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REVIEW

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Potential biomarkers of recurrent FSGS: a review

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Abstract

Focal segmental glomerulosclerosis (FSGS), a clinicopathological condition characterized by nephrotic-range proteinuria, has a high risk of progression to end-stage renal disease (ESRD). Meanwhile, the recurrence of FSGS after renal transplantation is one of the main causes of graft loss. The diagnosis of recurrent FSGS is mainly based on renal puncture biopsy transplants, an approach not widely consented by patients with early mild disease. Therefore, there is an urgent need to find definitive diagnostic markers that can act as a target for early diagnosis and intervention in the treatment of patients. In this review, we summarize the domestic and international studies on the pathophysiology, pathogenesis and earliest screening methods of FSGS and describe the functions and roles of specific circulating factors in the progression of early FSGS, in order to provide a new theoretical basis for early diagnosis of FSGS recurrence, as well as aid the exploration of therapeutic targets.

Keywords Focal segmental glomerulosclerosis, Renal transplantation, Biomarkers, Pathogenesis, Relapse, Pathophysiology

Introduction

Primary focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome and end-stage renal disease (ESRD) in both children and adults. The histological classification of FSGS mainly distinguishes the following types: FSGS that is not otherwise specified (NOS), collapsed variant, tip variant, cellular variant, and periportal variant, with the recurrence of each of these after renal transplantation [1]. Currently, kidney transplantation is the best choice for ESRD treatment. The recurrence of postoperative FSGS has become a major complication after kidney transplantation: the recurrence rate of FSGS after the first transplantation has been reported as 30%, and if the second transplantation is performed, it can reach about 80% [2]. To date, decisions to diagnose and treat recurrent FSGS after renal transplantation have been primarily based on proteinuria, serum creatinine, and the histopathology of renal biopsies [3]. However, due to the lack of early specific serological markers, healthcare professionals might miss the opportunity for early intervention, reducing the long-term survival of the transplanted kidney. Therefore, there is an urgent need to clarify the pathogenesis of FSGS and to determine specific biomarkers to improve the early diagnosis of FSGS recurrence. In this paper, we review the latest research progress on the pathophysiology and mechanism of FSGS recurrence in transplanted kidneys9 and discuss new biomarkers for early diagnosis and/or detection.

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Pathophysiology of FSGS

FSGS can be described as a pattern of glomerular lesions caused by podocyte injury, characterized by the obstruction of glomerular capillary collaterals by sclerotic material, where glomerulosclerosis is usually focal and segmental [4, 5]. It can be divided into two main types: primary FSGS and secondary FSGS, with the latter including hereditary, adaptive, infectious/inflammatory and drug-related FSGS [6, 7]. Primary FSGS is thought to be caused by yet unidentified circulating factors that can cause proteinuria production by affecting podocyte function and disrupting the glomerular filtration barrier [6]. Under normal physiological conditions, the podocyte consists of a cell body with primary and secondary foot processes that contain a large number of actin-based cytoskeletons. The primary processes of the connected podocytes extend to the surface of capillaries and form fine secondary foot processes, which are arranged in a specific spatial arrangement to produce slits. Each of these slits is bridged by the so called glomerular slit diaphragm, which forms a filtration barrier for the glomeruli [8–10]. This barrier is essential for the selective filtration of water and solutes, hindering the passage of macromolecules (e.g., albumin) and maintaining normal renal function [11]. FSGS lesions develop due to a variety of etiological factors [12]. The common initiation event is podocyte damage, which ultimately results in podocyte depletion, hence FSGS is considered to be a podocytopathy. The actin-based cytoskeleton is essential for maintaining an effective glomerular filtration barrier against proteinuria. Recently, it has been found that disruption of the podocyte's actin skeleton and lacunar membrane results in the disappearance of foot processes of podocytes, their increase in size and detachment from the glomerular basement membrane, and subsequent migration to the Bowman's gap, leading to the development of FSGS [13].

