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REVIEW

Advances in Focal Segmental Glomerulosclerosis Treatment From the Perspective of the Newest Mechanisms of Podocyte Injury

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Abstract: Podocyte injury was widely recognized as a fundamental mechanism driving the progression of focal segmental glomerulosclerosis (FSGS). Recent research has therefore focused on the development of targeted therapies aimed at disrupting specific pathogenic signaling cascades within podocytes, resulting in noteworthy advancements. The role of mechanisms such as alterations in the actin cytoskeleton, oxidative stress, mitochondrial dysfunction, and inadequate autophagy within the microenvironment of podocyte injury have garnered increasing attention. Corresponding targeted medications such as Abatacept, chemokine receptor (CCR) inhibitors, CDDO-Im (2-Cyano-3,12-dioxooleana-1,9-dien-28-imidazolide), adenosine monophosphate-activated protein kinase (AMPK) activators, and Adalimumab are currently under investigation. Notably, some medications such as Rituximab and Sparsentan, may simultaneously target multiple downstream mechanisms, Furthermore, exploring molecular strategies for established medications and developing novel treatments guided by biomarkers such as Anti-CD40 antibody, blood microRNA, urinary microRNA, and tumor necrosis factor-alpha (TNF-α) may provide additional therapeutic avenues for patients with FSGS.

Keywords: focal segmental glomerulosclerosis, podocyte injury, targeted therapies, biomarkers

Introduction

Focal segmental glomerulosclerosis (FSGS) is a common cause of adult nephrotic syndrome (NS), comprising 35% of biopsy-confirmed cases of nephrotic syndrome.[1] It represents a histopathological pattern resultant from podocyte injury, rather than a distinct disease entity. The pattern is characterized by the extensive fusion and disappearance of podocyte foot processes and the collapse of the basement membrane when observed under electron microscopy.[2] The global incidence of FSGS is continually increasing and has becoming the most common primary glomerular disease among the all primary glomerulonephropathies.[3,4] According to Sim et al,[5] FSGS has the highest risk for end-stage renal disease (ESRD) compared to other types of glomerulonephritis. Approximately 8.72% of patients with FSGS develop into ESRD annually, thereby imposing a significant burden on public health.[5] This disease is categorized into primary, hereditary, secondary, and idiopathic types, with primary focal segmental glomerulosclerosis (pFSGS) constituting approximately 17% of all cases.[6] In the absence of reliable biomarkers, pFSGS is typically diagnosed by exclusion,[7] identified by the abrupt onset of nephrotic syndrome and the hallmark feature of diffuse foot process effacement (FPE).[8]

Identifying patients with pFSGS is particularly important, as pFSGS patients who are treatment resistant have a higher risk of progressing to ESRD, potentially requiring maintenance dialysis or kidney transplantation.[9] However, approximately 32% of pFSGS patients experience a recurrence of disease in the early period following renal transplantation, with a median time of 1.5 months.[10] This raises a more complex treatment need for pFSGS. The latest Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for 2021 recommend high-dose corticosteroids should be the initial therapeutic approach for patients with pFSGS, anticipating a potential reduction in proteinuria within four

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months.[11] Patients who do not respond to this treatment require re-evaluation to rule out undiagnosed hereditary factors, as resistance to corticosteroid therapy is a shared characteristic among all hereditary forms of FSGS.[12] However, the heterogeneous etiology of FSGS has led to a lack of a definitive diagnostic algorithm for distinguishing between different FSGS subtypes.[2] The current classification schema, based on clinical and pathological features, may result in inappropriate or even detrimental treatments.[13] Moreover, the challenges of proteinuria recurrence and corticosteroids resistance persist.

Hence, a critical aspect of managing FSGS patients is to identify those who may benefit from specific treatments and to offer more targeted therapeutic options. In recent years, the focus of research has shifted towards therapies targeting podocyte-specific pathogenic signaling cascades. The development of new biomarkers is ongoing to identify potential specific subgroups, and progress in this area has been made. This review aims to encapsulate the latest insights into podocyte injury in FSGS and to discuss the research on biomarkers and the concept of precision medicine for FSGS.

Treatments and New Medications of FSGS

Despite gaining new understanding of the pathogenesis of FSGS, there remains a paucity of effective targeted therapies.[11] Over the past several decades, the treatment landscape for FSGS has seen minimal evolution, with the primary reliance on non-specific immunosuppressive agents such as corticosteroids and calcineurin inhibitors.[11] It is crucial that immunosuppressive regimens be tailored to focus on patients who are likely to benefit, while avoiding their use in those who are unlikely to respond favorably. Consequently, there is an imperative to explore innovative therapeutic approaches that specifically target the pathophysiological mechanisms underlying FSGS, in order to pave the way for new treatment modalities that overcome the limitations and adverse effects associated with conventional treatments. Tables 1 and 2 provide a summary of clinical trials for FSGS that have been completed and those that are currently ongoing. In the following sections, we offer a succinct, albeit not exhaustive, overview of the pathways leading to podocyte injury and the emerging therapeutic strategies they represent.

Podocyte Injury and FSGS

Under normal physiological conditions, podocytes are securely anchored to the glomerular basement membrane (GBM) via cell adhesion molecules, with adjacent foot processes intertwining to form the slit diaphragm. This distinctive architecture enables podocytes to withstand the substantial pressure exerted by the glomerular filtration barrier. When triggered by specific factors such as genetics, toxins, or inflammation, the disruption of this stable structure leads to the disconnection of podocytes from the GBM, initiating a cascade of events that results in further podocyte detachment.[24] This process can be conceptualized as an injury-protective strategy. In the early phase of the disease, the elimination of foot processes mitigates the adverse effects of podocyte detachment;[25] as the disease advances, the exposed podocyte areas undergo contraction and expansion, creating an expansive adhesive surface that directly attaches to the GBM. The collapse of capillaries and the involvement of parietal epithelial cells contribute to the segmental solidification of glomerular tufts.[26,27] Ultimately, the accumulation of extracellular matrix in the damaged regions forms segmental scars. Consequently, FSGS is not a distinct entity of glomerular disease but rather a pathological pattern characterized by podocyte injury. It delineates a pattern of injury that leads to progressive glomerulosclerosis, with foot process alterations under light microscopy serving as a common pathological signature.[28] Identifying the precise mechanisms underlying podocyte loss during injury may have implications for the treatment of FSGS in resource-constrained settings, offering additional pharmacological targets for delaying the progression of glomerulosclerosis (Figure 1).

