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KIDNEY DISEASE

Inhibition of FSP1-MYH9 Interaction Reduces TGF-β-induced Podocyte Injury: Potential Therapeutic Role of Trifluoperazine

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Introduction. Podocytes are crucial for maintaining the glomerular filtration barrier, and their injury is a major contributor to kidney diseases. FSP1 (Fibroblast-specific protein 1) has been implicated in various pathological conditions but its role in podocyte injury, especially under TGF-β (Transforming Growth Factor-Beta) stimulation, is not well understood. This study aims to explore the involvement of FSP1 and its interaction with MYH9 in TGF-β-induced podocyte damage and assess the therapeutic potential of Trifluoperazine (TFP).

Methods. Human podocytes were treated with TGF-β, followed by FSP1 knockdown using siRNA. A series of assays including CCK8, wound healing, F-actin staining, and CO-IP were performed to assess podocyte injury, migration, and FSP1-MYH9 interactions. The effects of TFP on these interactions and podocyte health were also evaluated.

Results. TGF-β increased FSP1 expression in podocytes, leading to cell damage. FSP1 knockdown reduced injury by improving cell viability and cytoskeletal integrity. CO-IP revealed that FSP1 interacts with MYH9 to promote podocyte injury. TFP treatment reduced FSP1-MYH9 interaction, alleviating podocyte damage.

Conclusion. FSP1 promotes TGF-β-induced podocyte injury through its interaction with MYH9, activating the P38 MAPK pathway. TFP disrupts this interaction, offering a promising therapeutic approach for treating podocyte-related kidney diseases.

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INTRODUCTION

Podocytes are essential components of the glomerular filtration barrier, which plays a critical role in the initiation and progression of glomerulopathies.[1] Podocyte injury is a key pathophysiological process in many kidney diseases, such as diabetic kidney disease, IgA vasculitis nephritis, and glomerulonephritis.[2-5] Injured podocytes can undergo cell death, foot process effacement, and proteinuria, leading to kidney dysfunction.[6] Therefore, identifying novel targets to mitigate podocyte injury is crucial for improving treatment outcomes.

Podocytes express specific proteins, such as

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nephrin and podocin, which form part of the slit diaphragm, a structure essential for filtration.[7,8] These proteins are used as markers to assess podocyte health and functional integrity.[9] In this study, we demonstrate that the podocytes exhibit protein expression patterns typical of healthy podocytes, reinforcing their relevance in studying disease-related damage.

One of the challenges in studying podocytes is their limited proliferative capacity, which makes detecting cellular responses to injury challenging.[10] CCK8 assays, which measure cell viability, have been shown to be effective in assessing podocyte injury, as they provide insight into the metabolic activity of these cells.[11] The CCK8 assay is appropriate for this study as it accurately reflects the degree of injury in cells with low proliferative potential.

FSP1 (Fibroblast-specific protein 1), also known as S100 calcium-binding protein A4, belongs to the S100 family of proteins and is involved in various biological processes.[12] It has been reported that secreted FSP1 activates the VEGFA pathway, inducing epithelial barrier dysfunction and inflammation.[13] In lung cancer, serum FSP1 can act as a biomarker to guide treatment strategies.[14] Additionally, FSP1 + cells can activate macrophages and the Notch signaling pathway, promoting renal fibrosis and inflammation in kidney diseases.[15] The expression of FSP1 in podocytes is associated with epithelial-to-mesenchymal transition (EMT)-like changes and has been recognized as a biomarker in tubulointerstitial fibrosis.[16] However, the role of FSP1 in TGF-β-treated podocytes remains unexplored.

MYH9 (myosin heavy chain 9) encodes the protein NMIIA, which acts as a molecular motor and plays a key role in cell migration, division, and polarization. MYH9 expression is elevated in various cancers, including gastric, lung, and colorectal cancers.[17,18] It has been shown that MYH9 interacts with MYH10 to recruit USP45, promoting cancer progression in ovarian cancer.[19] In acute kidney injury, APE2 interacts with MYH9 to induce mitochondrial fragmentation.[20] However, the interaction between MYH9 and FSP1 in podocyte injury remains unknown.