Circulating factors in the developmental history of FSGS

Since Hoyer et al. [14] first described recurrent FSGS in 1972, several articles have suggested that the mechanism of recurrent FSGS after renal transplantation may be related to circulating permeability factors and may even occur within minutes to hours after transplantation [15]. In Gallon et al's study [16], allografts that failed in the first recipient due to fulminant FSGS recurrence were transplanted into a second recipient. These allografts immediately resumed their function, with a reduction in proteinuria and serum creatinine levels, indicating a role of circulating factors in recurrent FSGS. In addition, there are case reports of infants born to mothers with primary FSGS being born with transient massive proteinuria, suggesting that the occurrence of proteinuria may be associated with the passage of circulating osmotic factors across the placenta [17]. Savin et al's [18] pioneering study provided the first experimental evidence for circulating factors. When they assayed plasma from patients with recurrent FSGS in vitro, they found that serum increased glomerular permeability to albumin. However, the exact biomolecules that cause the induction of FSGS are still unclear, as is the type of circulating factor. Some of the main circulating factors that have been studied so far include soluble urokinase-type plasminogen activator receptor (suPAR), anti-CD40 antibody, cardiolipin-like cytokine 1 (CLCF-1), apolipoprotein A-Ib (ApoA-Ib), calmodulin-dependent serine protein kinases (CASK), microRNAs, and transforming growth factor-β (TGF-β).

Soluble urokinase-type plasminogen activator receptor (suPAR)

SuPAR is the soluble form of urokinase-type plasminogen activator receptor (uPAR), a membrane-bound 45–55 kDa protein [19]. It is produced by cleavage of the GPI anchor of uPAR or secreted directly from transcripts as an alternative and is present in blood or other biological fluids [20, 21]. Wei et al. [22] found that higher pretransplantation suPAR concentrations were associated with a higher risk of FSGS recurrence post-transplantation, and that circulating suPAR causes foot process effacement, proteinuria, and FSGS-like glomerulopathy by activating podocyte αvβ3 integrins in the transplanted kidneys. They identified serum suPAR as a circulating factor that may contribute to FSGS. Alachkar et al. found that the use of plasma exchange reduced serum suPAR levels and suPAR-induced podocyte αvβ3 integrin activity in a cohort of patients with recurrent FSGS after renal transplantation [23], suggesting that suPAR is a detectable biomarker of FSGS recurrence after renal transplantation. The mechanisms involved in the development of recurrent FSGS by suPAR are presented in (Fig. 1) [24–31]. Nevertheless, Harel et al. [32] analyzed suPAR using an ELISA assay and concluded that it did not seem to be a useful marker of FSGS or a predictor of its recurrence after transplantation. Their further study confirmed that the injection of recombinant suPAR into mice at a high dose (100 μg) did not reveal the loss of podocytes with cytoskeletal disruption [33]. A recent report in patients with renal transplantation and infectious complications claimed that high suPAR levels do not indicate infection severity [34]. Similarly, the correlation between suPAR levels and graft function could not be confirmed, although suPAR levels were significantly reduced after transplantation [35]. Interestingly, although it remains controversial whether suPAR becomes a circulating factor in recurrent FSGS, the importance of suPAR in patients with recurrent FSGS continues to be recognized. The αvβ3 integrin signaling pathway is very important for suPAR to cause recurrent FSGS [22, 23], which provides a

