Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome in both adults and children. Patients with persistent heavy proteinuria tend to progress to end-stage renal disease rapidly, whereas patients who achieve complete remission have an extremely favorable prognosis with a 10-year renal survival rate of approximately 80%.1,2 Although degree of proteinuria is a good biomarker for disease activity in patients with FSGS, we still lack plasma biomarkers that aid in the evaluation of disease activity.

MicroRNAs (miRNAs), noncoding RNAs of approximately 22 nucleotides in length, play important roles in various physiologic and pathologic processes through post-transcriptional gene silencing.3 Recently, miRNAs also have been implicated in the development of FSGS. Gebeshuber et al.4 reported that FSGS could be induced by miR-193a through the downregulation of WT1 (Wilms tumor 1). We recently have shown that miR-30 protects podocytes by inhibiting deleterious Notch1 or p53 signaling activation in various injury models.5 Moreover, miRNAs are stably expressed in serum and plasma,6,7 and these circulating miRNAs can enter cells and regulate target gene expression therein.8 Several reports have suggested that circulating miRNAs can

**Background:** MicroRNAs (miRNAs) are stable in circulation, and their unique expression profiles can serve as fingerprints for various diseases. This study explored whether plasma miRNAs could be used as biomarkers to evaluate disease activity in patients with focal segmental glomerulosclerosis (FSGS).

**Study Design:** Retrospective and prospective cohorts.

**Setting & Participants:** 78 patients with FSGS with nephrotic proteinuria (protein excretion > 3.5 g/24 h), 35 patients with FSGS in complete remission, 63 patients with membranous nephropathy, 59 patients with diabetic nephropathy, and 69 apparently healthy controls were recruited. Plasma samples from 51 other patients with FSGS with nephrotic proteinuria were collected prospectively before and after steroid treatment.

**Predictors:** Plasma miRNA concentration.

**Outcomes:** Complete remission (protein excretion < 0.4 g/24 h), or no response (sustained protein excretion > 3.5 g/24 h after 8 weeks of steroid treatment).

**Measurements:** Quantitative reverse transcription–polymerase chain reaction analysis of plasma miRNAs.

**Results:** Increases in miR-125b, miR-186, and miR-193a-3p levels were identified in a pooled plasma sample of 9 patients with FSGS compared with that of 9 healthy controls and were confirmed with individual samples from patients with FSGS (n = 32) and healthy controls (n = 30). Areas under the receiver operating characteristic curves of miR-125b, miR-186, miR-193a-3p, and the 3 miRNAs in combination were 0.882, 0.789, 0.910, and 0.963, respectively. miR-125b and miR-186 concentrations were significantly lower in patients with FSGS in complete remission (n = 35) than those with nephrotic proteinuria (n = 37). In a prospective study, miR-125b and miR-186 levels declined markedly in patients with FSGS with complete remission (n = 29), but not those with no response (n = 22), after steroid treatment. Plasma miR-125b and miR-186 levels were not elevated in patients with membranous nephropathy (n = 63) and diabetic nephropathy (n = 59) regardless of degree of proteinuria. Last, plasma miR-186, but not miR-125b, level was correlated with degree of proteinuria in patients with FSGS (151 samples).

**Limitations:** Relatively small cohort size.

**Conclusions:** Plasma miR-186 may be a biomarker for FSGS with nephrotic proteinuria.


**INDEX WORDS:** Plasma miR-186; focal segmental glomerulosclerosis (FSGS); biomarkers; microRNA (miRNA); expression profile; nephrotic syndrome; proteinuria; remission; noncoding RNA; circulating miRNAs; kidney disease.
serve as biomarkers for the diagnosis of various diseases, including cancer.6,7,9-11 Altered levels of circulating miRNAs also have been found in patients with kidney diseases, including acute kidney injury,12 chronic kidney disease,13 and lupus nephritis,14 suggesting that miRNAs can be used as potential biomarkers for kidney diseases. However, there are no circulating miRNAs that have been correlated with the disease activity of FSGS.

In the present study, we screened for plasma miRNAs that are increased in patients with FSGS with nephrotic proteinuria using an miRNA profiling kit and performed cohort validation by quantitative reverse transcription–polymerase chain reaction (qRT-PCR) in order to identify the plasma miRNAs that are associated with FSGS and can serve as biomarkers of FSGS activity.