Mechanisms of Podocyte Injury

Hemodynamic Abnormalities

The unique structure of podocytes renders them susceptible to hemodynamic abnormalities. Under pathological conditions, the persistent challenges of high filtration and capillary hypertension lead to the eventual detachment of podocytes from the glomerular basement membrane (GBM).[29] In such instances, pharmacological interventions targeting hemodynamic abnormalities serve as a protective measure for podocytes. Typically, renin-angiotensin aldosterone system

Table 1 Summary of Main Completed Clinical Trials for FSGS

Study	Study design and interventions (T vs C)	Sample size (T vs C)	Follow-up (mo)	UP/C ratio (g/g)	eGFR (mL/min/1.73 m²)	Population	Primary outcome	Main outcomes (T vs C)	Result	Conclusion/ Explanation
DUPLEX [14]	Sparsentan 800 mg daily Irbesartan 300 mg daily	184/187	45	3.1 (2.3–4.5) 3.0 (2.1–4.7)	63.3 ± 28.6 64.1 ± 31.7	FSGS	Slope of eGFR; percentage of participants achieving partial remission endpoint at week 36	eGFR: −5.4 (−6.89, −3.93) −5.7 (−7.20, −4.29) PR: 42% vs 26%	There was no significant difference in the slope of eGFR between the two groups, the between-group difference in total slope was 0.3 mL per minute per 1.73 m² of body-surface area per year. (95% CI −1.7–2.4)	All proteinuria-based endpoints favored sparsentan group, but the eGFR-based assessment of renal function did not show a statistical difference between the two groups.
DAPA-FSGS [15]	Dapagliflozin 10 mg daily Placebo	45/59	28	3.3 (2.5, 7.6) 4.7 (2.6, 7.3)	40.3 ± 10.6 43.2 ± 12.1	FSGS	Composited endpoint of sustained ≥50% decline in eGFR, onset of ESKD or death from a kidney or cardiovascular cause	8.9% VS 11.9%	Compared with placebo, dapagliflozin treatment can reduce the risk of the primary composite endpoint, but this difference did not reach statistical significance. (hazard ratio [HR] = 0.62, 95% CI 0.17–2.17, P=0.753)	Dapagliflozin can reduce the rate of chronic eGFR decline, although this treatment efficacy did not reach statistical significance. But the slowing of chronic decline in eGFR may potentially show improvements in clinically meaningful renal outcomes in the long-term treatment.
Gipson et al[16]	Losmapimod 7.5–15 mg bid	17	6	8.0 (10.8, 1.3)	72 (36.0, 155.0)	FSGS	Number of participants with ≥50% proteinuria reduction and eGFR ≥70% of baseline	0	No patients achieved the primary endpoint, so the study was terminated following a prespecified interim analysis.	P38 MAPK inhibition with losmapimod did not result in ≥50% reduction of proteinuria in patients with FSGS, but study population heterogeneity may have contributed to the negative findings.

(*Continued*)

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Table 1 (Continued).

Study	Study design and interventions (T vs C)	Sample size (T vs C)	Follow-up (mo)	UP/C ratio (g/g)	eGFR (mL/min/1.73 m²)	Population	Primary outcome	Main outcomes (T vs C)	Result	Conclusion/ Explanation
FONT-I [17,18]	Adalimumab 24 mg/m² q 14 days Rosiglitazone 3 mg/m² bid	10/11	4	15.9 ± 10.4 5.5 ± 2.6	105 ± 50 131 ± 62	Refractory-FSGS	Pharmacokinetic assessment, tolerability, and safety	Not Applicable	Among 10 patients treated with adalimumab, proteinuria decreased by ≥50% in 4 cases.	Both groups of patients tolerated the treatment well. However, this is not sufficient to assess the safety or efficacy of adalimumab treatment and rosiglitazone treatment for refractory FSGS patients.
FONT-II [19]	Adalimumab 24 mg/m² q 14 days placebo galactose 0.2 g/kg/dose bid	7/7/7	6.5	4.9 (3.3, 11.5) 120 (81.1, 170) 120 (81.1, 170)		Refractory-FSGS	Number of participants with a reduction in proteinuria at 6 months by > 50% of the value at screening and stable eGFR	0/2/2	The recruitment for the trial did not reach the enrollment target, and none of the participants in the adalimumab treatment group achieved the primary outcome.	The proteinuria response is not related to the continuous changes in glomerular filtration activity measured by the predefined biomarkers in the serum. It is unreasonable to conduct a Phase II or III trial of adalimumab or galactose in patients with refractory FSGS in a non-selected cohort.
DUET[20]	Sparsentan 200–800 mg daily Irbesartan 300 mg daily	73/36	2	3.6 (0.4–18.7) 3.1 (0.9–10.7)	74.4 ± 37.3 74.5 ± 44.7	FSGS	Percent change in UP/C	−44.8 (−52.7, −35.7) −18.5 (−34.6, 1.7)	Patients receiving sparsentan showed a significant reduction in proteinuria compared to the irbesartan group, with a greater decrease in UP/C ratio. (odds ratio [OR] = 0.78, 95% confidence interval [CI] 0.73–0.98, P=0.006)	The improvement in proteinuria observed with sparsentan treatment is expected to have clinical significance in long-term renal outcomes, but the long-term renal protective effects of sparsentan remains to be determined.

FSGS-CT [21]	MMF 25–36 mg/kg + dexamethasone 0.9 mg/kg daily CsA 5–6 mg/kg daily	66/72	13	UK	110.1 (80.6, 169.6) 112.8 (75.6, 194.2)	SR-FSGS	Primary outcome is a 6-level ordinal variable defined based on the achievement of remission from proteinuria during the first 52 weeks	33.3% vs 45.8%	The difference between the two groups in achieving at least a partial remission was not statistically significant. (OR = 0.59, 95% CI 0.30–1.18, P=0.185).	There was no difference in proteinuria remission rates between the two groups. Due to the inclusion of high-dose corticosteroids in the experimental arm, an increased dose of steroid may not confer additional benefits to the remission rate. Therefore, the appropriate use of CsA warrants further evaluation.
Vincenti et al[22]	Fresolimumab 1–4 mg/kg daily Placebo	26/10	4	6.2 (2.0–16.7) 6.4 (2.2–13.7)	62.6 ± 37.4 60.0 ± 28.4	SR-FSGS	Percentage of patients achieving PR/CR in UP/C, AEs, SAEs, MEOIs	7.7% VS 0%	The study was terminated early before reaching the planned target of 88 randomized patients, and the pre-specified primary and secondary efficacy endpoints were not met.	Although there was no statistically significant difference in eGFR between the groups, the fresolimumab treatment group showed a favorable trend in preserving renal function, with patients exhibiting a stable eGFR profile.
PHOENIX[23]	Bardoxolone methyl 20–30 mg daily	18	3	0.2 (0.004, 1.0)	51.7 ± 18.1	FSGS	Change in eGFR from baseline to week 12	7.8 ± 2.2	Bardoxolone methyl consistently and significantly increased eGFR in patients with FSGS. (mean [±SE] changes from baseline in eGFR of 7.8 ± 2.2, p=0.003)	Data from PHOENIX support that the anti-inflammatory effects of Nrf2 activation with Bard may safely and effectively target multiple, diverse causes of CKD.
NCT 02592798	Abatacept on Day 1, 15, 29 and then every 28 days Placebo	17/19	4	UK	UK	FSGS, MCD	Percentage of Participants in Renal Response at Day 113	0% VS 7.7%	Abatacept therapy did not yield a significant renal advantage compared to placebo during both the double-blind and open-label periods of the clinical trial.	The identification of B7-1 as a potential indicator for the therapeutic rationale of abatacept treatment requires additional evaluation.