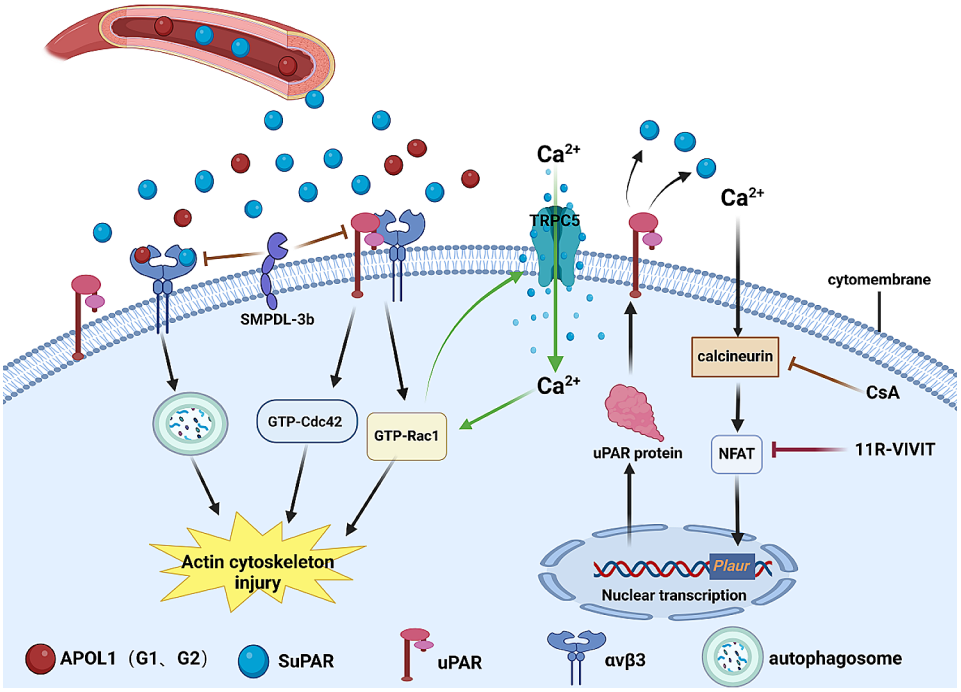

Fig. 1 Mechanisms of suPAR involvement in the development of recurrent FSGS. SuPAR is produced by uPAR and is present in blood or other biological fluids. It can synergistically activate αvβ3 integrins on podocytes through synergistic activation with APOL1 risk variants (G1, G2) and support the formation of three-part protein complexes on cell membranes, which further promotes autophagosome formation, leading to deregulation of the actin cytoskeleton and eventual cell detachment. The ability of uPAR to activate ate nintegrins promotes cell motility and the activation of small GTPases (e.g., Cdc42 and Rac1), which can lead to actin cytoskeletal damage, loss of foot, and proteinuria. Activation of Rac1 signaling leads to activation of TRPC5 ion channel, allowing transient Ca2 + influx into the podocyte and further activation of Rac1, which in turn encourages cytoskeletal remodeling of the podocyte (green arrow). SMPDL-3b on podocytes interferes with suPAR/uPAR and αvβ3 integrin binding, attenuating wi3 integrin activation and signaling. NFAT, a major regulator of Ca2+/calmodulin phosphatase signaling and transcription, binds to the Plaur gene promoter (which encodes uPAR) to increase uPAR expression on podocytes. The above response can be eliminated by the calmodulin phosphatase inhibitor CsA and the NFAT inhibitor 11R-VIVIT. *TRPC5, transient receptor potential canonical-5; SMPDL-3b, sphingomyelin phosphodiesterase-like 3b; NFAT, nuclear factor transcription factor of T cells; CsA, cyclosporin A. Created with BioRender.com*

new direction for future studies on FSGS recurrence after transplantation; nonetheless, larger studies are needed to test this conjecture.

Anti-CD40 antibody

CD40 is a type I 48 kDa sized transmembrane protein that is expressed on a wide range of hematopoietic cells (B cells, monocytes/macrophages, dendritic cells) and non-hematopoietic cells (activated epithelial, endothelial cells) [36]. CD40 ligand (CD40L) is mainly expressed by activated T cells and platelets and can be secreted into the bloodstream via platelets as a soluble protein [37]. It has been demonstrated that soluble CD40L binds to CD40 on podocytes and triggers various biological responses, leading to rearrangement of the actin cytoskeleton and loss of slit septal proteins [38]. Blocking the signal transduction stimulated by the binding of CD40 to its ligand CD40L is therefore necessary to maintain the structural function of the podocyte, and anti-CD40 blocking antibodies have such a role. Delville et al. [39] found that a panel of seven antibodies (CD40, PTPRO, CGB5, FAS, P2RY11, SNRPB2, and APOL2) could predict FSGS recurrence after transplantation with 92% accuracy. Meanwhile, anti-CD40 antibodies alone predicted recurrence with 78% accuracy. Kidney damage caused by anti-CD40 antibodies can be strongly associated with suPAR. Even though both suPAR and anti-CD40 antibodies isolated from FSGS patients induced podocyte damage in vitro and mice when used alone [13], the damage was more pronounced in mice when suPAR and anti-CD40 antibodies were used in combination. Harel et al. [33] revealed that there was a small surge in proteinuria following co-injection of suPAR with an anti-CD40 antibody, which supports that the two act synergistically to drive podocyte injury. The synergistic mechanisms are depicted in (Fig. 2) [13, 39, 40]. In addition, anti-CD40 antibodies have recently been found to be associated with severe steroid-resistant FSGS [41]. Overall, the synergistic effect of suPAR and anti-CD40 antibody is of great significance for the occurrence and development of post-transplant FSGS and has become a new target for research. Blocking anti-CD40 antibodies has emerged as a novel therapeutic measure for the treatment of FSGS recurrence, and the research of related