METHODS

Enrollment of Case Patients and Controls

All case patients and healthy controls were recruited at the National Clinical Research Center of Kidney Diseases of Jinling Hospital (Nanjing, China) from January 2011 through October 2013. A total of 78 patients with FSGS with nephrotic proteinuria, 35 patients with FSGS in complete remission, 63 patients with membranous nephropathy (MN; 32 with nephrotic proteinuria and 31 in complete remission), 59 patients with diabetic nephropathy (DN; 32 with nephrotic proteinuria and 27 with microalbuminuria), and 69 age- and sex-matched healthy volunteers (controls) were recruited for this study. In addition, plasma samples from 51 other patients with FSGS with nephrotic proteinuria were collected before and after steroid treatment, and this group of patients was used as a prospective cohort. Signed informed consent forms were obtained from all patients, and this study was approved by the Ethics Committee of Jinling Hospital.

Inclusion and Exclusion Criteria

Inclusion criteria were age 18 to 65 years, serum creatinine level ≤ 3 mg/dL, proteinuria with protein excretion > 3.5 g/24 h or < 0.4 g/24 h, microalbuminuria with albumin excretion between 30 mg/24 h and 300 mg/24 h for DN, and in the prospective study, no corticosteroid or other immunosuppressors (eg, calcineurin inhibitor) given at the time of enrollment.

Exclusion criteria were secondary FSGS and MN, DN with other chronic kidney disease, family history of kidney disease, pregnancy, lactation, and concurrence of cancer, heart, brain, liver, or hematopoietic system disease.

Definitions

FSGS and MN were diagnosed following previously described criteria,15,16 and DN was diagnosed clinically in patients who had type 2 diabetes mellitus17 and urine albumin excretion > 30 mg/24 h.

Nephrotic proteinuria is defined as urinary protein excretion > 3.5 g/24 h. Complete remission is defined as urinary protein excretion < 0.4 g/24 h after treatment. Microalbuminuria in patients with DN is defined as urinary albumin excretion from 30 to 300 mg/24 h. In the prospective study, no response is defined as sustained nephrotic proteinuria after 8 weeks of steroid treatment.

Healthy volunteers who were from the staff of Jinling Hospital and had no known kidney disease history were enrolled as controls. Women with pregnancy and lactation were excluded.

Study Design

The research approach of this study is shown in Fig 1. First, we used a TaqMan Low Density Array (Applied Biosystems) and pooled plasma samples from 9 patients with FSGS with nephrotic proteinuria and 9 healthy controls to identify plasma miRNAs that had significantly increased levels in patients with FSGS compared with controls (initial screening stage). We then confirmed miRNA upregulation by TaqMan probe–based qRT-PCR using plasma samples from a larger cohort of 32 patients with FSGS with nephrotic proteinuria and 30 controls (confirmation stage). Next, we compared plasma miRNA concentrations in another cohort of
37 patients with FSGS with nephrotic proteinuria and 35 in complete remission to determine whether levels of these plasma miRNAs returned to normal when complete remission was achieved (validation stage). In addition, plasma levels of these miRNAs were examined further in a prospective cohort of 51 patients with FSGS with nephrotic proteinuria before and after oral prednisone treatment with a daily dose of 1 mg/kg (maximum, 60 mg) as an initial treatment for at least 8 weeks. Of these patients, 29 achieved complete remission and the other 22 had no response. Last, plasma miRNA levels were examined in 63 patients with MN and 59 patients with DN to determine whether the increase in plasma miRNA levels was specific to FSGS.

**Plasma Preparation**

Peripheral blood was collected in EDTA tubes from all enrolled patients. All samples were processed within 4 hours after collection. Blood samples were centrifuged at 3,000 g for 10 minutes at room temperature followed by 10,000 g for 5 minutes at 4°C. Plasma supernatant was aliquoted into ribonuclease-free tubes and stored at −80°C.