Given that this study is conducted entirely in vitro, it is important to note the limitations of such experiments. While we demonstrate the interaction between FSP1 and MYH9 in podocyte injury under controlled conditions, we have yet to establish whether these proteins exhibit similar functional relevance in vivo. It remains to be determined whether the expression of FSP1 and MYH9 changes in actual disease states or under conditions that induce podocyte damage. Further research is needed to assess the potential of these proteins as therapeutic targets in vivo.

MATERIALS AND METHODS

Cell Culture and Treatment

Human podocytes were purchased from Xuanke Biotechnology (Shanghai, China). The cells were cultured in RPMI 1640 medium (Hyclone, Utah, USA), supplemented with 10% fetal bovine serum (FBS; Gibco, USA), and maintained in a humidified atmosphere containing 5% CO_2 at 37°C. Podocytes were exposed to different treatments, including medium alone, TGF-β (10 ng/ml; Promega, Madison, Wisconsin, USA), or Trifluoperazine (TFP) (20 μM). The duration of treatments and experimental conditions were standardized for consistency across assays.

Transfection

Small interfering RNAs (siRNAs) targeting FSP1 and MYH9 were obtained from GenePharma (Shanghai, China). Cells were transfected with siRNA using Lipofectamine 3000 (Invitrogen, USA) according to the manufacturer's protocol. Successful transfection and knockdown efficiency were confirmed through RT-qPCR and Western blot analyses.

CCK8 Assay

A CCK8 assay kit (Sigma, USA) was employed to assess cell viability, an important indicator of podocyte injury. Briefly, the kit was used to measure the metabolic activity of living cells. The absorbance was recorded at 450 nm using a microplate reader, reflecting the degree of podocyte viability under different experimental conditions. The CCK8 assay is particularly suitable for podocytes, which are cells with limited proliferative capacity, providing a robust measure of injury by capturing changes

in their metabolic activity.

Wound Healing Assay

Cells (2×10^5) were seeded into six-well plates and cultured until they reached 70 to 80% confluence. Following treatment, a scratch was made using a pipette tip to create a straight wound across the monolayer. The progress of wound healing was observed and recorded at specific time points to assess the migration ability of podocytes. This assay helped demonstrate changes in cellular motility associated with podocyte injury.

F-actin Staining

To examine cytoskeletal changes in podocytes, cells were fixed with a 3.7% (v/v) formaldehyde solution and permeabilized using a 0.2% (v/v) Triton X-100 solution. After several washes with PBS, the cells were stained with either fluorescein or rhodamine-labeled phalloidin to visualize F-actin structures. DAPI was used to stain cell nuclei. This assay provided insight into actin stress fiber patterns, which are critical for maintaining podocyte structure, especially under TGF-β-induced injury.

CO-IP Assay

For co-immunoprecipitation (CO-IP) experiments, treated cells were lysed using a buffer containing 40 mM HEPES (pH 7.4), 0.5% Triton X-100, 2 mM EDTA, and protease inhibitors. Cells were subjected to gentle shaking, followed by centrifugation at 12,000 × g for 10 minutes to separate the supernatant. The supernatant was incubated with a specific antibody overnight at 4 °C, followed by incubation with A/G agarose beads for 4 hours the next day. The samples were then separated by SDS-PAGE and analyzed by Western blotting to detect the protein-protein interactions.

Western Blot

Protein was extracted from treated cells using RIPA buffer (Byotime, China) supplemented with protease inhibitor cocktail tablets and phosphatase inhibitor PMSF (both from Roche, Switzerland). P38 and phosphorylated-P38 (p-P38) antibodies were obtained from CST. Protein samples were separated via SDS-PAGE, transferred to PVDF membranes, and detected using the appropriate antibodies to assess the expression levels of target proteins.

RT-qPCR

Total RNA was extracted from treated cells using TRIzol reagent. cDNA was synthesized using the HiScript III All-in-One RT SuperMix (Vazyme, China), following the manufacturer's instructions. Quantitative real-time PCR (qRT-PCR) was performed to measure gene expression levels using specific primers. GAPDH was used as the internal control, and relative gene expression.