Abbreviations: FSGS, Focal segmental glomerulosclerosis; SR-FSGS, Steroid-resistant focal segmental glomerulosclerosis; MCD, Minimal change disease; MMF, Mycophenolate mofetil; CsA, Cyclosporine A; PR, Partial remission; CR, Complete remission; UP/C, Urine protein-to-creatinine ratio; eGFR, Estimated glomerular filtration rate; AEs, Adverse events; SAEs, Serious adverse events; MEOIs, Major extracellular organ injury; ESKD, End-stage kidney disease; HR, Hazard ratio; CKD, Chronic Kidney Disease; T, Trial; C, Control; MAPK, Mitogen-activated protein kinase; UK, Unknown; 95% CI, 95% Confidence interval; OR, Odds ratio; mo, month; Nrf2, Nuclear factor erythroid 2-related factor 2; SE, Standard error.

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Table 2 Summary of Ongoing Main Clinical Trials for FSGS

NCT Number	Medication	Phase	Mechanism of action	Status	RCT (Y/N)	Population	Primary outcome	Completion
NCT06090227	Metformin	I/II	AMPK-activation	Recruiting	Y	FSGS	Slope of urinary NPHS2/Creatinine ratio 6 months following randomization	November 2027
NCT05441826	VB119	II	Anti-CD19 antibody	Terminated due to sponsor change	N	FSGS, MCD	The proportion of subjects in remission at end of treatment; incidence of SAEs, TEAEs and AESIs	October 2023
NCT03763643	Rituximab	III	Anti-CD20 antibody	Recruiting	Y	FSGS	The incidence of recurrence rates one-year post-transplantation.	December 2026
NCT04983888	Obinutuzumab	II	Anti-CD20 antibody	Active, not recruiting	N	FSGS	Change of 24-hour UTP in 6 months and 12 months	September 2025
NCT03703908	CCX140-B	II	CCR2 inhibitor	Terminated due to program not advancing	N	FSGS	Number of subjects with a reduction in UPCR of at least 20% by Week 12	June 2020
NCT05183646	DMX-200	III	CCR2 inhibitor	Recruiting	Y	FSGS	Percent change in UPCR in 35 weeks, slope of eGFR in 35 weeks and 104 weeks; incidence and severity of treatment-related AEs and any AESIs and SAEs at week 216	June 2026
NCT05267262	R3R01	II	Decreasing fat levels of the podocyte	Recruiting	N	FSGS, Alport Syndrome	Change in UP/C and the incidence of AEs in 12 weeks	June 2025
NCT03493685	Sparsentan	III	Dual endothelin angiotensin receptor antagonist	Active, not recruiting	Y	FSGS	The slope of eGFR in 108 weeks; the percentage of participants achieving partial remission endpoint in 36 weeks	February 2026
NCT04573920	Atrasentan	II	Dual endothelin angiotensin receptor antagonist	Active, not recruiting	N	FSGS, Alport syndrome, IgAN, DN	The change in UPCR in 12, 24 and 30 weeks	July 2026
NCT05003986	Sparsentan	II	Dual endothelin angiotensin receptor antagonist	Recruiting	N	FSGS, MCD IgAN, IgAV, Alport Syndrome	Change in UP/C over 108 weeks; the incidence of TEAEs, SAEs, AEs leading to treatment discontinuation and AESIs	May 2025
NCT02683889	ACTH	III	Immunosuppression	Active, not recruiting	N	FSGS	Rate of recurrence confirmed by renal transplant biopsies two years post-transplant; the rate of recurrence of proteinuria two years post-transplant	June 2024

NCT05237388	Baricitinib	II	JAK-STAT inhibitor	Recruiting	Y	APOL1-associated FSGS, APOL1-associated HTN-CKD	Percent change in UACR monthly for 6 months	March 2026
NCT03448692	PF-06730512	II	SLIT2 inhibitor	Terminated due to lack of efficacy	N	FSGS	Percentage Change in UPCR at week 13	May 2022
NCT06466135	WAL0921	II	SuPAR antibody	Recruiting	Y	FSGS, TR-MCD, DN, IgAN, PMN	Incidence of treatment emergent AEs at week 36	March 2026
NCT04387448	GFB-887	II	TRPC5 inhibitor	Terminated due to business reasons	Y	FSGS, TR-MCD, DN	Percentage change in UPCR and UACR in 12 weeks	November 2022
NCT04950114	GFB-887	II	TRPC5 inhibitor	Terminated due to business reasons	N	FSGS, TR-MCD	Incidence and severity of AEs	November 2022
NCT05213624	BI 764198	II	TRPC6 inhibitor	Recruiting	Y	FSGS	Number of patients achieving at least 25% reduction in 24-hour UPCR at week 12	February 2025
NCT05704400	Rituximab + Daratumumab	II	Anti-CD20 antibody + Anti-CD38 antibody	Recruiting	N	FSGS, MDNS, MRNS	Number of treatment-related AEs in week 12; number of months in remission in week 12	March 2025
NCT05312879	VX-147	II/III	APOL1 inhibitor	Recruiting	Y	APOL1-associated proteinuric kidney disease	Percent change of UPCR at week 48; eGFR slope over 48 weeks and at study completion	June 2026

Abbreviations: FSGS, Focal segmental glomerulosclerosis; RCT, Randomized controlled trial; Y/N, Yes/No; UACR, Urine albumin-to-creatinine ratio; AEs, Adverse events; TEAEs, Treatment-emergent Adverse events; AESIs, Adverse events of special interest; SAEs, Serious adverse events; FSGS, Focal segmental glomerulosclerosis; MCD, Minimal change disease; IgAN, IgA Nephropathy; IgAV, IgA Vasculitis; DN, Diabetic nephropathy; HTN-CKD, Hypertensive chronic kidney disease; APOL1, Apolipoprotein L1; MRNS, Multidrug resistant nephrotic syndrome; MDNS, Multidrug dependent nephrotic syndrome; AMPK, Adenosine monophosphate-activated protein kinase; eGFR, Estimated glomerular filtration rate; MCD, Minimal change disease; TR-MCD, Treatment-resistant minimal change disease; PMN, Primary membranous nephropathy; 24-hour UTP, 24-hour Urine total protein; UPCR, Urine protein-to-creatinine ratio; ACTH, Adrenocorticotropic hormone; JAK-STAT, Janus kinase-signal transducer and activator of transcription; SLIT2, Slit guidance ligand 2; SuPAR, Soluble urokinase-type plasminogen activator receptor; TRPC5, Transient receptor potential canonical 5; TRPC6, Transient receptor potential canonical 6; AEs, Adverse events.