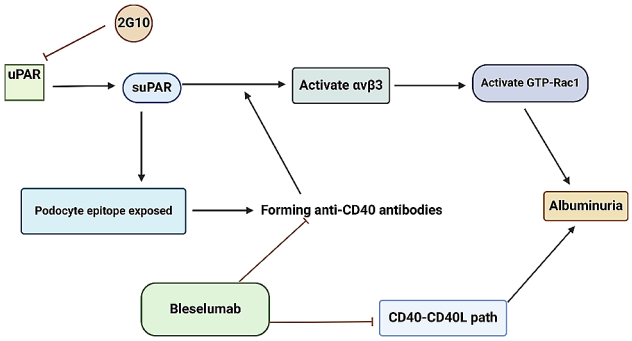

Fig. 2 Role of anti-CD40 antibody combined with suAPR in the development of recurrent FSGS. SuAPR is the soluble form of uAPR. Anti-uPAR antibody (2G10) blocks uAPR and further leads to a reduction in suAPR. The presence of suPAR causes the exposure of cryptic podocyte epitopes, resulting in the formation of anti-CD40 antibodies in rFSGS, which can trigger proteinuria by prolonging suPAR-mediated integrins and/or the corresponding signaling pathways (e.g., Rac-1 activation). The anti-CD40 blocking antibody Bleselumab hampers recurrent FSGS after renal transplantation by preventing anti-CD40 autoantibodies or by blocking the CD40-CD40 ligand signaling pathway. Created with BioRender.com

drugs is gradually moving into clinical application [40, 42, 43], rendering anti-CD40 antibodies promising biomarkers for recurrent FSGS.

Cardiolipin-like cytokines

Cardiolipin-like cytokine 1 (CLCF-1), also known as CLC-1, B-cell stimulating factor-1, and novel neurotrophic factor-3 [44], is a member of the IL-6 family of B-cell stimulating cytokines with a predicted molecular weight of 22 kDa. CLCF-1 has a permeabilizing activity that initiates signaling through the JAK/STAT pathway in glomerular podocytes [45]. Plasma concentrations of CLCF-1 were found to be 100-fold higher in patients with recurrent FSGS than in controls [46]. CLCF-1 may play a dual role in the pathogenesis of recurrent FSGS (Fig. 3) [18, 47, 48]. However, Chebotareva et al. [49] recently found no correlation between the serum levels of CLCF-1 and glomerular filtration rate, percentage of sclerotic glomeruli, or severity of tubulointerstitial fibrosis when they compared the laboratory profiles with the clinical and histological features of nephritis. It seems that more studies are needed to validate CLCF-1 as a

