excessive deposition of ECM and abnormal inflammatory response. Based on previous studies, we hypothesized that SP-A, or more specifically SP-A2, may be a fibrotic factor during renal fibrosis and may be regulated by miR-183. We first investigated correlation between miR-183 expression and SP-A expression in mouse models of renal fibrosis. The relationship between miR-183 and SP-A2 was further studied in human tubular epithelial cells. We also investigated the influence of miR-183 on expression of inflammatory factors.

Materials and methods

Induction of renal fibrosis models in mice

C57BL/6 mice (6 weeks of age) were used to induce renal fibrosis. The mice were purchased from the Model Animal Research Center of Nanjing University (Nanjing, China) and were housed in an animal facility with standard food and water, ad libitum. All animal studies were conducted in accordance with the Ethical Guide for the Care and Use of Laboratory Animals. Our study protocol was approved by the Ethical Committee of the First Affiliated Hospital of Kunming Medical University. Fifty-four mice were randomly arranged into three groups: model group, sham group, and negative control (NC) group. For induction of renal fibrosis, mice in the model group were submitted to unilateral ureteral obstruction (UUO), as described previously [15]. Briefly, the mice were anesthetized with (10 μl ketamine + 1 μl xylazine)/g body weight. The abdominal cavity was opened and the left ureter was ligated twice. Sham operations were done without ureteral ligation. On day 3, day 7, and day 14, six mice of each group were sacrificed to collect renal tissues and blood samples.

Histological analysis

For histological examination, renal tissues were fixed overnight in 10% formalin and embedded in paraffin. Tissues were then cut into 5 μm sections, followed by hematoxylin and eosin (H&E) staining, Masson's trichrome staining, and microscopic examination.

Cell culture and transfection

HK-2 cell lines, the human renal tubular epithelial cell lines, were used in *in vitro* experiments. Cells were purchased from Shanghai Bioleaf Biotech Co. Ltd (Shanghai, China). The cells