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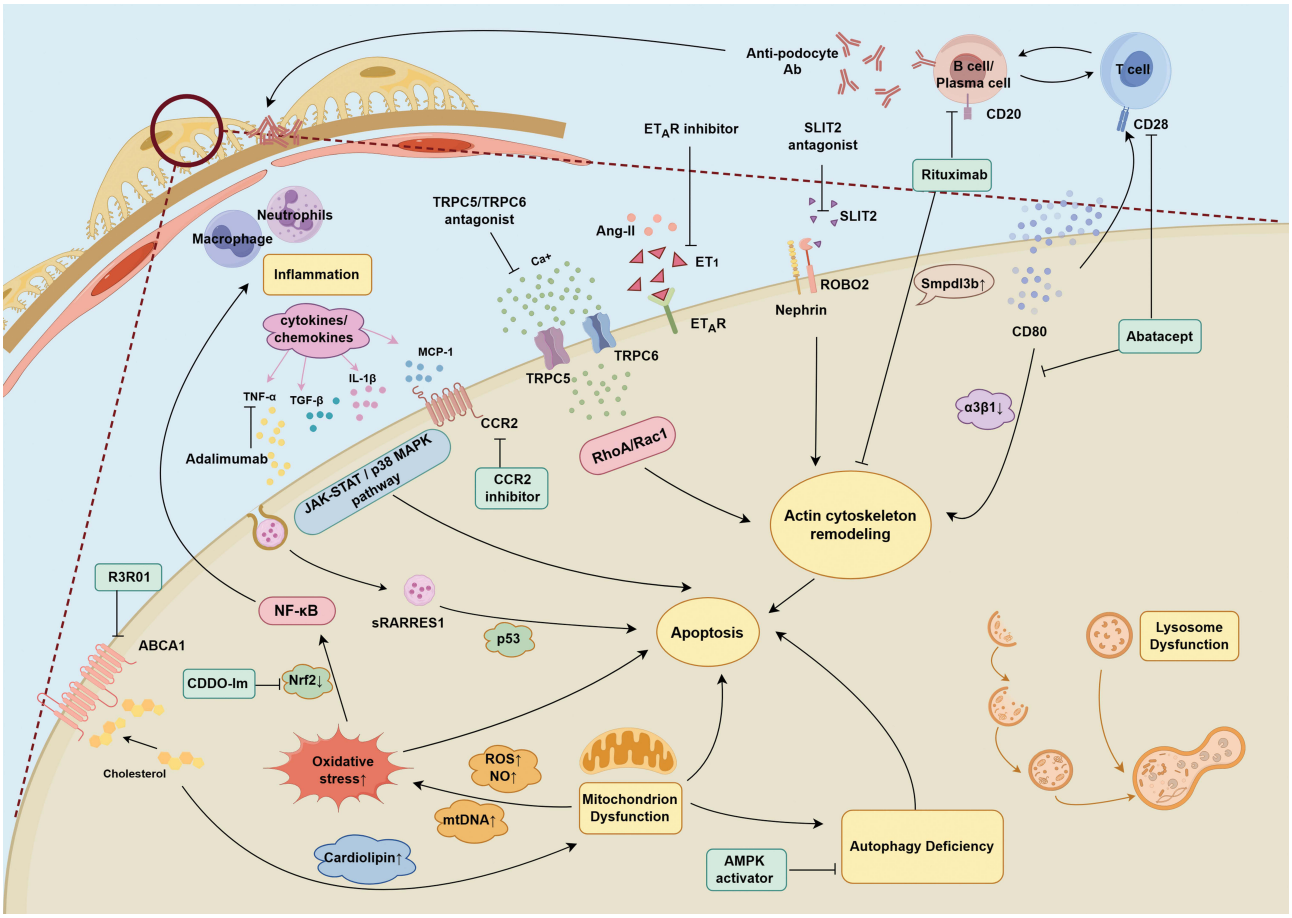

Figure 1 Mechanisms of Podocyte Injury and Corresponding Pharmacological Targets Beyond the established injury mechanisms such as inflammation and modifications to the actin cytoskeleton, additional contributors including potentially pathogenic antibodies, deficits in autophagy, oxidative stress, and mitochondrial dysfunction play a role in this process. Innovative therapeutic agents, like the slit guidance ligand 2 (SLIT2) antagonists, CDDO-Im (2-Cyano-3,12-dioxooleana-1,9-dien-28-imidazolide), C–C chemokine receptor 2 (CCR2) inhibitors and adenosine monophosphate-activated protein kinase (AMPK) activators, are under development, aiming to expand the treatment repertoire for patients suffering from focal segmental glomerulosclerosis (FSGS).

(RAAS) inhibitors can non-specifically alleviate proteinuria in all forms of FSGS by reducing the transmural pressure in glomerular capillaries.[30] Consequently, supportive treatment with RAAS antagonists is recommended for all FSGS patients with persistent proteinuria.[11]

The DUPLEX study provides an updated evaluation of the efficacy of sparsentan, a dual endothelin-angiotensin receptor antagonist, in the treatment of FSGS patients.[14] A total of 371 patients with a urine protein-to-creatinine ratio (UPCR) > 1.5 g/g were randomly assigned to receive either sparsentan or irbesartan, with the primary efficacy endpoint being the estimated glomerular filtration rate (eGFR) at the time of final analysis. Although the difference in eGFR slope between the groups was not statistically significant at week 108, all proteinuria-based endpoints favored sparsentan, aligning with the long-term findings observed during the open-label extension treatment period of the DUET study.[14,31] We concur with the authors' assertion that the DUPLEX study is inherently limited by the heterogeneity of the subject population, and thus, the interpretation of the results should be approached with caution. The study is currently in an open-label extension phase, which may elucidate the relationship between short-term proteinuria benefits and long-term renal function preservation.