Statistical Analysis

Statistical analyses were performed using Student's *t*-test or one-way ANOVA to compare differences among experimental groups. A *P* value of less than .05 was considered statistically significant. Data are presented as mean ± standard deviation (SD) for all experiments.

RESULTS

FSP1 Expression is Increased in TGF-β-Treated Podocytes

To evaluate the expression of FSP1 in podocytes under TGF-β treatment, we treated podocytes with TGF-β for 24 hours and assessed FSP1 mRNA levels using RT-PCR. The results showed a significant increase in FSP1 expression in TGF-β-treated podocytes compared to the untreated control (Figure 1A). Western blot analysis further confirmed the upregulation of FSP1 at the protein level in TGF-β-treated podocytes (Figure 1B). These results suggest that FSP1 plays a role in the TGF-β-induced changes in podocytes, indicating its potential involvement in podocyte injury.

FSP1 Knockdown Alleviates Podocyte Injury

To assess the functional role of FSP1 in podocyte injury, we knocked down FSP1 expression using siRNA and examined several markers of podocyte health. The CCK8 assay was used to evaluate cell viability. TGF-β treatment significantly reduced cell viability, while FSP1 knockdown reversed this effect, indicating a protective role for FSP1 knockdown in podocyte injury (Figure 2A).

We also performed TUNEL staining to assess cell apoptosis. The results showed that TGF-β

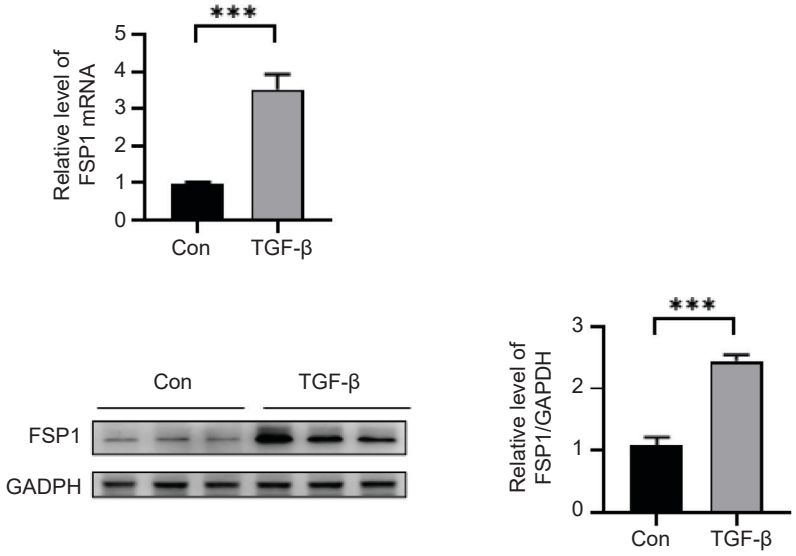


Figure 1. FSP1 Expression is increased in TGF-β-Treated Podocytes. FSP1 mRNA level evaluation by RT-PCR after TGF-β treatment. FSP1 protein level detection by western blot after TGF-β treatment (n = 3) (*P < .05, **P < .01, ***P < .001)

treatment increased podocyte apoptosis, but FSP1 knockdown significantly reduced the number of apoptotic cells (Figure 2B). Additionally, a wound healing assay was used to evaluate cell migration. TGF-β treatment promoted podocyte migration, but this effect was mitigated by FSP1 knockdown (Figure 2C).

Given that the integrity of podocyte foot processes is crucial for maintaining glomerular function, we examined actin stress fiber patterns using F-actin staining. TGF-β-treated podocytes displayed disrupted F-actin fibers, indicative of foot process injury. However, FSP1 knockdown restored the normal stress fiber structure, suggesting its role in protecting podocyte cytoskeletal integrity (Figure 2D). Collectively, these findings demonstrate that FSP1 knockdown reduces podocyte injury caused by TGF-β treatment.