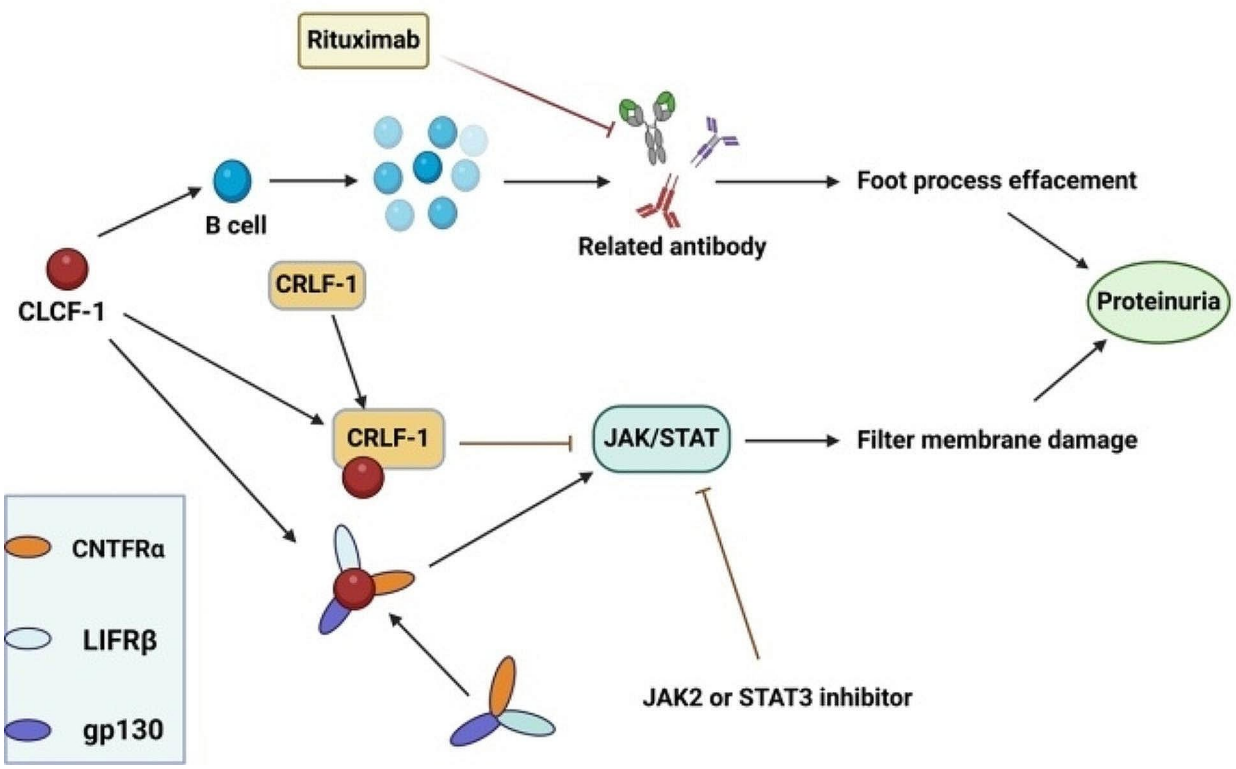

Fig. 3 Possible mechanisms by which CLCF-1 causes recurrent FSGS. Firstly, CLCF-1 amplifies IgG-producing B-cell populations, leading to B-cell activation, which in turn leads to the production of associated antibodies whose targets include proteins expressed by podocytes, an effect that is attenuated by the anti-B-cell antibody rituximab. Secondly, through the binding of CLCF-1 to the tripartite receptor complex composed of CNTFRα, gp130 and leukemia inhibitory factor-oducing B-cell populations, aling pathway is activated, leading to an increase in glomerular albumin permeability. The heterodimeric binding of CLCF-1 to its chaperone, cytokine receptor-like factor-1 (CRLF-1), and inhibitors of JAK2 or STAT3 activation block the renal damaging effects of CLCF-1. Created with BioRender.com

potential biomarker, especially the involvement of the JAK/STAT pathway as the key pathogenic mechanism.

Apolipoprotein A-Ib

Apolipoprotein A-I (ApoA-I) is one of the most abundant proteins in the plasma and is composed of 243 amino acids [50]. It is the major protein component of high-density lipoprotein (HDL), widely known for regulating cholesterol trafficking and protecting against cardiovascular disease (CVD), also modulating inflammatory and immune responses [51]. Apolipoprotein A-Ib (ApoA-Ib) is its high-molecular-weight form generated by the erroneous processing of the ApoA-I precursor [52], which has recently been found to be specifically present in the urine of patients with recurrent FSGS after renal transplantation. Lopez-Hellin et al. [53] reported that the appearance of ApoA-Ib preceded histological damage and demonstrated the early detection of elevated ApoA-Ib in the urine of patients with transplanted FSGS, whereas no elevation of ApoA-Ib was found in patients with non-recurrent FSGS and other nephropathies, with a sensitivity of up to 92.8% and a specificity of 98.1%. A multicentre cohort study [54] also found that the abundance of ApoA-Ib in the urine of patients with FSGS recurrence was much higher than that of other ApoA-I forms. The relevant mechanism may be that the reabsorption of ApoA-Ib is impaired by three uncleaved amino acids, which are present in the urine through an unknown mechanism preventing the transport of ApoA-Ib into tubular cells by either the cubilin-megalin complex or the ABCA-1 protein [52, 55]. Although the above studies have confirmed the superiority of urinary ApoA-Ib in the diagnosis of recurrent FSGS, further studies are needed to investigate the mechanism of occurrence of the above phenomenon.

Table 1 Roles played by relevant miRNAs in causing FSGS

miR-193a	Inhibits WT1, leading to downregulation of the expression of podocyte proteins (renin and CD2AP) and impairing podocyte homeostasis. This brings about the proliferation and activation of PEC (glomerular wall epithelial cells), loss of their repair function, and deposition of glomerular extracellular matrix.
miR-19b-3p	Promotes M1 macrophage activation to cause renal injury and tubulointerstitial inflammation
miR-378a-3p	Inhibits renal connexin expression, leading to podocyte injury and glomerular basement membrane alterations
miR-155-5p	Promotes renal oxidative stress and inflammation and accelerates the progression of renal fibrosis in FSGS
miR-186-5p	Circulating Pathogenic Factors Drive Renal Inflammation and Tissue Damage in FSGS Patients
miR-1470	Inhibits fibrosis formation via MMP13
miR-4483	Promotes fibrosis formation through 3TIMP1