Moreover, recent findings suggest that sodium-glucose cotransporter 2 (SGLT2) inhibitors may benefit non-diabetic proteinuric chronic kidney disease (CKD) patients by mitigating hemodynamic injury. Specifically, inhibiting SGLT-2 activity can reduce the reabsorption of Na+ and glucose in the proximal tubules, leading to stimulation of the macula densa to regulate renin release, subsequent constriction of the afferent arteriole, and a decrease in glomerular capillary pressure. Although the DAPA-FSGS subgroup analysis did not reveal statistically significant effects, the estimated

treatment effect was similar to that observed in the overall study population.[32] FSGS patients treated with dapagliflozin exhibited a reduced rate of chronic eGFR decline, implying that this treatment may confer long-term benefits to the population.[15]

Podocyte Actin Cytoskeleton

The finely tuned actin cytoskeleton enables podocytes to attach stably to the glomerular basement membrane (GBM). Any factor that causes changes in the cytoskeleton will lead to the disruption of the stable structure, resulting in podocyte FPE and proteinuria. Several gene mutations that regulate the actin cytoskeleton or podocyte attachment have been found to cause familial FSGS.[33–35] The Rho family of small GTPases, as the main regulators of the actin cytoskeleton, are closely associated with the development of proteinuric nephropathy.[36] Among them, the overactivation of Rac1 can promote transient receptor potential canonical 5 (TRPC5) mediated podocyte Ca2+ influx, leading to imbalance of the podocyte cytoskeleton and increased migration ability.[37] The gain-of-function mutation in transient receptor potential canonical 6 (TRPC6) also a cause of autosomal dominant familial FSGS. TRPC5 inhibitors and TRPC6 inhibitors have shown podocyte protective effects in FSGS rat models, but their efficacy in human patients still is uncertain.[38,39] The clinical efficacy trials of TRPC5 inhibitors evaluated in pFSGS were terminated due to the recruitment difficulties (NCT04387448). Another study on the efficacy of TRPC6 inhibitors is ongoing, with an expected enrollment of 60 FSGS patients for evaluation (NCT05213624).

Endothelial cells within the glomerulus express slit guidance ligand 2 (SLIT2) protein, which binds to the surface of podocytes via the roundabout receptor for SLIT2 (ROBO2), affecting actin polymerization related to nephrin and interfering with the normal formation of podocyte foot processes.[40] The SLIT2/ROBO2 signaling can also reduce podocyte adhesion, leading to podocyte detachment and loss.[41] However, PF-06730512, a ROBO2 signaling inhibitor, has not achieved the expected beneficial effects in FSGS patients.[42] The phase II trial of PF-06730512 had to be terminated prematurely due to lack of efficacy (NCT03448692).

Studies on high-risk FSGS renal transplant recipients have shown that patients treated with rituximab have a significantly reduced risk of proteinuria recurrence after transplantation, which may be related to the direct podocyte protective effect of rituximab.[43] Rituximab stabilizes the podocyte cytoskeleton through a sphingomyelin phosphodiesterase 3b (SMPDL-3b)-dependent mechanism, protecting podocytes from actin remodeling, an effect that is independent of its immunosuppressive activity. However, these observations need further validation to confirm the causal relationship.

B7-1 (CD80) is an immunoregulatory protein expressed by antigen-presenting cells that facilitates T cell activation and T cell-dependent B cell responses through interaction with CD28, thus providing co-stimulatory signals. Recent research has demonstrated that the damaged podocytes of certain FSGS patients can also express B7-1 protein, suggesting a potential link to the pathogenesis of diseases. At the mechanistic level, podocytes firmly anchor to the GBM through adhesion receptors, which include integrins, syndecans, and dystroglycan. The high expression of the α3β1 integrin is particularly important, since it can directly participate in the formation of adhesion complexes by connecting the actin cytoskeleton with membrane proteins, and recruiting adaptor and effector proteins.[44] The upregulation of B7-1 inactivated the β1 integrins, impacting the assembly of adhesion complexes, which in turn leads to pathogenic podocyte migration.[45] Therefore, abatacept, a B7-1 inhibitor, has been shown to exert therapeutic benefits by disrupting the B7-1-β1 integrin interaction. Nonetheless, questions have been raised regarding the reliability of B7-1 detection and the clinical efficacy of abatacept. Several studies have encountered difficulties in staining for B7-1 in podocytes.[46,47] Additionally, negative outcome was observed in the clinical trial of abatacept for the treatment of FSGS, with no expected reduction in proteinuria shown (NCT02592798). Further investigation is necessary to determine the utility of B7-1 positivity as a novel biomarker for identifying subgroups of FSGS that are potentially more responsive to abatacept therapy.[48]

Autophagy Deficiency

Autophagy is a cellular self-digestion process that occurs through the formation of vesicles within the endoplasmic reticulum, encapsulating damaged organelles or proteins, which are subsequently delivered to lysosomes for degradation and subsequent recycling. In the context of podocyte-related diseases, autophagy functions as a homeostatic mechanism that is activated in response to disease-induced stress. It is critically involved in the formation and maintenance of the

intact cytoskeleton within podocytes.[49] This process is primarily regulated by two pivotal molecules: adenosine monophosphate-activated protein kinase (AMPK) and the mammalian target of rapamycin complex 1 (mTORC1). AMPK activates autophagy, whereas mTORC1 inhibits it. Animal models have demonstrated that podocyte autophagy deficiency can precipitate oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, and proteinuria, culminating in podocyte loss and glomerulosclerosis.[50,51] Moreover, in the Minimal Change Disease (MCD) animal model, the administration of autophagy inhibitors exacerbates proteinuria and podocyte injury, eliciting pathological alterations akin to those observed in FSGS.[52] Consequently, the activation of AMPK may represent a novel therapeutic target for podocyte-related diseases by promoting the renewal of autophagosomes. Metformin (MF), an AMPK activator and mTORC1 inhibitor, is currently the subject of a Phase II clinical trial to assess its efficacy and safety as an adjunctive treatment for FSGS (NCT06090227).[53]

Mitochondrial Dysfunction

Under physiological conditions, mitochondria supply podocytes with efficient energy through oxidative phosphorylation (OXPHOS). However, when the antioxidant systems of mitochondria are compromised, mitochondrial reactive oxygen species (mtROS) are overproduced, and the cellular antioxidant capacity diminishes, leading to the accumulation of reactive oxygen species (ROS) and nitric oxide (NO) in renal tissue.[54] Kidneys have been demonstrated to be susceptible to mitochondrial diseases.[55] Several mutations in genes encoding coenzyme Q10 synthesis enzymes related to mitochondrial OXPHOS have been reported in patients with familial FSGS.[54,56] Early administration of coenzyme Q10 supplementation could be advantageous for this patient cohort.[57] Notably, this is an emerging field, emphasizing early and precise genetic screening for mitochondrial kidney disease may prevent unnecessary treatment toxicity and slow disease progression in patients.

Oxidative Stress/Inflammation

In preclinical models of FSGS, activation of inflammatory signaling pathways, including nuclear factor κB (NF-κB),[58] P38 mitogen-activated protein kinase (MAPK),[59] and Janus kinase-signal transducer and activator of transcription (JAK-STAT),[60] has been observed, accompanied by a significant upregulation of related molecules such as monocyte chemoattractant protein-1 (MCP-1)[61] and interleukin-1 (IL-1).[62] These findings indicate that oxidative stress and glomerular chronic inflammation are critical drivers of FSGS progression.