FSP1 Binds to MYH9 and Exacerbates Podocyte Injury

To investigate the molecular mechanisms underlying FSP1-mediated podocyte injury, we used the STRING database to predict potential binding partners of FSP1(Figure 3A). MYH9, a protein known to be involved in cancer invasion and metastasis, was identified as a candidate binding partner of FSP1. To confirm this interaction, we performed a CO-IP assay, which demonstrated that FSP1 binds to MYH9 in podocytes (Figure 3B-C).

Next, we examined the effect of MYH9 knockdown on podocyte injury. MYH9 knockdown reduced cell viability, which had been increased by TGF-β treatment. Similarly, TUNEL staining indicated that MYH9 knockdown decreased cell apoptosis (Figure 3D), and wound healing assays showed a reduction in cell migration (Figure 3E). Furthermore, MYH9 knockdown reduced P38 phosphorylation, a key signaling event in podocyte injury (Figure 3F). These results indicate that FSP1 promotes podocyte injury through its interaction with MYH9, potentially by activating the P38 MAPK signaling pathway[21].

TFP Reduces FSP1-MYH9 Binding and Alleviates Podocyte Injury

Given that TFP has been reported to improve renal function in models of lupus nephritis, we investigated whether TFP could mitigate podocyte injury by targeting the FSP1-MYH9 interaction[22]. CO-IP assays showed that TFP treatment reduced the binding between FSP1 and MYH9 (Figure 4A-B).

We then assessed the effects of TFP on podocyte health. TFP treatment reduced cell viability, which had been elevated by TGF-β treatment. TUNEL staining confirmed that TFP decreased

