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REVIEW

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Soluble urokinase plasminogen activator receptor (suPAR) and glomerular disease in children: a narrative review

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Abstract

Background: Focal segmental glomerulosclerosis (FSGS) is a chronic glomerular disease that responds poorly to treatment, with a large proportion of patients progressing to end-stage renal disease in spite of initial aggressive treatment. It is worth emphasizing that the FSGS group has still a high recurrence rate after kidney transplantation. Therefore, understanding the factors involved in the pathogenesis of FSGS will help nephrologists better understand the pathogenesis as well as find out specific targeted therapies. Circulating immune factors have long been implicated in the pathogenesis of FSGS, and recent studies have suggested that soluble urokinase plasminogen activator receptor (suPAR) is one of the good candidates for this hypothesis. The aim of this review study was to analyze the value of suPAR in glomerular disease, especially in clinical studies.

Methods: In this review study, the PubMed database was searched using relevant keywords (suPAR, circulating permeability factors Children, FSGS, and children). Descriptive and cross-sectional studies were reviewed in the current study with the main focuses on the role of suPAR in FSGS, nephrotic syndrome, and the relation to progression of renal failure, especially the research in children.

Results: Overall, 32 studies from different countries were selected. These clinical studies on suPAR have shown the following: (i) the role of suPAR in the diagnosis of FSGS has not yet been confirmed, and (ii) there is strong evidence demonstrating a significant relationship between suPAR and the severity of kidney disease as well as a high value of suPAR in predicting the steroid responsiveness of nephrotic syndrome.

Conclusion: Researching on circulating permeability factors in FSGS is a current trend, which opens new avenues in targeted diagnosis and treatment. suPAR is a promising candidate, and urinary suPAR has also shown advantages over serum suPAR; therefore, more research on this issue is needed in the future.

Keywords: Permeability, Glomerulosclerosis, Focal segmental

Background

FSGS is a common glomerular disease, characterized by focal and segmental obliteration of glomerular capillary tufts in the glomeruli. This disease has various manifestations such as hematuria, nephrotic-range proteinuria, and renal failure. They often respond poorly to treatment, and up to 50% of FSGS patients may progress to chronic kidney disease after 5–10 years [1, 2]. Understanding the causes of FSGS will improve treatment outcome [2]. Recently, scientists have suggested that circulating permeability factors may be involved in the pathogenesis of this disease such as soluble urokinase plasminogen activator receptor, cardiotropin-like cytokine factor 1 (CLCF1), or hemopexin [3]. CLCF1 is 100 times higher in patients with NS recurring after kidney transplantation compared to that of normal people. CLCF1 reduced

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nephrine expression in the culture of podocyte [4]. Hemopexin activates serum protease during nephrotic syndrome recurrence. Hemopexin reorganizes the cytoskeleton of the podocyte and destroys the selective permeability of the glomerular basement membrane [5]. suPAR binds to and activates αvβ3-integrin of podocytes, leading to the activation of GTPase Rac-1, then activates Src tyrosine kinase, and modifies TRPC6 channel, changes in the motility of podocytes, and deletion of podocyte foot process, causing proteinuria [6]. This is a new research direction that can help find out new diagnostic methods as well as targeted therapy. However, after many failed trials, scientists suggest suPAR is a promising candidate.

In this article, we will focus on analyzing the role of suPAR in glomerular disease, especially in clinical studies.

Methods

In order to investigate the value of suPAR in the glomerulonephritis, 32 research articles published from 2011 to 2021 were reviewed in this paper. Current clinical research on suPAR with kidney disease appears to have been quite meager. These articles mainly focused on the role of suPAR in FSGS, nephrotic syndrome, and the relation to progression of renal failure, especially the research in children.

By searching the PubMed database with the keywords "suPAR," "circulating permeability factors," and "children," "FSGS", we selected all the titles and abstracts of English language papers on circulating permeability factors in primary FSGS. Two researchers were determined eligible articles with regard to relevance to the present topic. Then, we further studied the full texts of the selected papers. Furthermore, an expert panel performed a critical appraisal to summarize the findings and make them applicable. Finally, the extracted data were categorized under proper subheadings, and the manuscript was prepared. Then, the complete manuscript was reviewed, revised, and approved by all of the authors.

suPAR

suPAR is a soluble form of uPAR. In healthy cells, the expression of uPAR is limited in the cell membrane. However, uPAR is strongly expressed in many different cell types in pathophysiological processes. For example, increased expression in osteoclasts during bone resorption, increased expression in macrophages, vascular smooth muscle cells, and endothelial cells during atherogenesis. uPAR also has a role in mobilizing activated T cells, monocytes, and polymorphonuclear leukocytes to the site of inflammation [7]. In the soluble form, suPAR is found in the blood, urine, and cerebrospinal fluid.