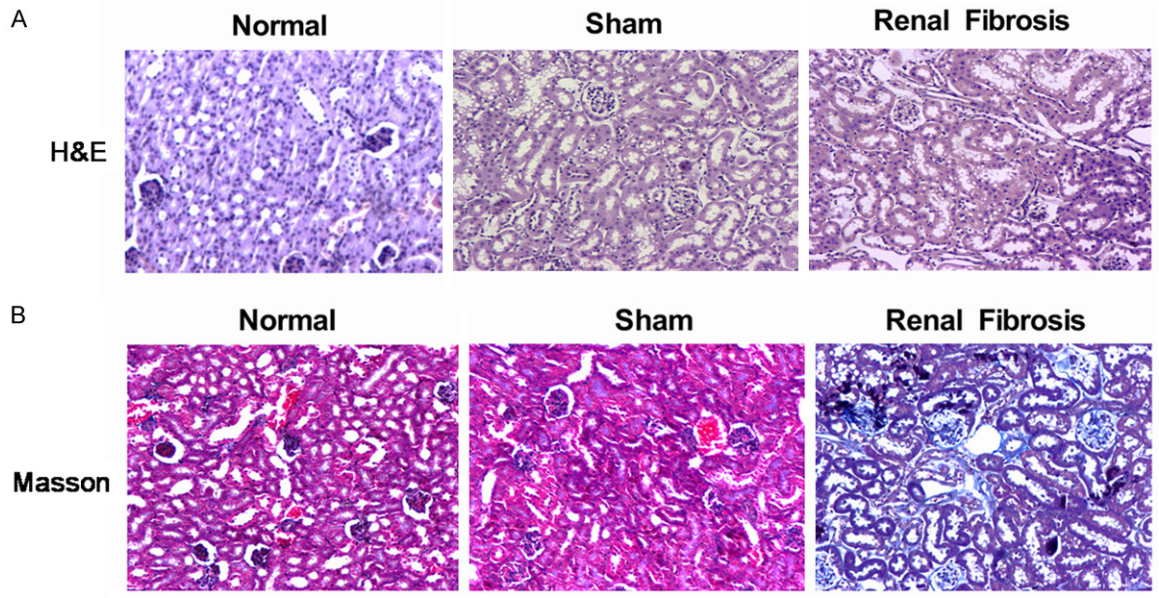

Figure 1. Histopathological changes of mouse kidneys with renal fibrosis (magnification ×100). C57BL/6 mice were submitted to unilateral ureteral obstruction (UUO) for inducing renal interstitial fibrosis. A. H&E staining. B. Masson staining.

were maintained as instructed with DMEM/F12 + 10% fatal bovine serum at 37°C in a humidified hood with 5% CO_2. Culture media were purchased from Thermo Fisher Scientific (Gibco®, Carlsbad, CA, USA). Cells were treated with transforming growth factor (TGF)-β1 (10 ng/ml) for 48 hours to induce fibrosis. To modulate miR-183 expression levels, HK-2 cells were transfected with hsa-miR-183-5p mimic (5'-UAUGGCACUGGUAGAAUUCACUG-3') or hsa-miR-183 inhibitor (5'-AGUGAAUUCUACCAGUGCCAUA-3', synthesized by GenePharma, Shanghai, China). All transfections were done using Lipofectamine 2000 reagent (Invitrogen®, Thermo Fisher Scientific, Carlsbad, CA, USA), according to manufacturer instructions. The cells were harvested, 48 hours after transfection, for further studies.

Total mRNA preparation and real-time RT-PCR

Total RNA was extracted from renal tissues and cells using TRIzol Reagent (Takara, Dalian, China). First strand cDNA was synthesized using PrimeScript RT Master kit (Takara, Dalian, China). Quantitative real-time PCR was carried out using SYBR ExScript RT-PCR (Takara, Dalian, China) on ABI 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA), according to manufacturer instructions. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as endogenous control. Relative expression of SP-A and type I collagen in each sample was normalized to the level of GAPDH using the $2^{-\Delta\Delta Ct}$ method [16]. Expression of miR-183 was measured using Hairpin-it miRNAs qPCR Quantitation Kit (GenePharma, Shanghai, China). U6 small nuclear RNA was used as an internal control for miR-183. Primers used are provided in **Table 1**.

Total protein preparation and Western blotting

Renal tissues and cells were homogenized in RIPA lysis buffer (Beyotime Biotechnology, Shanghai, China) to prepare total protein lysates. The concentration of protein was measured using BCA protein assay kit (Beyotime Biotechnology, Shanghai, China). Protein samples (20 μg/lane) were separated by electrophoresis on 10% polyacrylamide gel and then transferred onto polyvinylidene fluoride (PVDF) membranes. The membranes were blocked with 5% non-fat milk and incubated with primary antibodies overnight at 4°C. The next day, membranes were incubated with horseradish peroxidase (HRP)-conjugated secondary antibody at room temperature. The blots were visualized with enhanced chemiluminescence method using ECL kit (Beyotime Biotechnology, Shanghai, China) and detected using ChemiDoc™XRS+ imaging system (Bio-Rad, Hercules, CA, US). Antibodies used in the study