Calmodulin-dependent serine protein kinase

CASK is a ubiquitously expressed multi-structural domain scaffolding protein, predominantly in neurons and podocytes, which mediates the link between the extracellular matrix and actin and is involved in cytoskeleton composition [56]. In Beaudreuil et al's study [56], when mice were given intravenously administered recombinant-CASK (rCASK), they had alterations in their podocytes and developed high levels of proteinuria. The aforementioned effect might be brought about by rCASK-induced modifications to the podocytes' cytoskeleton and associated proteins, which could affect the podocytes' permeability. In fact, FSGS will result from the podocyte alterations mentioned above [1, 57]. A team of researchers found increased expression of CASK in plasma-derived exosomes from FSGS patients after transplantation [58]. By collecting purified exosomes from the serum of patients with recurrent FSGS, healthy controls and proteinuria-free transplant recipients, they found that the expression level of intra-serum exosomes of CASK was significantly elevated in the group of patients with recurrent FSGS. They further demonstrated that the presence of CASK leads to alterations in the actin cytoskeleton and podocyte motility phenotype. The above studies confirmed that CASK is closely associated with the development of FSGS in animals and humans, while more research is needed to further explore the role and mechanisms played by CASK in primary or recurrent FSGS.

MicroRNAs

MicroRNAs (miRNAs) are a class of non-coding single-stranded RNAs with an average length of 22 nucleotides, that function to regulate the expression of target genes [59]. The roles played by relevant miRNAs in causing FSGS are listed in Table 1. MiR-193a is mainly expressed by glomerular wall epithelial cells in renal cells. Overexpression of miR-193a represses the nephroblastoma protein (WT1), resulting in downregulation of the expression of podocyte proteins (nephrin and CD2AP), which impairs podocyte homeostasis and leads to FSGS [60]. Wang L et al. [61] also demonstrated that increased miR-193a levels can be used as a non-invasive marker for diagnosis and outcome assessment in FSGS patients. In addition, high miR-193a expression favors the proliferation of PECs (glomerular wall epithelial cells), resulting in the activation of a large number of PECs that lose their reparative function, acquire a pro-fibrotic and proliferative phenotype and lead to glomerular extracellular matrix deposition, a hallmark of the disease [62, 63]. Interestingly, APOL1 risk variants (G1 and G2) also enhance miR-193a expression in podocytes and cause damage to them [64]. The relevant pathogenesis mechanism may be related to the synergistic activation of αvβ3