The gene coding for uPAR (PLAUR) is located on chromosome 19q13.2, containing 7 exons and 6 introns. This gene is encoded for 313 amino acids containing 3 domains DI-DII-DIII (positions of 1–92, 93–191, and 192–282) [8]. Structurally, uPAR is a cytosolic glycoprotein-bound glycosylphosphatidylinositol GPI (Fig. 1). It contains 3 units DI, DII, and DIII, and each unit contains about 90 amino acids encoded by different exons located on the Plaur gene (Table 1). uPAR binds to the cell membrane at position DIII. Cleaving uPAR from the cell membrane by many enzymes and at the GPI binding site or DI-DII junction leads to suPAR which can be DI-II-III (suPAR I-III), DII-III (suPAR II), and DI (suPAR I). Only suPAR I-III activates the integrin pathway [9, 10].

suPAR I-III contains all the DI, II, and III units but lacks the GPI anchor, which at first glance looks worthless, but the receptor has only undergone a slight change so it still functions as a receptor.

HØyer-Hansen commented that DI is required for vitronectin activity. Gardsvoll and Ploug found that five sites for vitronectin binding were on the DI segment (Trp 32, Arg 58, Ile 63) and on the DI-II junction (Arg 91 and Tyr 92). Thus, suPAR I-III can bind to vitronectin and act as uPAR. The scientists found that when uPAR is overexpressed, it produces suPAR, and a uPAR/suPAR concentration ratio of 1/2 is most effective for vitronectin binding.

suPAR II-III lacks the DI segment, so it will not be able to bind to vitronectin, and cannot act similarly as uPAR. However, upon further investigation, the scientists found that the suPAR II-III fragments containing SRSRY at positions 88–92 act as a chemical agent and operation based on the concentration gradient, acting on cells through the transmembrane receptor 7. Its biochemical

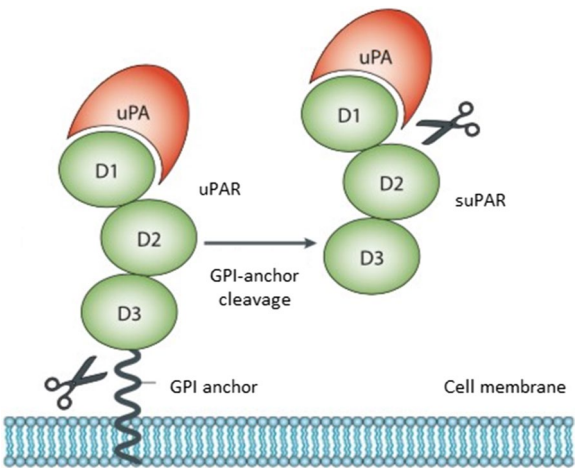

Fig. 1 Molecular structure of uPA [11]

Table 1 uPAR fragments

Fragments	Physical characteristics	Molecular Mass kDa	Structure	Localization
uPAR I-III	Full length + GPI anchor	55–60		Membrane-bound
uPAR II-III	Cleaved + GPI anchor	45–50		Membrane-bound
suPAR I-III	Full length − GPI anchor	55–60		Soluble
suPAR II-III	Cleaved − GPI anchor	40–45		Soluble
suPAR I	Full length − cleaved − GPI anchor	16		Soluble

effects are still unclear, but it is hypothesized that it activates neutrophils during acute inflammatory activities.

suPAR I only contains a DI fragment with a molecular weight of about 16kDa, has a much lower affinity than uPAR, so it has almost no biochemical effect. It is eliminated rapidly and is not quantifiable in the blood [8].

Mechanism of suPAR on glomeruli

suPAR exerts several direct effects on podocytes, including downregulation of nephrine and podocin [12], which occurs after the activation of αvβ3-integrins, a known receptor or co-receptor for suPAR [13].