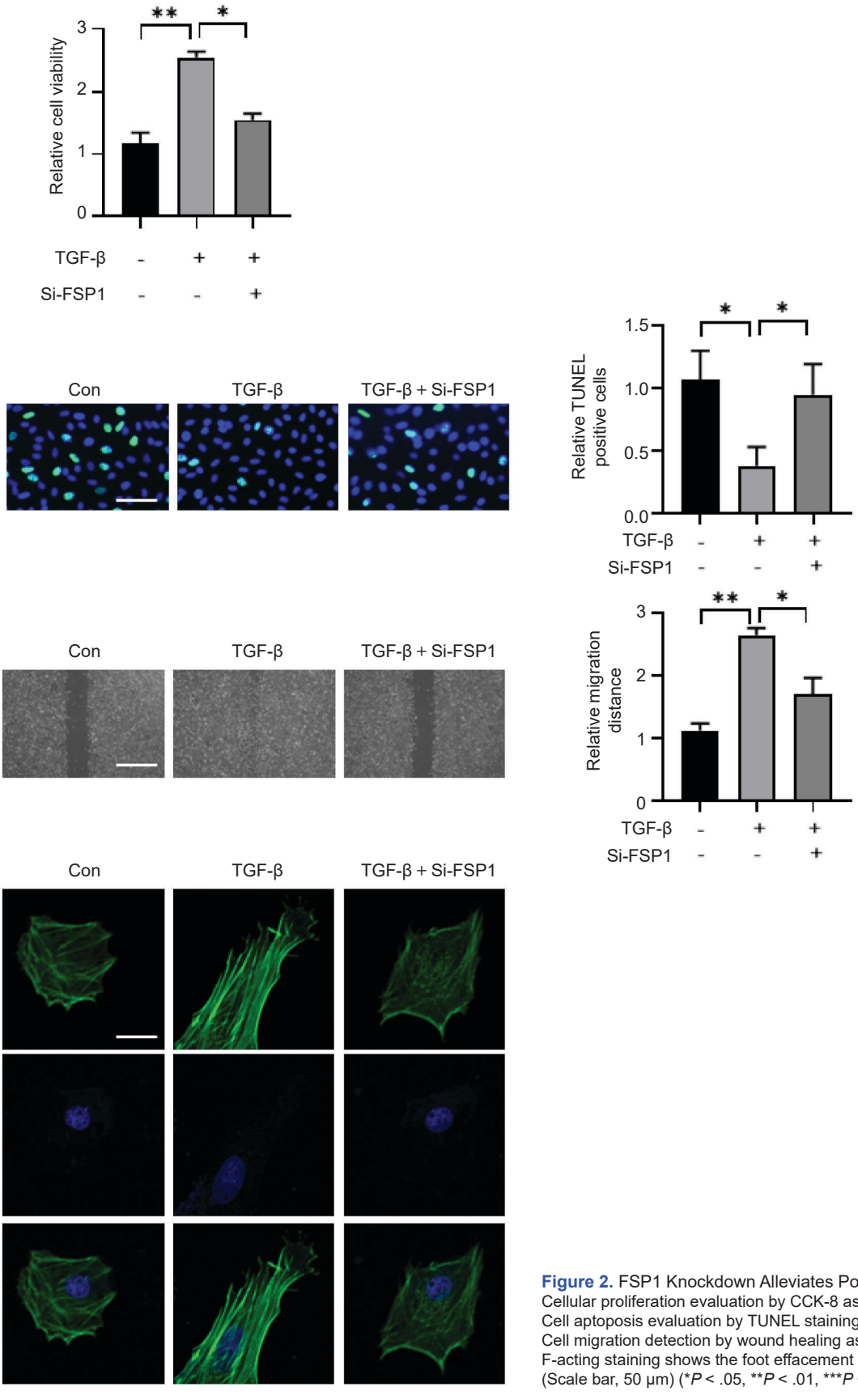
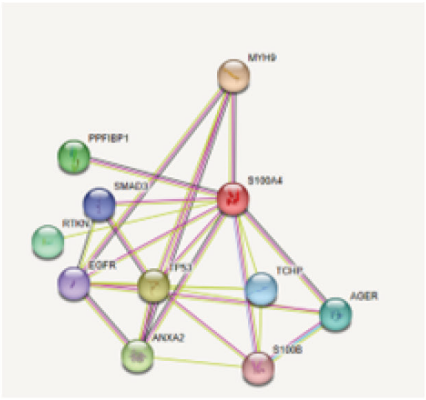
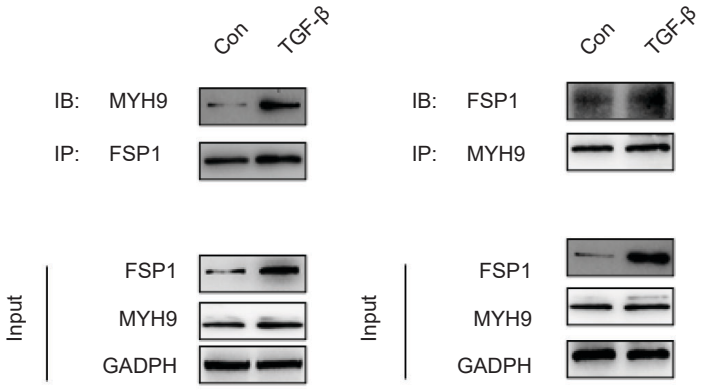
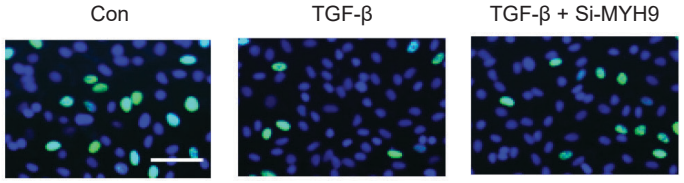
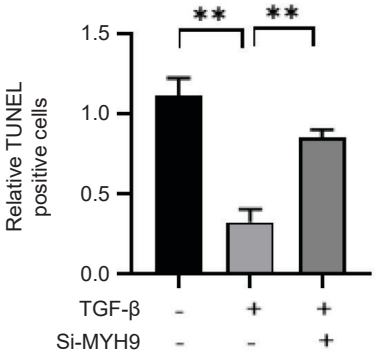


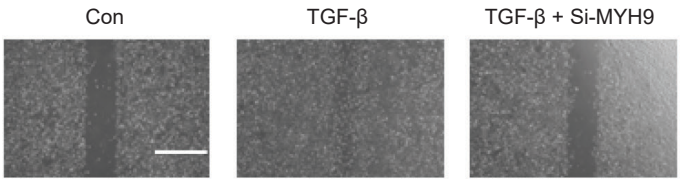
Figure 2. FSP1 Knockdown Alleviates Podocytes Injury
Cellular proliferation evaluation by CCK-8 assay
Cell aptoposis evaluation by TUNEL staining
Cell migration detection by wound healing assay
F-acting staining shows the foot effacement
(Scale bar, 50 μm) (*P < .05, **P < .01, ***P < .001)