**Analysis of Pooled Plasma Samples**

For TaqMan Low Density Array analysis, total RNA was extracted from pooled plasma samples using TRIzol Reagent (Invitrogen) according to previously described methods. Briefly, 2 volumes of TRIzol were added to plasma samples and the mixture was vortex mixed, then centrifuged. Supernatant was extracted twice with phenol/chloroform solution, 1 volume of isopropanol was added to the supernatant, and the sample was centrifuged to precipitate RNA. miRNA profiles of the samples were obtained by TaqMan Low Density Array analysis using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems). TaqMan Array Human MicroRNA A+B Cards Set v3.0 was used in this study, which consists of probes for 754 different human miRNAs. U6 small nuclear RNA was used as an internal control for data normalization. Relative abundances of the miRNAs are presented according to the threshold cycle (CT) values observed in the qPCR assay. Fold change of an miRNA in the FSGS group relative to the control group was calculated by the comparative CT method (2−ΔΔCT, method, where ΔΔCT = (CTmiRNA − CTU6)FSGS − (CTmiRNA − CTU6control)). miRNAs that had a CT < 30 and a 2-fold or higher increase in patients with FSGS with nephrotic proteinuria compared with healthy controls were chosen for further study.

**Analysis of Individual Plasma Samples**

For the miRNA qRT-PCR assay, total RNA was isolated from 100 μL of plasma with a 1-step phenol/chloroform purification protocol as previously described. TaqMan probe–based qRT-PCR (Applied Biosystems) was carried out according to the manufacturer’s instructions. Briefly, 2 μL of total RNA was reverse transcribed to complementary DNA (cDNA) using avian myeloblastosis virus reverse transcriptase (TaKaRa) and a stem-loop primer (Applied Biosystems). Real-time PCR was performed using a TaqMan PCR kit and was run on an Applied Biosystems 7900 Sequence Detection System. All samples were analyzed in triplicate.

**Determination of Absolute Concentration of miRNAs**

Synthetic miRNA oligonucleotides were purchased from TaKaRa, and 2 × 10^15 μmol was used for cDNA synthesis following the method described. Serial dilutions of cDNAs were made to achieve concentrations of 10^3, 10^4, 10^5, 10^6, and 10^7 fmol/μL for synthetic miRNAs. Diluted samples were subjected to qRT-PCR, and Ct values were plotted against the concentrations to construct standard curves. The absolute concentration of the circulating miRNAs was calculated based on the equation generated by the standard curve (Fig S1A-C, available as online supplementary material).

**Statistical Analysis**

Statistical analysis was performed using SPSS software, version 18.0 (SPSS Inc). The t test was used to determine significant differences in plasma miRNA concentrations between any 2 groups. Paired t test was used to determine significant differences in plasma miRNA concentrations before and after steroid treatment. Receiver operating characteristic (ROC) curves were established to determine the sensitivity and specificity of the miRNAs for predicting active FSGS. Pearson correlation analysis was conducted to calculate the correlation between level of an miRNA and a clinical feature. P < 0.05 was considered statistically significant.

**RESULTS**

**Identification of Upregulated miRNAs in FSGS Patients With Nephrotic Proteinuria**

We first screened for differentially expressed plasma miRNAs in patients with FSGS with nephrotic proteinuria relative to healthy controls using miRNA PCR arrays. We used plasma but not serum for the analysis because the release of certain miRNAs during the coagulation process might alter the true repertoire of circulating miRNAs. For efficient and cost-effective screening, we pooled plasma samples from 9 patients with FSGS with nephrotic proteinuria randomly selected from the enrolled cohort and from 9 healthy controls. The clinical information obtained from the 9 patients with FSGS and 9 healthy controls is shown in Table S1. The array analysis showed that patients with FSGS with nephrotic proteinuria had a plasma miRNA profile that was significantly different from that of healthy controls (Fig 2A). Of 186 miRNAs detectable in the FSGS pooled sample and 232 miRNAs detectable in the healthy controls pooled sample, 161 miRNAs were common in the 2 samples. Among miRNAs detectable in only the FSGS samples, 17 had CT values < 30; among the miRNAs detectable in both samples, 28 were upregulated (>2-fold) in patients with FSGS relative to healthy controls and had CT values < 30.