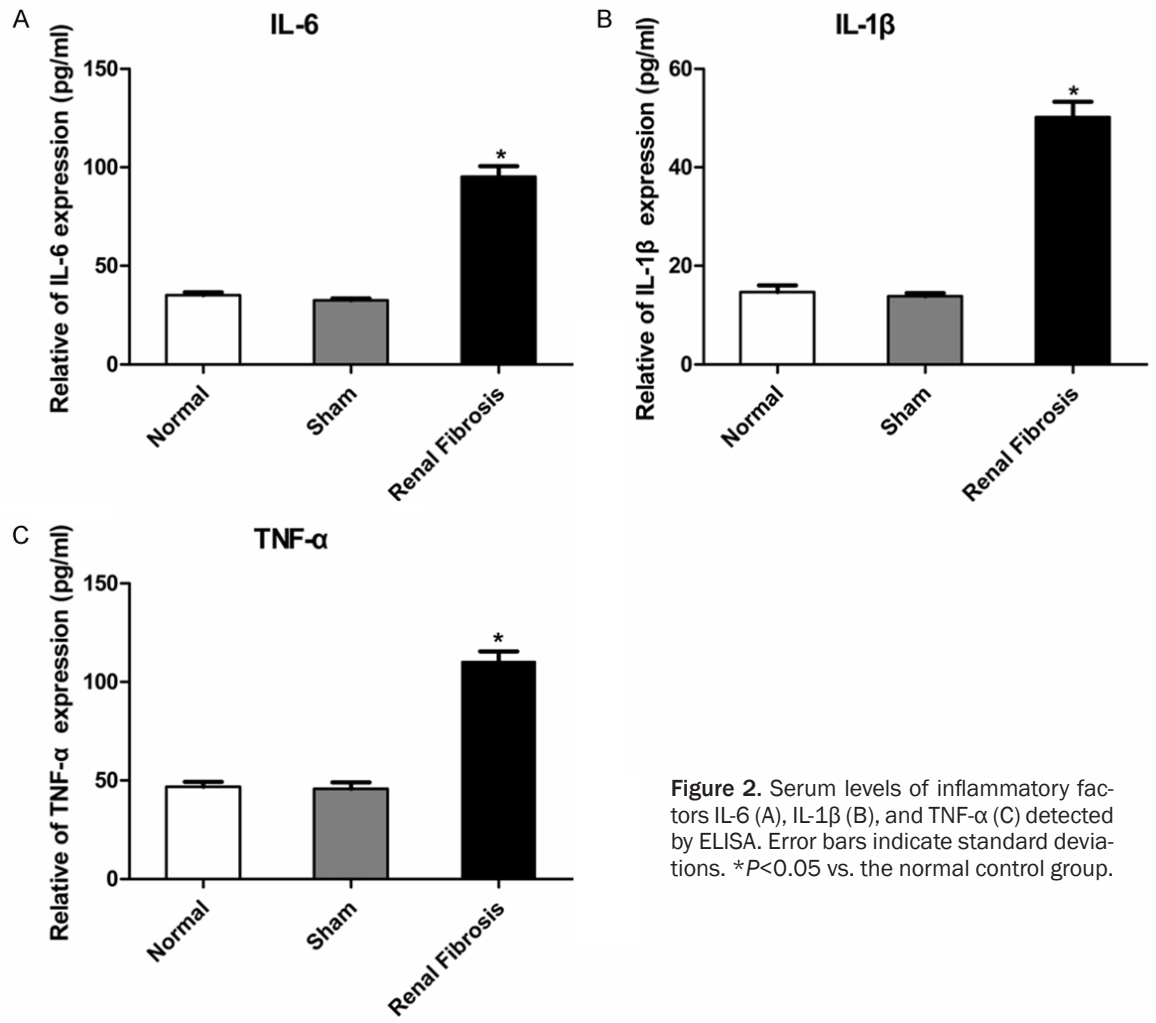

Figure 2. Serum levels of inflammatory factors IL-6 (A), IL-1β (B), and TNF-α (C) detected by ELISA. Error bars indicate standard deviations. **P*<0.05 vs. the normal control group.

were: rabbit polyclonal antibody to mouse surfactant protein A (1:1000, ab115791), rabbit polyclonal antibody to human surfactant protein A (1:1000, ab87674), rabbit monoclonal antibody to GAPDH (1:1000, ab181603), HRP-conjugated goat anti-rabbit IgG (1:2000, ab6721). All of the antibodies were purchased from Abcam Inc. (Cambridge, MA, USA). GAPDH was used as endogenous control.