Recently, Kim et al. [6] showed in an experimental study that the addition of suPAR markedly increased steady-state surface expression and membrane stretch of TRPC6 (transient receptor potential cation channel subfamily C member 6) channel-activated cell membranes in cultured podocytes. This effect was similarly observed in several different blood samples from patients with FSGS relapse. Furthermore, this effect can be attenuated by administration of an αvβ3-Integrin inhibitor or by suPAR immunoadsorption. In this regard, evidence suggests that TRPC6 is involved in the pathogenesis of chronic kidney disease, including mutations of TRPC6 in familial FSGS patients [14], and increased TRPC6 expression in glomeruli of patients with glomerular disease including primary FSGS [15].

Furthermore, genetic inactivation of TRPC6 (the deletion of an essential exon of TRPC6 gene) reduces the progression of glomerular diseases in mice models and protects against FSGS in experiment with mice [16]. In this study, Kim et al. provided details regarding the transduction pathway in which suPAR regulates podocyte function. suPAR is thought to act through αvβ3-integrin, causing an increase in cellular reactive oxygen species (ROS) mediated at least in part by NADPH-oxidase 2 (Nox2). Increased cytosolic oxidative stress activates Src tyrosine kinase, and Src tyrosine kinase phosphorylates tyrosin binding sites of podocyte TRPC6 as well as directly interacts with intracellular domains near carboxyl terminals and amino acids of TRPC6, leading to changes in TRPC6 channel activity [6, 17].

In summary, suPAR binds and activates αvβ3-intergrin in podocytes, leading to the activation of GTPase Rac-1, the activation of Src tyrosine kinase, the modification of TRPC6 channel, the changes in the motility of podocyte foot process, and deletion of podocyte foot process. And proteinuria is a consequence characterized by podocyte deletion (Fig. 2).

suPAR and kidney disease

Initial studies of suPAR with chronic kidney disease suggested a role as a circulating factor promoting primary FSGS. Serum suPAR concentration elevated in patients with primary FSGS and markedly increased in patients who relapsed after renal transplantation [18]. Meanwhile, later studies have questioned the usefulness of serum suPAR as a specific biomarker for primary FSGS [19].

It was initially reported that total plasma suPAR concentration increased in a small group of patients with FSGS, especially in recurrent FSGS, and this association was later found to be stronger when measuring suPAR concentration in urine [20, 21]. In addition to the context of FSGS, the large longitudinal follow-up studies have found that the elevated blood or urine concentration of suPAR in patients with normal baseline renal function are associated with the chronic kidney disease in the future and impaired glomerular filtration rate [22, 23],