We then performed qRT-PCR analysis of the 45 miRNAs individually in the 2 pooled plasma samples and confirmed the upregulation (fold change > 2) of 6 miRNAs in the FSGS sample (Fig 2B). Of 6 miRNAs, miR-125b, miR-186, and miR-193a-3p had CT values < 30; thus, they were selected for further study. As shown in Fig 2B, fold changes in miR-125b, miR-186, and miR-193a-3p were 9.75, 2.62, and 3.22, respectively. We next confirmed upregulation of these 3 miRNAs in a separate group of patients with FSGS with nephrotic proteinuria (n = 32) and healthy controls (n = 30; Table S2). qRT-PCR results showed that miR-125b, miR-186, and miR-193a-3p were present at significantly higher levels in patients with FSGS relative to
controls, with average fold changes of 5.77, 3.04, and 3.44, respectively (Fig 2C-E).

**ROC Curve Analysis of miR-125b, miR-186, and miR-193a-3p**

To determine whether plasma miR-125b, miR-186, and miR-193a-3p levels could serve as biomarkers to predict FSGS with nephrotic proteinuria, we tested their ability to discriminate patients with FSGS with nephrotic proteinuria from healthy controls. Concentrations of these 3 miRNAs in plasma samples were used to generate ROC curves to evaluate the predictive capability of these miRNAs for FSGS with nephrotic proteinuria. Results showed that areas under the ROC curves (AUCs) of miR-125b, miR-186, and miR-193a-3p were 0.882 (95% confidence interval [CI], 0.802-0.963), 0.789 (95% CI, 0.674-0.903), and 0.910 (95% CI, 0.840-0.981), respectively (Fig 3A-C; Table S3). When 5.706 fmol/L is used as a cutoff of the miR-125b plasma concentration for FSGS positivity, optimal specificity and sensitivity of 80.0% and 81.3%, respectively, can be obtained according to the ROC analysis. Accordingly, optimal specificity and sensitivity of miR-186 were 90.0% and 62.5% (at 38.352 fmol/L), respectively; for miR-193a-3p, these values were 93.3% and 78.1% (at 8.011 fmol/L), respectively. These results indicate that all 3 miRNAs can be used to discriminate patients with FSGS with nephrotic proteinuria from healthy controls. Moreover, the combination of the 3 miRNAs (3-miRNA panel) exhibited better predictive power compared with any individual miRNA, with AUC of 0.963 (95% CI, 0.914-1.000; Fig 3D; Table S3), specificity of 93.3%, and sensitivity of 90.6% (Table S3).

**miR-125b and miR-186 Levels in FSGS Patients in Complete Remission**

We also tested the ability of plasma miR-125b, miR-186, and miR-193a-3p levels to discriminate patients with FSGS with nephrotic proteinuria from those in complete remission based on 37 patients with nephrotic proteinuria and 35 patients in complete remission (Table S2). qRT-PCR analysis showed that
levels of plasma miR-125b and miR-186, but not miR-193a-3p, were significantly higher in patients with FSGS with nephrotic proteinuria when compared with those in complete remission (Fig 4A-C). ROC curve analysis showed that plasma miR-186 level was capable of discriminating patients with FSGS with nephrotic proteinuria from those in complete remission, with AUC of 0.802 (95% CI, 0.700-0.905; Fig 4D; Table S3), optimal specificity of 71.4%, and sensitivity of 81.1% (at 39.05 fmol/L). The ability of plasma miR-125b level to discriminate patients with FSGS with nephrotic proteinuria from patients with FSGS in complete remission was decreased, with AUC of 0.699 (Fig 4E; Table S3). A 2-miRNA panel including miR-186 and miR-125b had AUC of 0.821 (95% CI, 0.722-0.919; Fig 4F; Table S3) and optimal specificity and sensitivity of 74.3% and 78.4%, respectively (Table S3).