Detection of inflammatory factors

Inflammatory factors of IL-1β, IL-6, and TNF-α were detected in blood samples and cell culture supernatants. BD OptEIA and ELISA kits for mouse cytokines and human cytokines were used, respectively (BD Biosciences, San Diego, CA, USA).

Statistical analysis

At least three independent experiments were performed for transfection: RT-PCR, Western blotting, and ELISA. Typical results are presented in this paper. Continuous variables are reported as mean ± standard deviation (SD). Differences among different groups were analyzed by one-way ANOVA using SPSS software version 19.0. Multiple comparisons were analyzed by least significant difference (LSD) test. All comparisons were two-tailed and a statistically significant difference was indicated when P value < 0.05.

Results

Expression of miR-183 and SP-A altered in UUO-induced fibrotic mouse kidneys

Although complete ureteral obstruction is not a usual cause for humans, the UUO model is accepted as a useful tool of tubulointerstitial fibrosis *in vivo*. Subsequent responses to UUO include interstitial inflammation, tubular cell death, and fibrosis, from 7 days [17]. Therefore,

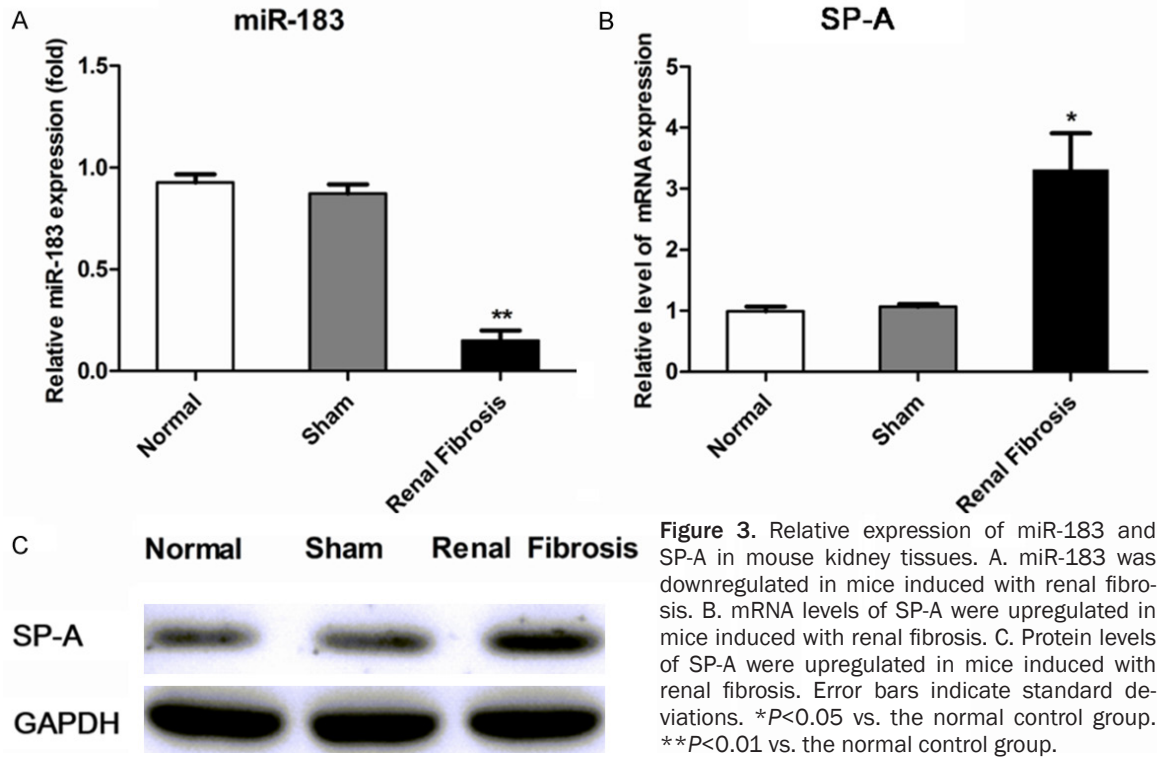

Figure 3. Relative expression of miR-183 and SP-A in mouse kidney tissues. A. miR-183 was downregulated in mice induced with renal fibrosis. B. mRNA levels of SP-A were upregulated in mice induced with renal fibrosis. C. Protein levels of SP-A were upregulated in mice induced with renal fibrosis. Error bars indicate standard deviations. *P<0.05 vs. the normal control group. **P<0.01 vs. the normal control group.