Nuclear factor erythroid 2-related factor 2 (Nrf2) serves as a pivotal regulator of intracellular oxidative stress and inflammatory mechanisms. Its activation is crucial for cells to resist oxidative damage and inflammatory damage. In mouse models of FSGS, oxidative stress is closely associated with glomerular injury, inflammation, and fibrosis progression.[63,64] This suggests a vicious cycle of interactions. Damaged podocytes can secrete chemokines, recruiting immune cells and cytokines to the site of injury, thereby inducing glomerular inflammation. Meanwhile, the down-regulation of Nrf2 and activation of NF-κB in these pathological processes, further aggravating cellular damage.[58]

Tumor necrosis factor-alpha (TNF-α), a pivotal regulator of inflammatory pathways, may lead to podocyte injury through multiple downstream mechanisms and contribute to the progression of glomerular disease environments. Recent evidence suggests that there may be a specific subset of FSGS cases activated by an intrinsic TNF-α-podocyte pathway.[65,66] The pathogenic TNF-α may originate from macrophages or other renal myeloid cells since the targeted deletion of TNF-α in podocytes did not reduce proteinuria in a glomerular injury model.[67] Furthermore, TNF-α can induce expression of retinoic acid receptor responder protein-1 (RARRES1) in podocytes, followed by its internalization via endocytosis, results in the inhibition of RIO kinase 1 (RIOK1) function and subsequent activation of p53, leading to podocyte apoptosis.[68] This discovery indicates that soluble RARRES1, originating from podocytes, is capable of directly inducing damage to both podocytes and renal tubular epithelial cells.[69] MCP-1 and tissue inhibitor of metalloproteinases-1 (TIMP-1) are vital downstream elements of the TNF-α pathway. A recent study has reported the clinical trial results of using the urinary MCP-1 and TIMP-1 as biomarkers to predict the TNF-α activation in FSGS.[70] Although adalimumab resulted in a heterogenous efficacy response, a subgroup of patients had better-preserved kidney function, which corresponded with candidate mechanistic-predictive biomarkers evaluated by urinary MCP-1 and TIMP-1. Urinary MCP-1 and TIMP-1 may serve as non-invasive biomarkers for identifying the subset of FSGS patients with TNF-α

activation as a key driver of kidney injury. However, their potential for predicting the therapeutic response to TNF-α blockers needs to be confirmed in a larger patient cohort.

The C-C chemokine receptor 2 (CCR2) is the functional ligand-binding receptor for MCP-1. In both preclinical and clinical studies of FSGS, a significant increase in the expression of CCR2 and MCP-1 in the glomeruli has been observed. Importantly, in CCR2-deficient FSGS mice, there was a reduction in renal inflammatory infiltration, mitigation of damage, and significant improvement in glomerulosclerosis and tubulointerstitial fibrosis. A Phase 3 dose-escalation trial of CCX140-B (NCT03703908), a specific inhibitor of CCR2, for the treatment of FSGS patients was terminated due to limited progress in the study.

Despite the evaluation of some anti-inflammatory strategies in FSGS patients, challenges persist in translating these strategies from the preclinical laboratory stage to effective clinical treatments for FSGS.

Fibrosis

Transforming growth factor-β (TGF-β) drives fibroblast proliferation and the accumulation of extracellular matrix (ECM) by activating the Smad signaling pathway, exacerbating the process of renal fibrotic remodeling and tissue damage.[71] Furthermore, TGF-β can also induce podocyte apoptosis through the P38 MAPK-driven apoptosis signaling pathway.[72] Losmapimod is an oral P38 MAPK inhibitor, it not only effectively inhibits the production of inflammatory cytokines, but also suppresses the fibrotic induction pathway of TGF-β.[73] Nevertheless, the outcomes of the single-arm Phase 2 study evaluating its efficacy in alleviating proteinuria in FSGS patients were unsatisfactory (NCT02000440).[16] None of the participants met the composed primary endpoint of ≥50% decrease in urinary protein reduction. Rosiglitazone is a novel antifibrotic medication that has also demonstrated renal protective effects in FSGS animal models. However, the trial results evaluating its efficacy in corticosteroid-resistant FSGS patients did not meet expectations (NCT00814255).[17]

Circulating Permeability Factors

Investigations into potential circulating permeability factors have enhanced our understanding of the pathophysiological mechanisms underlying FSGS. The concept of circulating permeability factors originates from the groundbreaking study conducted by Gentili and et al in 1954.[74] This study included an experiment with ethical implications, where plasma from patients with idiopathic nephrotic syndrome (INS) was administered to healthy individuals, resulting in the transient appearance of proteinuria. Despite indications that the plasma of these patients contained a pathogenic agent, the technological limitations of the era precluded the accurate identification of the specific pathogenic plasma constituent. On this basis, Gentili and coworkers introduced a pioneering hypothesis suggesting that a certain serum-borne factor might exist that is capable of disrupting the glomerular filtration barrier, leading to the development of proteinuria. Clinical observations, such as the rapid induction of proteinuria in normal rats by the serum of recurrent FSGS patients and the recurrence of proteinuria in 50% of kidney transplant recipients post-transplantation,[75,76] strongly support the hypothesis of circulating factors. Several potential circulating factor candidates have been proposed, including cardiac-like cytokine-1 (CLCF-1), soluble urokinase-type plasminogen activator receptor (suPAR), and anti-CD40 antibodies. However, there is a notable lack of confirmatory research, the molecular characteristics of the presumed circulating permeability factors remain undefined.

CLCF-1

The pathogenic potential of CLCF-1 has been elucidated through more than 20 years of research by the Savin group.[76–78] Through comprehensive analysis of the plasma constituents in patients with recurrent FSGS, they identified a small protein with an estimated molecular weight of less than 30kDa, which was subsequently confirmed as CLCF-1 using galactose chromatography. Nevertheless, the therapeutic application of galactose to inactivate CLCF-1 in FSGS has yielded inconsistent outcomes. A pilot study involving galactose supplementation in seven patients with steroid-resistant nephrotic syndrome (SRNS) demonstrated a significant reduction in permeability factor activity following galactose administration, yet no improvement in proteinuria was observed.[79] Additionally, a Phase II clinical trial (NCT00814255) in patients with refractory FSGS reported that only two of seven participants in the galactose group achieved the primary endpoint.[19]