**miR-125b and miR-186 Levels in FSGS Patients After Steroid Treatment**

According to the mentioned results, we speculated that the elevated plasma miR-125b and miR-186 levels in patients with FSGS with nephrotic proteinuria would return to normal in patients who achieved complete remission, but not in those who retained nephrotic proteinuria. We thus prepared a prospective cohort consisting of 51 patients with FSGS with nephrotic proteinuria (Table S4) and examined their plasma miR-125b and miR-186 levels before and after steroid treatment for 8 weeks. We found that both miR-125b and miR-186 levels were decreased significantly in the group of 29 patients who achieved complete remission ($P = 0.002$ and $P = 0.002$, respectively; Fig 5A and B). Particularly miR-186 was almost restored to the level observed in healthy controls ($P = 0.07$). In contrast, levels of both miRNAs were unchanged in
the group of 22 patients who exhibited no response to steroid therapy (Fig 5C and D). It is worth noting that miR-125b and miR-186 levels in the complete remission and no response groups were similar before steroid treatment ($P = 0.4$ and $P = 0.9$, respectively).

**miR-125b and miR-186 Levels in Patients With MN and DN**

To test whether increases in plasma miR-125b and miR-186 levels were specific to FSGS or simply associated with a proteinuric kidney disease, we measured plasma miR-125b and miR-186 in 63 patients with MN (32 with nephrotic proteinuria, 31 in complete remission) and 59 patients with DN (32 with nephrotic proteinuria, 27 with microalbuminuria; Table S5). qRT-PCR results showed that miR-125b and miR-186 levels in plasma samples from patients with MN and DN regardless of proteinuria degree were similar to those of healthy controls (Fig 6A and B) and much lower than those in patients with FSGS with nephrotic proteinuria, as shown in Fig 2C and D.

**Correlation of miR-125b and miR-186 Levels and Degree of Proteinuria in FSGS Patients With Nephrotic Proteinuria**

We further examined the relationship between plasma miR-125b and miR-186 concentrations and urinary protein levels in patients with FSGS with nephrotic proteinuria using Pearson correlation analysis. We used data from 151 plasma samples and the corresponding proteinuria data from 129 patients with FSGS with nephrotic proteinuria for the analysis, among which the data for the 22 patients with no response in the prospective study were collected twice, that is, before and after steroid treatment, and used in the analysis. Results showed that plasma miR-186 concentrations were correlated significantly with urinary protein levels ($R = 0.185; P = 0.02$; Fig 7A). In contrast, there was no significant correlation...
between plasma miR-125b concentration and degree of proteinuria (Fig 7B). Pearson correlation analysis also was performed between levels of the 2 miRNAs and other clinical parameters of the FSGS patients with no response; however, no correlations were observed (Table S6).

**DISCUSSION**

Recent studies have demonstrated the diagnostic value of circulating miRNAs in various diseases.6-8 However, the question of whether circulating miRNAs can be used as biomarkers to evaluate FSGS disease activity has not been explored. To identify potential plasma miRNA-based biomarkers for FSGS, we compared expression profiles of plasma miRNAs in patients with FSGS and healthy controls using miRNA PCR arrays and TaqMan probe–based qRT-PCR assays and found that plasma miR-125b, miR-186, and miR-193a-3p were upregulated in patients with FSGS with nephrotic proteinuria relative to healthy controls. We further found that plasma miR-125b and miR-186 levels could discriminate patients with FSGS with nephrotic proteinuria from those in complete remission.

To more definitively conclude that miR-125b and miR-186 can serve as biomarkers of FSGS activity, we examined plasma miR-125b and miR-186 levels of a prospective cohort consisting of 51 patients with FSGS with nephrotic proteinuria before and after steroid treatment. Consistent with previous results, miR-125b and miR-186 levels were lowered in the group of 29 patients who achieved complete remission but not in the 22 who had no response, further demonstrating that miR-125b and miR-186 levels can serve as biomarkers for FSGS activity. In addition, because a plasma miRNA level change upon steroid treatment could indicate steroid responsiveness at 8 weeks, it is possible that this change can be used to predict the response to steroid treatment in patients with FSGS. Of course, well-designed prospective studies are needed to prove this possibility. Additionally, plasma levels of miR-186, but not miR-125b, were correlated with degree of proteinuria in patients with FSGS with nephrotic proteinuria, suggesting that miR-186 is a better biomarker compared with miR-125b for FSGS activity.