we used this procedure to induce renal fibrosis in mice. Mouse SP-A is encoded by single gene *SFTPA*. First, we investigated whether miR-183 and SP-A were differentially expressed in UUO-induced mouse kidneys. As shown in **Figure 1**, HE and Masson staining indicated cell damage and collagen deposition in UUO-treated mice compared with the sham group and negative control. Meanwhile, ELISA detected higher serum levels of IL-1β, IL-6, and TNF-α in the UUO group, indicating that renal fibrosis was associated with activated inflammation response (**Figure 2**). Expression of miR-183 was significantly reduced, too, in kidney tissues of the UUO group (**Figure 3A**). We also detected expression of SP-A by RT-PCR and Western blot. As shown in **Figure 3B** and **3C**, both mRNA and protein levels of SP-A increased in UUO-induced mice. In other words, SP-A and miR-183 demonstrated the opposite expression pattern.

Expression of miR-183 and SP-A2 are altered in TGF-β1-treated HK-2 cells

Because mice only express SP-A, in order to further reveal the relationship between miR-183 and SP-A2, we next performed *in vitro* experiments using human renal tubular epithelial cells. TGF-β signaling pathways are recognized as major mediators of renal fibrosis. TGF-β1 can stimulate accumulation of ECM and promote epithelial to mesenchymal transition [18]. Therefore, TGF-β1 is commonly used to treat cells as an *in vitro* fibrosis model. We tested whether expression of miR-183 and SP-A2 were altered in TGF-β1-treatedrenal tubular epithelial cells. As shown in **Figure 4**, TGF-β1 treatment could inhibit miR-183 expression and promote SP-A2 expression. Consistent with the results in mice, more inflammatory factors of IL-1β, IL-6, and TNF-α were secreted into the culture medium when cells were treated with TGF-β1 (**Figure 5**). These results confirmed that miR-183 and SP-A2 were differentially expressed when cells were induced to fibrosis.

miR-183 modulates SP-A2 expression and inflammation in HK-2 cells

To further confirm that there is a negative association between miR-183 expression and SP-A2 expression, we transfected HK-2 cells with miR-183 mimic and investigated influence on TGF-β1 induction. As shown in **Figure 4**, compared with the TGF-β1 group, overexpression of miR-183 inhibited SP-A2 expression and reduced type I collagen. Higher miR-183