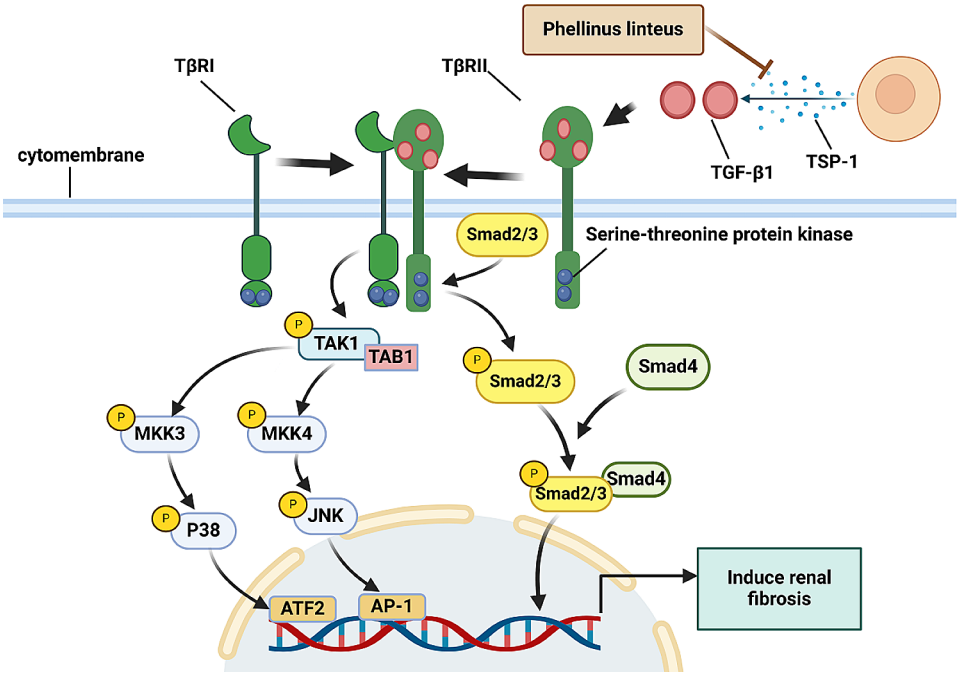

Fig. 4 TGF-β1 induces renal fibrosis pathway signaling. TGF-duces renal fibrosis pathway signalhe development ofinvolves the binding of active TGF-β1 to TβRII, which recruits and transphosphorylates Tans. The intracellular structural domains of Tcruits and of primary or recurrent FSGS.f TGF-β with the progression o This transphosphorylation activates T of Tcruits and of primary or recurrent orylates Smad2 and Smad3. Phosphorylated Smad2/3 forms an oligomeric complex with Smad4, which is subsequently translocated to the nucleus to regulate the transcription of relevant target genes, inducing kidney fibrosis. In addition, under unstimulated conditions, TAK1 binds to TβRI. In the non-canonical pathway, TAK1 is activated by TGF-anslocated to the nucleus to regulate the transcription of relevant target autophosphorylation of TAK1, triggering downstream signaling pathways such as the MKK4-JNK or MKK3-p38 cascade, leading to the activation of the transcription factors ATF-2 and AP-1 and inducing renal fibrosis. *Phellinus linteus* inhibits TGF-eusn of the transcription factors *TSP-1*, *platelet response protein-1; TβRI*, *type I TGF-β receptor; TβRII*, *type II TGF-β receptor; TAK1*, *TGF-β-activated kinase 1; Table 1*, *TAK1-binding protein 1; MKK*, *mitogen-activated protein kinase kinase; JNK*, *c-Jun N-terminal kinase. Created with BioRender.com*

integrins on podocytes by SuPAR and APOL1 risk variants (G1 and G2), which promotes the formation of autophagosomes, leading to dysregulation of the actin cytoskeleton and eventual cell detachment. Other than that, exosomal miR-19b-3p can cause renal injury by promoting M1 macrophage activation, and its expression positively correlates with the severity of albuminuria and plays a key role in tubulointerstitial inflammation [65]. MiR-378a-3p mediates the inhibition of glomerular matrix protein (nephronectin) expression [66], leading to podocyte injury and glomerular basement membrane alterations. Increased expression of miR-155-5p, measured in renal tissues, promotes oxidative stress and inflammation in the kidney and accelerates the progression of renal fibrosis in FSGS [67]. Xu et al. [68] recently found that exosomal circulating pathogenic factor miR-186-5p drives renal inflammation and tissue damage in FSGS patients. MiR-1470 inhibits via MMP13 fibrosis formation and miR-4483 promotes fibrosis formation through 3TIMP1, both of which also play important roles in FSGS formation [69]. The above studies affirm the critical role of miRNAs in podocyte biology and their potential utility in the clinical management of glomerular diseases, providing targets for exploring the in-depth mechanisms and therapeutic interventions of miRNAs that accelerate the progression of FSGS. To completely comprehend the role of miRNA regulation in primary or recurrent FSGS, more thorough research is still required due to the intricacy of the process.

Transforming growth factor-β

Transforming growth factor-β (TGF-β) is a cytokine with pleiotropic effects. TGF-β is responsible for the differentiation, proliferation and other immune functions of many types of cells. Both proliferative and fibrotic glomerulopathies have been associated with elevated expression of TGF-β [4]. TGF-β has three isoforms in mammals: TGF-β1, TGF-β2 and TGF-β3, with TGF-β1 considered to be a pro-fibrotic mediator in a variety of renal diseases [70, 71]. Platelet reactive protein-1 (TSP-1) is a physiological activator of TGF-β1 [72]. Activated TGF-β1 binds directly to type II receptors, which recruit, bind and transphosphorylate type I receptors, stimulating their protein kinase activity. Type I and type II receptors contain serine-threonine protein kinases in their intracellular compartments, and activated type I receptors phosphorylate either Smad2 or Smad3 [73]. Phosphorylated Smad2/3 forms an oligomeric complex with