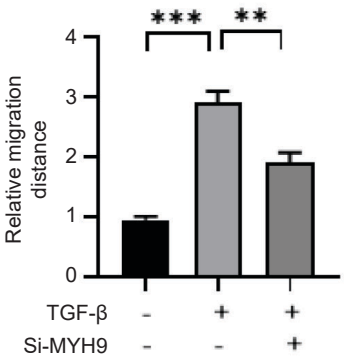


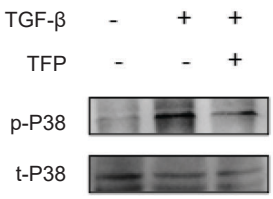












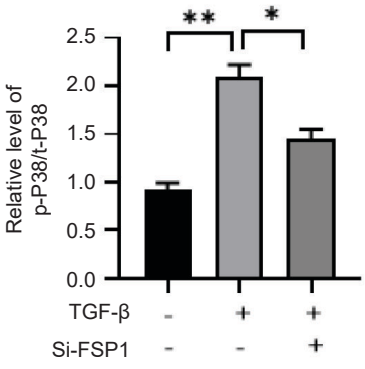


Figure 3. FSP1 Binds to MYH9 and Exacerbates Podocyte Injury
A. String database use to predicate the interaction between FSP1 and MYH9
B-C. Use of CO-IP to indicate that FSP1 could interact with MYH9
D. Cell apoptosis evaluation by TUNEL staining
E. Cell migration was detection by wound healing assay.
F. p-P38 level detection by western blot
(Scale bar, 50 μm) (*P < .05, **P < .01, ***P < .001)