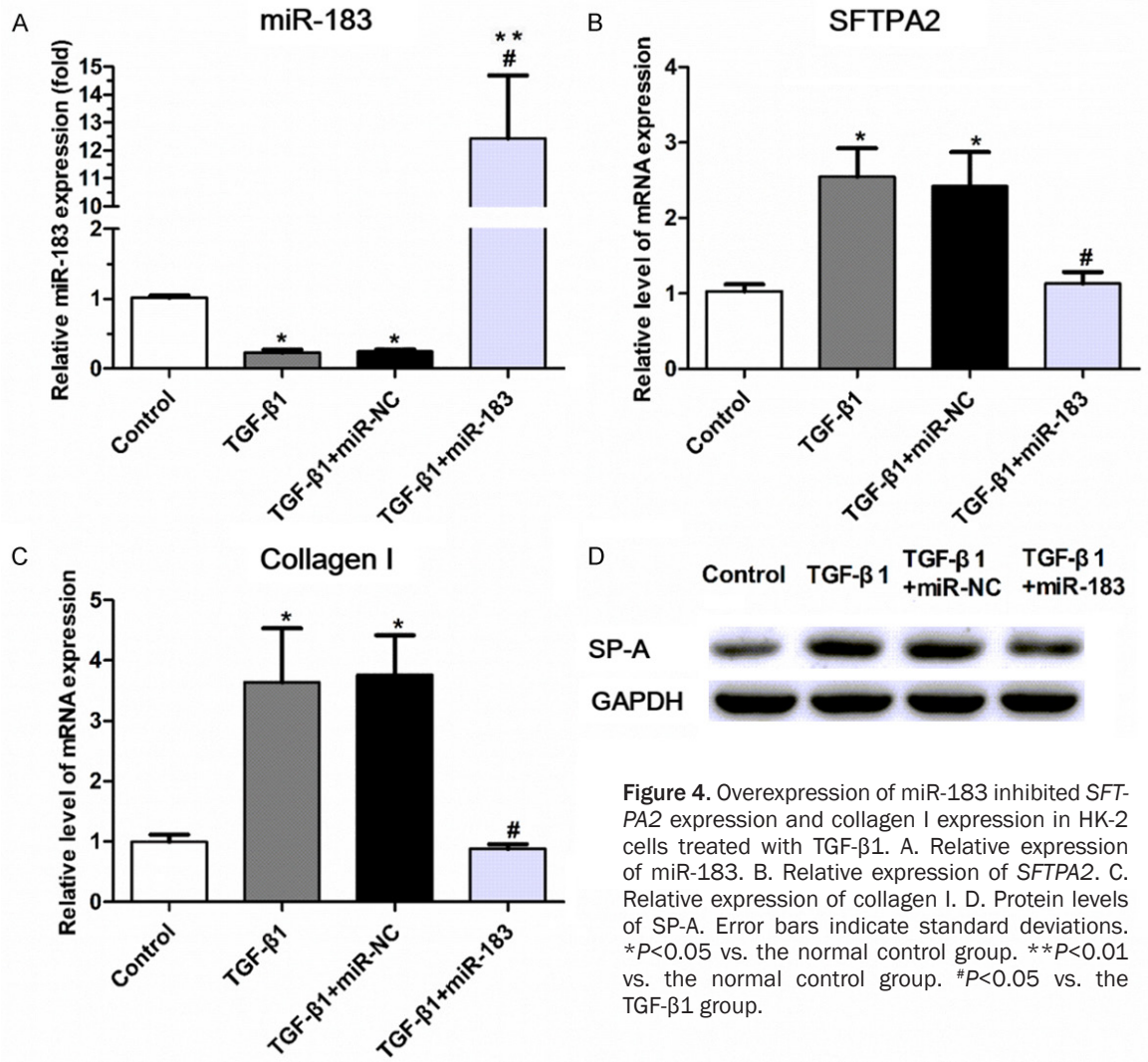

Figure 4. Overexpression of miR-183 inhibited *SFTPA2* expression and collagen I expression in HK-2 cells treated with TGF-β1. A. Relative expression of miR-183. B. Relative expression of *SFTPA2*. C. Relative expression of collagen I. D. Protein levels of SP-A. Error bars indicate standard deviations. **P*<0.05 vs. the normal control group. ***P*<0.01 vs. the normal control group. #*P*<0.05 vs. the TGF-β1 group.

levels also reduced secretion of inflammatory factors (**Figure 5**). Transfecting cells with non-homologous controls did not change the expression of SP-A2, collagen I, or inflammatory factors. These results prove that SP-A2 expression could change in answer to miR-183 levels. In addition, miR-183 levels have an effect on collagen expression and inflammation reaction.