SuPAR

Urokinase-type plasminogen activator receptor (uPAR) is a GPI-anchored membrane protein that can bind to uPAR activator, integrins, and other receptors, and it can be cleaved to release the soluble form, suPAR, from the plasma membrane. Wei and et al found that overexpression of uPAR in podocytes can activate the αvβ3 integrin pathway, leading to FPE and proteinuria in a rat model.[80] Furthermore, suPAR was shown to activate podocyte β3 integrin signaling in the absence of uPAR expression, thereby inducing FSGS-like nephropathy. The integrity of this pathway is crucial for renal injury, as the disease phenotype was only observed in mice expressing suPAR capable of binding to β3 integrins.[81] The Wei research team also reported that approximately 70% of patients with pFSGS exhibited elevated serum suPAR levels and patients with higher pre-transplant suPAR levels were at a significantly increased risk of FSGS recurrence post-transplantation. However, some reports suggest that serum suPAR levels in pediatric FSGS patients were unrelated to transplantation status and remained unchanged before and after transplantation.[82] Similarly, serum suPAR levels did not appear to differentiate between patients with and without FSGS recurrence following transplantation.[83] Therefore, the role of suPAR in identifying FSGS cases at risk for post-transplant recurrence should be interpreted with caution. Elevated serum suPAR levels may not disease-specific, as they can be observed in advanced chronic kidney disease of diverse etiologies.[83] A clinical trial of suPAR antibody is currently ongoing, aiming to evaluate the safety and efficacy of WAL0921 in glomerular kidney diseases such as FSGS, MCD, and primary membranous nephropathy (NCT06466135). This Phase 2 studies may provide new insights into the role of suPAR in the progression and treatment strategies of FSGS.

Anti-CD40 Antibodies

The Delville team found that a combination of seven autoantibodies was highly efficient in predicting post-transplant FSGS recurrence, with an accuracy rate of up to 92%.[84] Among them, anti-CD40 antibodies achieved a high accuracy rate of 78% in predicting recurrence. Furthermore, the injection of purified anti-CD40 antibodies, extracted from patients with recurrent FSGS, into mice significantly induced suPAR-mediated proteinuria in the mice. However, the production of pathogenic antibodies is only part of the disease occurrence. Kairaitis and et al reported that even after glomerular injury, CD40L blockade could provide renal protective effects.[85] This suggests that CD40-CD40 ligand interactions may have a broader role in the pathogenesis of FSGS, not solely dependent on B-cell responses. Hence, the role of CD40 receptors and anti-CD40 antibodies in the pathogenesis of FSGS requires further research for definitive confirmation.

Biomarkers and Precision Medicine

The precise classification of FSGS subtypes has long been challenging due to the heterogeneity of the patient population and the lack of reliable biomarkers. In an ideal scenario, biomarkers should be derived from prospective cohort studies with clearly defined research objectives, and their validation should be conducted across different subgroups within the context of multicenter studies to reliably reflect the underlying molecular drivers of heterogeneity. Advances in glomerular transcriptomics and proteomics have opened new avenues for the discovery of FSGS biomarkers. These biomarkers have the potential to be utilized for disease diagnosis, prognostic risk assessment, and prediction of treatment outcomes (Table 3). For example, the identification of non-invasive biomarkers would substantially enhance the detection rate of FSGS patients who are ineligible for renal biopsy. For patients exhibiting signs of kidney involvement beyond a single organ, it is prudent to broaden the indications for genetic testing. This approach could potentially confer benefits to patients before the advancement of renal disease, as these individuals may not be responsive to or suitable for conventional corticosteroid therapy. The nephrology field is anticipating a paradigm shift from standard treatments to the adoption of precision medicine for personalized patient diagnosis and therapy. Nevertheless, the realization of personalized and precision medicine objectives is hindered by a scarcity of comprehensive precision medicine trials. The ongoing Nephrotic Syndrome Study Network (NEPTUNE) Match, as the first application of precision medicine in nephrology, is poised to address these challenges.[86] Large-scale, multicenter prospective trials are needed to develop new medications and expand treatment options for patients. Simultaneously, research and repurposing of known medications may expand our understanding of FSGS.

Table 3 Biomarkers for FSGS

Purpose	Biomarkers	Study	Findings and interpretation	Questions and flaws
Diagnosis	Genetics			
	NPHS1, NPHS2, WT1, LAMB2	Sadowski et al[33]	A high prevalence of monogenic mutations in pediatric cases of families with SRNS suggests the value of genetic evaluation, which can contribute to the molecular genetic diagnosis, etiological classification and therapeutic research of SRNS.	Compared to children with SRNS or FSGS, adults with non-familial FSGS rarely have identifiable monogenic causes.
	COL4A3, COL4A4	Voskarides et al[34]	COL4A3 and COL4A4 gene mutations are associated with familial FSGS, particularly under certain conditions, contributing to FSGS development.	Mutations in COL4A3 and COL4A4 genes are significantly linked to Alport syndrome, with some rare variants potentially misclassified as familial FSGS.
	CD2AP, TRPC6, ACTN4, INF2, ANLN	Lepori et al[35]	A few genetic mutations are linked to adult-onset FSGS, with additional mutations found in rare familial forms.	The observation of varying expressivity in familial adult-onset FSGS suggests that the phenotype of dominant genetic diseases may be triggered by additional factors.
	PDSS2, COQ2, COQ6, COQ8B/ ADCK4	Schijvens et al[56]	Mutations in genes encoding coenzyme Q10 synthesis enzymes, which are involved in mitochondrial oxidative phosphorylation OXPHOS, have been documented in patients with familial FSGS.	Genetic screening should be promptly considered in adolescents or younger individuals presenting with nephrotic syndrome, and in patients of any age who exhibit nephrotic syndrome along with extra-renal manifestations.
	APOL1	Kopp et al[87]	The expression of the APOL1 alleles G1 and G2 polymorphisms is significantly linked to a higher risk of adult-onset FSGS in African Americans.	The allelic variants that increase the risk of FSGS have not yet been elucidated in terms of their specific pathogenic mechanisms.
	Circulation permeability factor			
	CLCF-1	Savin et al[77]	Proteomics analysis of plasma components from patients with recurrent FSGS identified a potential pathogenic role for CLCF-1.	Using galactose which can inactivate CLCF-1 to treat FSGS has not achieved anticipated results.
	suPAR	Wei et al[81]	Circulating suPAR induces FSGS-like kidney disease in experimental rats by activating the $\alpha v\beta 3$ integrin mechanism in podocytes, and the integrity of this induction pathway is essential for kidney damage.	Serum suPAR levels are indistinguishable between recurrent and non-recurrent FSGS post-transplant patients and are non-specific, being elevated in advanced CKD of various origins.
	Anti-CD40 antibody	Delville et al[84]	A group of seven autoantibodies showed high efficiency in predicting recurrent FSGS after transplantation, with an accuracy rate of up to 92%. And the accuracy rate of anti-CD40 antibody reached as high as 78%.	The efficacy of the anti-CD40 antagonistic monoclonal antibody Bleselumab in preventing the recurrence of primary FSGS in renal transplant recipients did not show significant effectiveness.
	Anti-nephrin antibodies	Shirai et al[88]	Analysis of post-transplant FSGS indicates that during relapse, graft biopsies show punctate IgG deposits co-localized with nephrin, suggesting that circulating anti-nephrin antibodies may be a potential pathogenic factor.	Anti-nephrin antibodies have also been identified in minimal change disease, warranting further large-scale studies for confirmation.
	Transmembrane protein			
	B7-1	Yu et al[45]	B7-1 contributes to the pathogenesis of FSGS by inducing the inactivation of $\beta 1$ integrin on podocyte surfaces, thereby promoting pathogenic podocyte migration.	The reliability of B7-1 measurements is subject to question, and abatacept therapy for FSGS has not demonstrated the anticipated benefits in terms of proteinuria reduction.
	sRARRES1	Feng et al[69]	Soluble RARRES1 derived from podocytes can directly initiate damage to both podocytes and tubules, thereby driving the progression of glomerular disease environments.	Cytotoxic effects are observed exclusively in the soluble form of the protein (sRARRES1) following cleavage by matrix metalloproteinase 23, and this enzyme is selectively expressed at high levels in podocytes.
	A-2 macroglobulin gene of glomerular endothelial cells	Menon et al[89]	Single-cell transcriptomics identifies A2M as a key downstream mediator of endothelial activation in FSGS, with high expression levels correlating with poorer prognosis.	The limitations of single-cell analysis, such as potential selective cell loss during the dissociation process.
	Urinary peptidomic classifier	Catanese et al[90]	The urine peptide classifier pFSGS93 can effectively distinguish pFSGS, sFSGS, and other CKD patients.	The classification system did not include genetics FSGS cases and its sensitivity has not been independently validated in a cohort of primary FSGS patients.