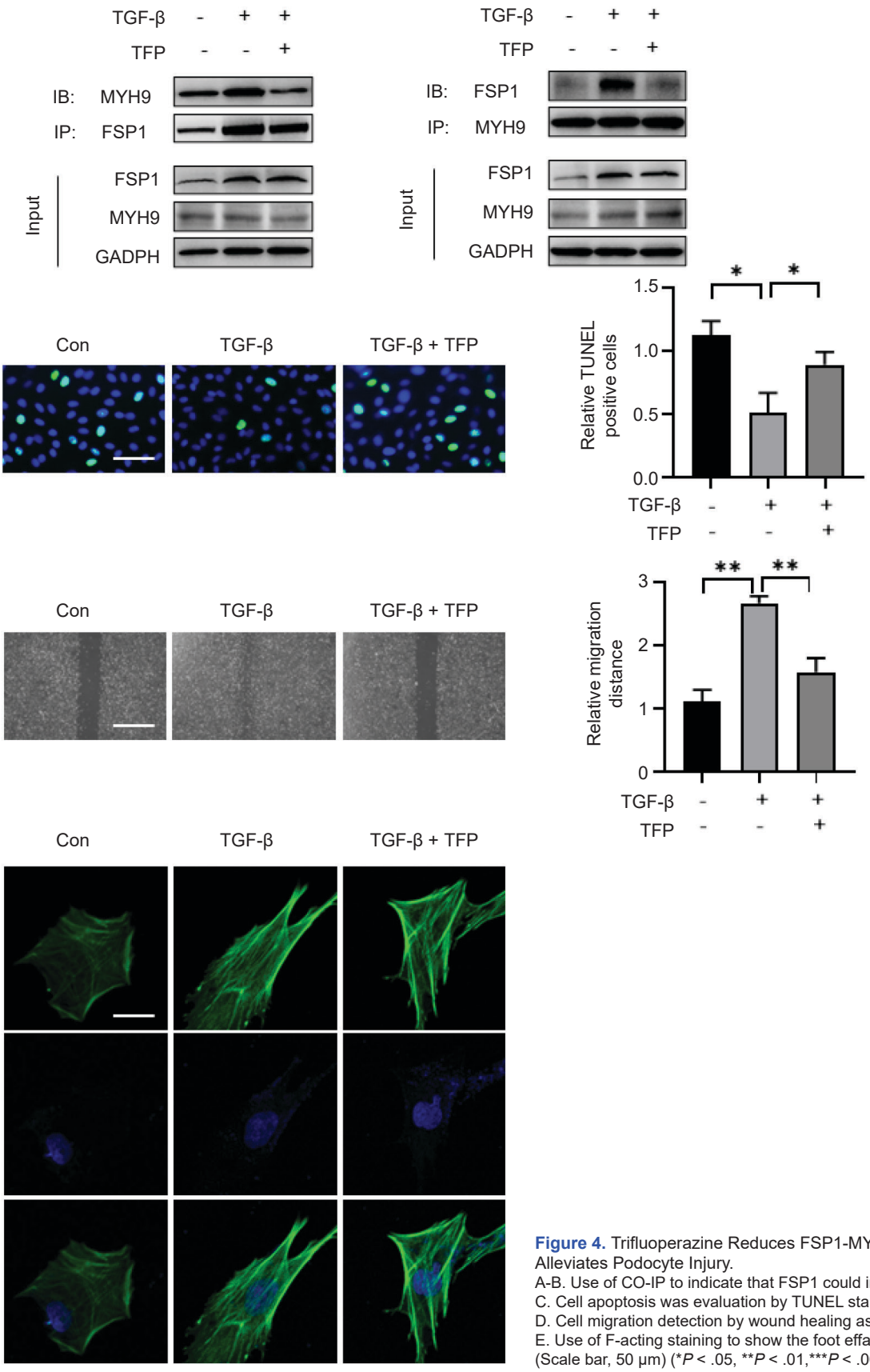


Figure 4. Trifluoperazine Reduces FSP1-MYH9 Binding and Alleviates Podocyte Injury.
A-B. Use of CO-IP to indicate that FSP1 could interact with MYH9.
C. Cell apoptosis was evaluation by TUNEL staining.
D. Cell migration detection by wound healing assay
E. Use of F-acting staining to show the foot effacement
(Scale bar, 50 μm) (**P* < .05, ***P* < .01,****P* < .001)

cell apoptosis (Figure 4C), and wound healing assays showed a reduction in podocyte migration following TFP treatment (Figure 4D). Additionally, F-actin staining demonstrated that TFP treatment restored the normal actin stress fiber structure in podocytes, which had been disrupted by TGF-β treatment (Figure 4E). These results suggest that TFP alleviates podocyte injury by reducing the interaction between FSP1 and MYH9.

DISCUSSION

Podocyte injury is a key contributor to kidney diseases, leading to outcomes such as cell apoptosis, foot process effacement, and eventual kidney dysfunction.[23-5] Increasing evidence has demonstrated that TGF-β plays a central role in regulating cell migration, proliferation, and adhesion in kidney diseases. It has been reported that TGF-β1 activates the Smad and MAPK signaling pathways, promoting integrin-β3 expression.[23,26] Our study further expands on these findings by showing that TGF-β treatment leads to significant changes in podocyte viability, migration, and actin cytoskeleton integrity.

We demonstrated that FSP1 expression is upregulated in podocytes following TGF-β treatment. FSP1 has been recognized as a biomarker in tubulointerstitial fibrosis due to its association with epithelial-to-mesenchymal transition (EMT)-like changes.[27] Previous studies have indicated that FSP1 expression is elevated in high glucose-treated podocytes via the RAC/PAK1 signaling pathway.[28] Our results are consistent with these findings, confirming that FSP1 is upregulated in response to TGF-β in podocytes, contributing to injury.

The role of FSP1 in promoting podocyte injury was further explored through knockdown experiments. We found that FSP1 knockdown significantly reduced podocyte injury by restoring cell viability, reducing apoptosis, and improving cytoskeletal integrity. This suggests that FSP1 may be a key mediator of TGF-β-induced podocyte damage, making it a promising therapeutic target.