Discussion

In this study, we investigated the role of miR-183 during renal fibrosis, both *in vivo* and *in vitro*. Our results indicated that miR-183 was downregulated during renal fibrosis. Aberrant expression of miR-183 upregulated its target, SP-A2, and was related with increased expression of inflammatory factors IL-1β, IL-6, and TNF-α. In cell models, we also found that collagen expression was modulated by miR-183 levels. As far we know, this is the first study that has shown the involvement of miR-183 and SP-A2 in renal fibrosis. Another study reported that SP-A played a role in sepsis-induced acute kidney injuries by modulating inflammation reaction and apoptosis [19]. Compared with intensive studies on pulmonary disease, the exact role of SP-A in kidney disease is not well known and certainly warrants more attention.

Evidence has accumulated that SP-A is crucial for lung defense against inhaling challenges. Mice express only one gene of SP-A while human SP-A is composed of two subunits, SP-A1 and SP-A2. SP-A1 and SP-A2 are both functional with varying degrees of activity [2, 20]. SP-A2 seems to be more important for the

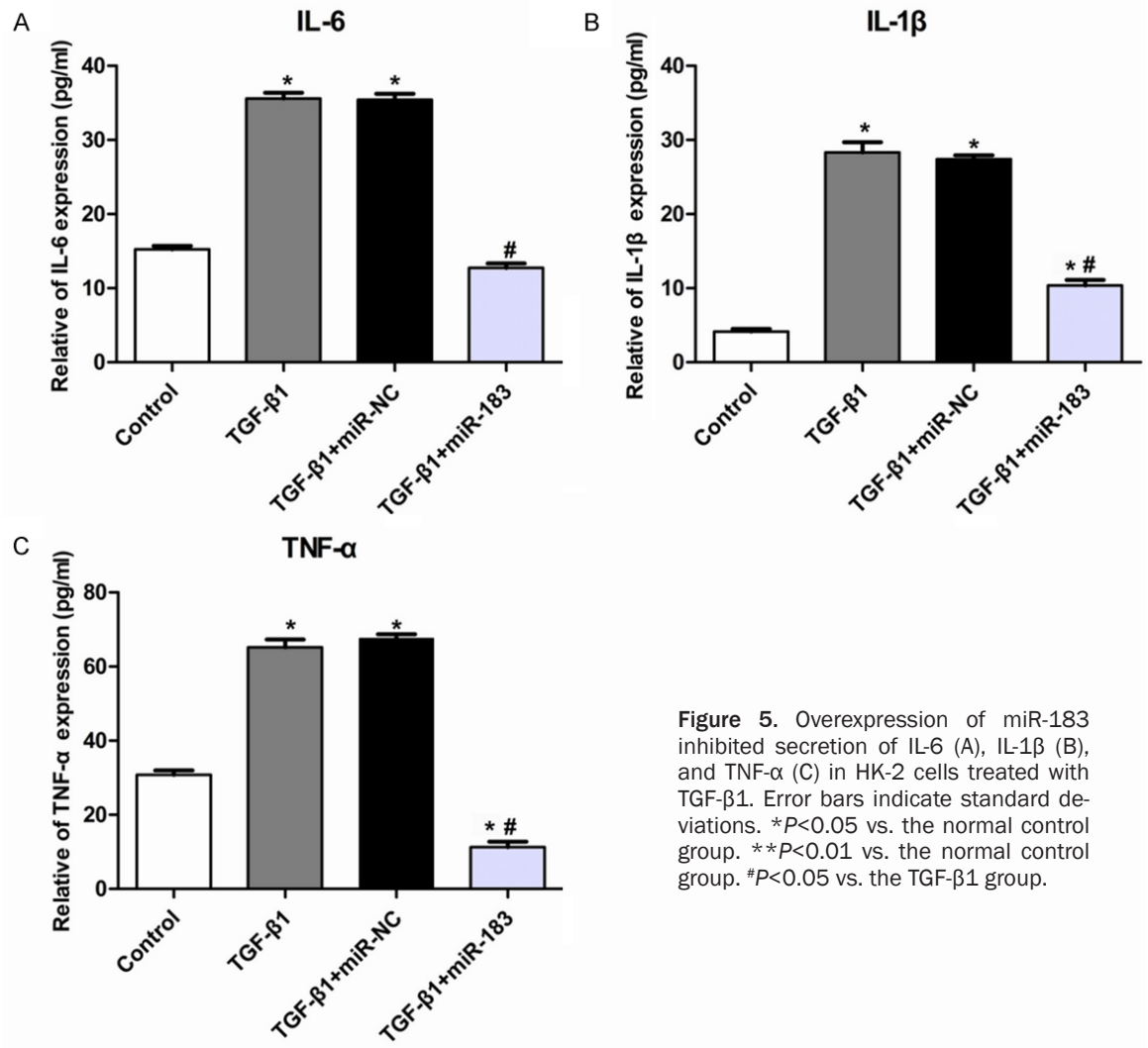

Figure 5. Overexpression of miR-183 inhibited secretion of IL-6 (A), IL-1β (B), and TNF-α (C) in HK-2 cells treated with TGF-β1. Error bars indicate standard deviations. **P*<0.05 vs. the normal control group. ***P*<0.01 vs. the normal control group. #*P*<0.05 vs. the TGF-β1 group.

mature functional SP-A. Differential expression of SP-A2 has been associated with total SP-A levels and low SP-A levels have been connected with poor outcome in patients receiving lung transplants [21]. The importance of SP-A2 for pulmonary fibrosis was further indicated in GWAS [8]. Therefore, we focused on SP-A2 in our current research. Our study provides new insight that SP-A2 is involved in renal fibrosis. The role of SP-A in innate immunity has been reported by many researches (see review [22] and [23]). In response to injurious stimulation, SP-A could initiate inflammatory responses to clear foreign organisms. Our study showed that SP-A2 levels are associated with secretion levels of inflammatory factors. TGF-β is a central mediator of renal fibrosis via signaling pathways such as Smad2, Smad2, and mitogen-activated protein