(*Continued*)

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Table 3 (Continued).

Purpose	Biomarkers	Study	Findings and interpretation	Questions and flaws
Prognosis	Plasma TNF-α	Mariani et al[66]	In patients with FSGS where the TNF-α pathway is activated, there is a significantly increased risk of rapid disease progression. Additionally, markers of TNF pathway activation have been used to predict the effectiveness of targeted therapies.	Adalimumab monoclonal antibody therapy for refractory FSGS has not consistently demonstrated therapeutic efficacy.
	Urinary microRNA	Zhang et al [91,92]	Urinary miR-196a is an independent risk factor for predicting progression in FSGS. And urinary miR-196a, miR-30a-5p, and miR-490 all can serve as biomarkers for assessing disease activity.	Cohort sizes in related studies are small, and the association of urine microRNA elevation with podocyte injury needs additional validation.
	Plasma microRNA	Zhang et al[93]	Plasma miR-186 correlates with FSGS proteinuria levels and the plasma microRNA panel can be used for independent diagnosis and prognostic prediction of FSGS.	Limited research is available, and plasma miR-196a levels are no discernible differences between a subset of FSGS patients and healthy controls.
Treatment response	Urinary MCP-1 and TIMP-1	Trachtman et al[70]	Urinary MCP-1 and TIMP-1 may serve as non-invasive biomarkers for identifying the subset of FSGS patients with TNF-α activation as a key driver of kidney injury.	The study sample size is limited, and the potential of urinary MCP-1 and TIMP-1 to predict the therapeutic response to TNF-α blockers needs to be confirmed in a larger patient cohort.
	T lymphocyte activation markers	Chan et al[94]	T cell activation subpopulation-related prognostic markers can be utilized to identify FSGS patients with a favorable response to rituximab treatment.	Limited sample size and bias toward steroid-resistant participants may limit findings' applicability and reliability. Larger, diverse FSGS cohorts are needed for validation and deeper insight into T/B cell subset profiles.

Abbreviations: FSGS: Focal segmental glomerulosclerosis; SRNS: Steroid-resistant nephrotic syndrome; CLCF-1: Cardiotrophin-like cytokine factor 1; suPAR: Soluble urokinase-type plasminogen activator receptor; CKD: Chronic kidney disease; sRARRES1: Soluble retinoic acid receptor responder element 1; A2M: Alpha-2 macroglobulin; TNF-α: Tumor necrosis factor-α; MCP-1: Monocyte chemoattractant protein-1; TIMP-1: Tissue inhibitor of metalloproteinases-1; OXPHOS: Oxidative phosphorylation.

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Conclusion

Over the past few decades, although our understanding of the mechanisms of podocyte injury in FSGS has deepened, there remain unanswered questions. Specifically, research on podocyte autophagy, oxidative stress, mitochondrial function, and related areas is still in its nascent stages, and nephrologists have a significant journey ahead in translating this knowledge into therapeutic resources. The mechanisms discussed in this review may represent other promising targets for the delay of podocyte injury, aiming to provide some references for the development of precision medicine approaches in the treatment of FSGS.

Abbreviations

AMPK, Adenosine monophosphate-activated protein kinase; B7-1, CD80; CCR2, C–C chemokine receptor 2P; CLCF-1, Cardiac-like cytokine-1; CKD, Chronic kidney disease; Egfr, Estimated glomerular filtration rate; ESRD, End-stage renal disease; FPE, Foot process effacement; FSGS: Focal segmental glomerulosclerosis; GBM, Glomerular basement membrane; GPI, Glycosylphosphatidylinositol; IL-1, Interleukin-1; INS, Idiopathic nephrotic syndrome; JAK-STAT, Janus kinase-signal transducer and activator of transcription; KDIGO, Kidney Disease: Improving Global Outcomes; MCD, Minimal change disease; MCP-1, Monocyte chemoattractant protein-1; MF, Metformin; mTORC1, Mammalian target of rapamycin complex 1; mtROS, Mitochondrial reactive oxygen species; NEPTUNE, Nephrotic Syndrome Study Network; NF-κB, Nuclear factor κB; NO, Nitric oxide; Nrf2, Nuclear factor erythroid 2-related factor 2; NS, Nephrotic syndrome; OXPHOS, Oxidative phosphorylation; pFSGS, Primary focal segmental glomerulosclerosis; RAAS, Renin-angiotensin-aldosterone system; RARRES1, Retinoic acid receptor responder protein-1; RIOK1, RIO kinase 1; ROS, Reactive oxygen species; ROBO2, Roundabout receptor for SLIT2; SGLT2, Sodium-glucose cotransporter 2; SLIT2, Slit guidance ligand 2; SMPDL-3b, Sphingomyelin phosphodiesterase 3b; SRNS, Steroid-resistant nephrotic syndrome; SuPAR, Soluble urokinase-type plasminogen activator receptor; TGF-β, Transforming growth factor-β; TIMP-1, Tissue inhibitor of metalloproteinases-1; TNF-α, Tumor necrosis factor-alpha; TRPC5, Transient receptor potential canonical 5; TRPC6, Transient receptor potential canonical 6; UPCR: Urine protein-to-creatinine ratio; uPAR, Urokinase-type plasminogen activator receptor; αvβ3, Alpha-v beta-3.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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