We also have validated that the increase in miR-125b and miR-186 levels is specific for FSGS. We found that these miRNA levels were not increased in plasma samples from patients with MN or DN, although these patients had nephrotic proteinuria. Some studies have shown altered expression levels of
circulating miRNAs in different kidney diseases or experimental models, including chronic kidney diseases, acute kidney diseases, an experimental unilateral ureteral obstruction model, children’s idiopathic nephrotic syndrome, and hemolytic uremic syndrome. Interestingly, none of these studies showed altered plasma miR-125b or miR-186 expression, suggesting that their elevation likely is unique to patients with FSGS. Of course, further studies are needed to validate these findings.

The pathogenesis of FSGS remains unclear. Identification of the cell origins of plasma miR-125b and miR-186 may provide important clues for understanding the potential roles of these miRNAs in the pathogenesis of FSGS. It has been proposed that abnormal activation of immune responses may be involved in the development of FSGS, and we speculated that upregulation of these miRNAs in plasma of patients with FSGS might be associated with T cells or other immune cells. For example, upon activation, immune cells may directly secrete these miRNAs into circulation or may act on other cell types in the body that produce and secrete these miRNAs into circulation. Further effort is required to test this hypothesis. Because miR-186 can target genes including PTTG1, FOXO1, P2X7 receptor, and AKAP12, which are involved in cell-cycle control, AKT signaling, insulin signaling, and calcium signaling, respectively, increased circulating miR-186 levels could contribute to the development of FSGS by reaching and entering podocytes or other renal cells and functioning within these cells. Studies have shown that circulating miRNAs can reach remote recipient cells and function within them. miR-125b can activate nuclear factor-kB (NFkB) signaling, which can induce podocyte apoptosis and immune cell activation. Macrophages that overexpress miR-125b can more effectively activate T cells. The roles of miR-125b in activation of the immune system indicate that miR-125b may be involved in the development of renal injury, consistent with our observation that plasma miR-125b level is correlated with FSGS activity.

The present study has several limitations. Because FSGS is heterogeneous in pathogenesis, it is difficult to
identify a biomarker that is suitable for all FSGS cases. This heterogeneity also necessitates use of a large
cohort to validate a candidate biomarker in patients with different subclasses of this disease. An additional
limitation of this study was that our findings were based on Chinese patients with FSGS and may not be
generalizable to other groups, because the pathogenesis of FSGS may vary in different ethnic populations.

To our knowledge, this is the first study reporting plasma miRNA-based biomarkers for detecting FSGS
disease activity. Identification of differentially expressed plasma miRNAs in patients with FSGS, particularly
miR-186, may provide an alternative tool to aid FSGS diagnosis and monitoring. A full understanding of the
target genes of miR-125b and miR-186, as well as of the molecular mechanisms by which plasma levels of these
miRNAs are linked to FSGS activity, may help elucidate the pathogenesis of FSGS and broaden the clinical
applications of these miRNAs.

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Contributions: Research conception and study design: Z-HL,
SS; research and data analysis: CZ, WZ, H-MC, CL, JW. Each
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script drafting or revision and accepts accountability for the overall
work by ensuring that questions pertaining to the accuracy or
integrity of any portion of the work are appropriately investigated
and resolved. Z-HL takes responsibility that this study has been
reported honestly, accurately, and transparently; that no important
aspects of the study have been omitted; and that any discrepancies
from the study as planned have been explained.

SUPPLEMENTARY MATERIAL

Table S1: Clinical features of FSGS patients with nephrotic
proteinuria and controls whose plasma samples were pooled for
assay.

Table S2: Clinical features of FSGS patients with nephrotic
proteinuria or in complete remission and controls who were sub-
jected to plasma miRNA comparisons.

Table S3: ROC curve analysis of ability of miRNAs to
discriminate FSGS patients with nephrotic proteinuria from con-
trols and those in complete remission.

Table S4: Clinical features before and after steroid treatment
of FSGS patients in the prospective study.

Table S5: Clinical features of MN and DN patients and controls.

Table S6: Correlation analysis between levels of plasma miR-
NAs and clinical characteristics of FSGS patients with nephrotic
proteinuria.

Figure S1: Standard curves of miR-125b, miR-186, and miR-
193a-3p.

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