Mechanistically, our study identifies MYH9 as a critical binding partner of FSP1 in podocytes. MYH9 is known to play important roles in cell migration, division, and polarization in various cancers. In kidney diseases, MYH9 has been linked to the promotion of mitochondrial fragmentation in acute kidney injury.[29,30] One study showed that MYH9 could activate GSK3β/β-Catenin Signaling to promote esophageal squamous cell carcinoma.[29] However, the interaction between FSP1 and MYH9 in podocyte injury has not been previously described. Our co-immunoprecipitation experiments confirmed that FSP1 binds to MYH9, and MYH9 knockdown reduced podocyte injury by decreasing cell viability and migration. Furthermore, MYH9 knockdown suppressed P38 phosphorylation, a signaling event associated with podocyte injury, implicating the FSP1-MYH9 axis in the activation of the P38 MAPK pathway.

Although our study focuses on in vitro experiments, the relevance of FSP1 and MYH9 in vivo remains to be fully elucidated. The expression of these proteins in actual disease states or conditions that induce podocyte damage has not yet been established. Future studies should explore the expression of FSP1 and MYH9 in clinical samples from patients with kidney diseases such as diabetic nephropathy or lupus nephritis. This will help determine whether these proteins play a functional role in disease progression and whether they could serve as biomarkers or therapeutic targets in vivo.

TFP, a phenothiazine derivative used in clinical practice as an antipsychotic agent, has shown potential in renal protection. TFP has been reported to mitigate doxorubicin-induced cardiotoxicity via the NF-κB pathway and to improve renal function in nephritis models.[30] Our findings suggest that TFP alleviates podocyte injury by disrupting the interaction between FSP1 and MYH9. This reduction in binding between FSP1 and MYH9 resulted in improved podocyte viability, reduced apoptosis, and restored cytoskeletal integrity, highlighting TFP as a potential therapeutic agent for podocyte-related kidney injuries.

Limitations and Future Directions

One limitation of this study is that it was conducted entirely in vitro, which may not fully reflect the complexities of in vivo kidney disease. While we demonstrated the importance of the FSP1-MYH9 interaction in podocyte injury, it

is essential to validate these findings in animal models or clinical samples. Investigating the expression levels of FSP1 and MYH9 in patients with kidney diseases, such as diabetic nephropathy, glomerulonephritis, or lupus nephritis, would provide further insight into their potential as therapeutic targets. Additionally, the pathways downstream of the FSP1-MYH9 interaction, including P38 MAPK activation, warrant further investigation to determine their role in disease progression and treatment.

Our study identifies FSP1 as a critical mediator of TGF-β-induced podocyte injury through its interaction with MYH9. FSP1 knockdown mitigates podocyte damage, while TFP disrupts the FSP1-MYH9 interaction, offering a novel therapeutic strategy for treating podocyte-related kidney injuries. Further in vivo studies are required to establish the clinical relevance of these findings and explore the potential of FSP1 and MYH9 as biomarkers and therapeutic targets.

CONCLUSION

In this study, we demonstrated that FSP1 expression is upregulated in TGF-β-treated podocytes, contributing to podocyte injury. Knockdown of FSP1 significantly alleviated this injury by restoring cell viability, reducing apoptosis, and improving cytoskeletal integrity. Mechanistically, we identified MYH9 as a critical binding partner of FSP1, and the interaction between these two proteins plays a key role in activating the P38 MAPK signaling pathway, exacerbating podocyte damage.

Moreover, we showed that TFP, a clinically available antipsychotic agent, reduces the interaction between FSP1 and MYH9, thereby mitigating podocyte injury. This highlights the potential therapeutic value of TFP in the treatment of podocyte-related kidney injuries.

While our findings offer new insights into the molecular mechanisms of podocyte injury, further in vivo studies are needed to establish the clinical relevance of FSP1 and MYH9 as therapeutic targets and to explore their potential as biomarkers in kidney disease. Overall, our study provides a foundation for developing novel strategies to treat podocyte injury and kidney diseases.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of Nanjing Medical University, approval number IACUC-036594.

INFORMED CONSENT TO PARTICIPATE

Informed consent was not required in this study.

COMPETING INTERESTS

The authors declare that they have no competing interests

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

FUNDING

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