Smad4. These complexes translocate to the nucleus and further regulate the transcription of target genes, leading to renal fibrosis [74, 75]. The Smad signaling pathway is well recognized as the primary mechanism for TGF-β1 activation. Non-classical TGF-β signaling pathways play an important role in renal fiber development. For example, TGF-β1 activates the serine/threonine kinase TGF-β-activated kinase 1 (TAK1), which in turn activates downstream signaling cascades such as MKK4/7-JNK and MKK3/p38 responses [76, 77]. TGF-β1 induces renal fibrosis pathway signaling (Fig. 4) [72–79]. The medicinal mushroom *Phellinus linteus* was recently found to inhibit nephrosclerosis by inhibiting TSP-1-activated TGF-β1 signaling [79]. In addition, Strehlau et al. [80] found that intrarenal TGF-β1 transcript levels were higher in children with FSGS than in children with microscopic lesions, suggesting that TGF-β1 gene transcripts are a hallmark of progressive kidney damage typical of FSGS. The research results collectively suggest that TGF-β could be an ideal candidate for a biomarker, which is observed in kidney lesions in FSGS [81]. Recently, Husain et al. [82] conducted an experimental animal study and observed the loss of WT1-expressing podocytes and a significant increase in the expression of TGF-β with the progression of FSGS, which is in agreement with the theory hypothesized in several literatures that TGF-β plays an integral role in the development of primary or recurrent FSGS.

Other possible circulating factors

Recently, CPF (circulating permeability factor)-containing plasma from FSGS patients was found to induce the accumulation of lipid droplets and perilipin-2 expression in podocytes, and perilipin-2 was proposed to be identified as a potential biomarker [83]. In addition, colony-stimulating factor-1 (CSF-1) protein induced molecular phenotypic and functional changes in PEC, leading to its activation and consequent pro-fibrotic phenotype as well as a reduction in foot cell markers, suggesting that CSF-1 plays an important role in FSGS [62]. A recent study by Shirai's team identified circulating anti-renin antibodies as a possible candidate for CPF involved in the pathogenesis of recurrent FSGS after transplantation [84]. Although the pathogenic roles of the above-circulating factors in FSGS are not yet clear, enhancing the study of related circulating factors and clarifying the pathogenesis are expected to provide new therapeutic targets for primary and recurrent FSGS.

Conclusion

The consequences of recurrent FSGS following kidney transplantation makes early detection and screening crucial tasks. To guide the development of new, more effective therapies that improve the long-term outcome of renal transplantation and increase the long-term survival of transplanted kidneys, reliable circulating permeability factors can be used as specific biomarkers. These can also help reduce renal injury from renal biopsy and aid in the prompt diagnosis of post-transplant FSGS. The mechanism of FSGS recurrence is intricate, involving interactions between synergistic effects of many targets and several signaling pathways that are active during the recurrence process. Consequently, it is challenging to accurately describe the critical function that target proteins play in this process, as well as the network-like interaction between related signaling pathways. The continuous development of medical technology and in-depth exploration of the mechanism of FSGS recurrence after renal transplantation is expected to provide new opportunities for effective diagnosis and treatment.

Abbreviations

FSGS	Focal Segmental Glomerulosclerosis
ESRD	End-stage renal disease
suPAR	Soluble urokinase-type plasminogen activator receptor
uPAR	Urokinase-type plasminogen activator receptor
TRPC5	Transient receptor potential canonical-5
SMPDL-3b	Sphingomyelin phosphodiesterase-like 3b
NFAT	Nuclear factor transcription factor of T cells
CsA	Cyclosporin A
CLCF-1	Cardiolipin-like cytokine 1
ApoA-Ib	Apolipoprotein A-Ib
CASK	Calmodulin-dependent serine protein kinase
microRNAs	Non-coding single-stranded RNAs
TGF-β	Transforming growth factor-β
MCD	Microcosmic dysplastic kidney disease
CD40L	CD40 ligand
rFSGS	Recurrent FSGS
LIFRβ	Leukemia inhibitory factor-β
CRLF-1	Cytokine receptor-like factor-1
rCASK	Recombinant-CASK
WT1	Nephroblastoma protein
PEC	Glomerular wall epithelial cell
TβRI	TGF-β receptor type I
TβRII	TGF-β receptor type II
TSP-1	Platelet reactive protein-1
TAK1	TGF-β-activated kinase 1
Tab1	TAK1-binding protein 1
MKK	Mitogen-activated protein kinase kinase
JNK	C-Jun N-terminal kinase
NGAL	Human neutrophil gelatinase-associated lipid transport protein
MDA	Malondialdehyde
CPF	Circulating permeability factor
CSF-1	Colony stimulating factor-1

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Author contributions

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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