kinases (MAPKs). More information can be found in the review by Boor et al. [24]. We also need to mention that mice are not perfect models for *in vivo* studies of SP-A2 because strict SP-A is different than human SP-A1 and SP-A2. This is why we used human renal tubular epithelial cells to perform more *in vitro* assays. Ideally, humanized transgenic mice that express human SP-A2 should be used. This fact will be considered in future studies.

miRNAs have been shown to regulate numerous molecular reactions and widely affect pathologic processes [25]. Previous studies have identified multiple miRNAs that are related with renal fibrosis. miR-21, miR-443, and miR-192 were pathological miRNAs in renal fibrosis while miR-29 and miR-200 were protective miRNAs (see review [26]). The role of

miR-183 has been studied a lot in cancers including lung cancer [27, 28], colorectal cancer [29], breast cancer [30], prostate cancer [31], and esophageal squamous cancer [32]. Our research identified miR-183 as a novel renal fibrosis-related miRNA. These results were observed in animal models. Although the UUO procedure is a good model of renal fibrosis, there are also some disadvantages including lack of proteinuria and urine output. This model cannot exactly stimulate human CKD expression. The results of this study should be interpreted carefully. The possibility of using miR-183 as a biomarker for renal fibrosis should be further investigated in other models and clinical practice. Notably, there are sequence polymorphisms existing in the seed region of *SFTPA2* mRNA. However, previous studies have proven that the binding efficiency of miR-183 to *SFTPA2* is not affected [14].

In summary, we have proven that miR-183 could suppress type I collagen deposition and attenuate inflammatory factor expression through targeting SP-A2 expression. Our findings suggest that miR-183 and its target SP-A2 have potential to be therapeutic targets for treating renal fibrosis.

Acknowledgements

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jun Li, Department of Nephrology, The First Affiliated Hospital of Kunming Medical University, 295 Xicang Road, Kunming 650032, P.R. China. Tel: 86-871-65324888; Fax: 86-871-65336015; E-mail: ynlijun@hotmail.com

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