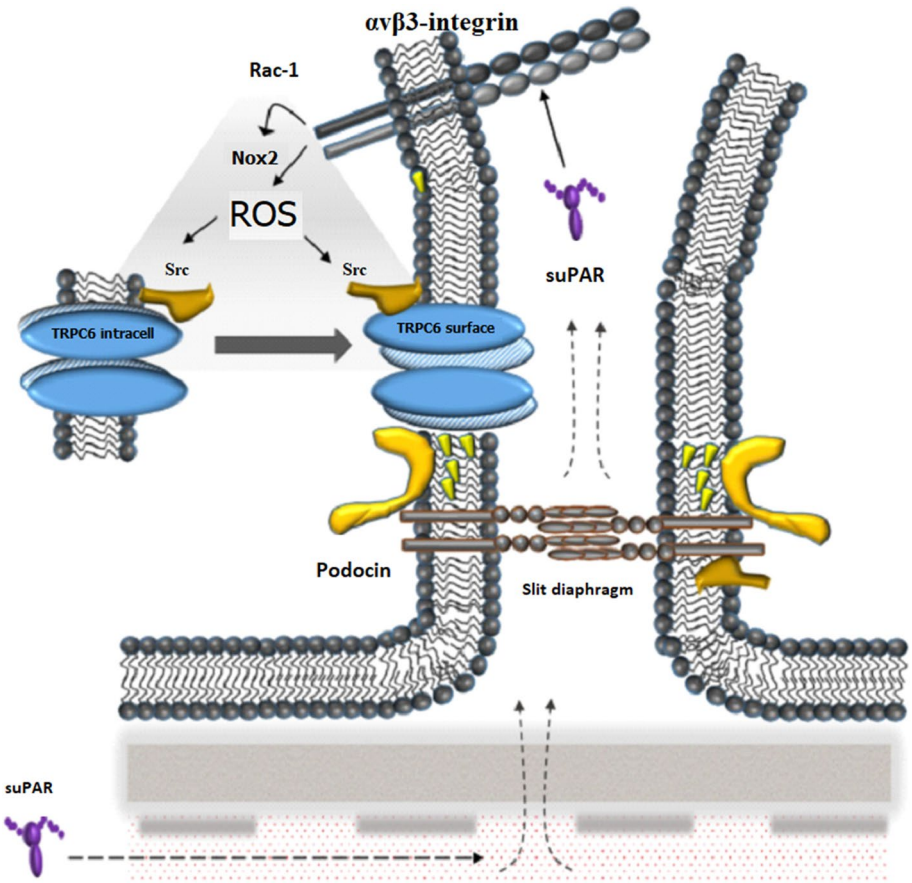

Fig. 2 Mechanism of suPAR on glomeruli [6]

and other medical conditions including cardiovascular disease, cancer, infections, and diabetes [24].

suPAR and FSGS

Over the past 10 years, there have been many studies on the role of suPAR in FSGS (Table 2), but the results later differed from the initial studies. One of the explanations is the difference in suPAR assays [25].

Summary of studies over the past 10 years on serum suPAR in the FSGS group has not been conclusive, but later studies tend to reject the role of serum suPAR in the pathogenesis of FSGS.

suPAR and nephrotic syndrome (NS)

Initially, suPAR was suspected to be involved in the pathogenesis of FSGS, a common lesion of NS, so it was doubtful whether suPAR was involved in treatment response in NS. A summary of suPAR studies related to treatment response in NS is listed below (Table 3).

The above studies suggest a high value of suPAR in differentiating the steroid responsiveness of NS, which further confirms the role of suPAR in predicting the severity of kidney disease.

suPAR and progression of renal failure

When studying the relationship between suPAR and FSGS which responds poorly to treatment and has a high rate of end-stage renal failure, the researchers found that suPAR has a predictive value in kidney failure in patients with normal renal function (with high quality of evidence) (Table 4).

Urinary suPAR

The previous studies demonstrated these advantages of urinary suPAR: Firstly, because urinary suPAR is adjusted based on the urinary suPAR/creatinine ratio, it reduces the effect of glomerular filtration rate on suPAR concentration. Secondly, suPAR could be produced by damaged podocytes, so the urinary suPAR concentration would include both serum suPAR and the suPAR from the podocytes. That helps separate FSGS damage more clearly than other non-renal diseases. Finally, the subunits of suPAR that want to cause glomerular damage

Table 2 Summary of studies on suPAR related to FSGS

Year	*Study*	*N. cases*	*Patient population*	*suPAR (pg/ml)*	*Comments*
2011	Wei et al. [18]	78	Mean age: 27 years old, 60% male	70%> 3000pg/ml	Be a multi-center research Have control group suPAR> 3000pg/ml accounted for 45/63 patients with FSGS, 4/11 patients with membranous nephritis (MN) and no patient with MCD.
2012	Wei et al. *(PodoNet and CT)* [26]	*70*	Mean age: 19 years old, 55% male *Average age <18* years old	4588±203/CT *3497 ± 195/ Podonet*	Have control group (i) If suPAR # 3000pg/ml was threshold for diagnosis FSGS, 83% of the patients was positive in the CT group and 55.3% of the patients was positive in the PodoNet group. (ii) The inflammation was not a compatible factor for increasing suPAR concentrations in FSGS
2013	Huang et al. [21, 27]	74	Mean age: 29 years old, 68% male	2923	Be a multi-center research (i) suPAR concentration in the FSGS group significantly increased compared to MCD (mean: 2050 pg/ml) and MN (mean: 2029 pg/ml) (ii) Plasma suPAR concentration did not differentiate primary and secondary FSGS
2016	Chen et al. [28]	40	18 patients with FSGS and 22 patients with MCD Mean age > 18 years old		suPAR concentration in FSGS (3670±170 ng/ml) was significantly higher than suPAR concentration in MCD (2030 ± 180 ng/ml).
2018	Verdelho et al. [19]	90	Mean age: 49 years old, 61% female 61 patients were performed renal biopsy: there were 30 cases with FSGS		Serum suPAR did not help distinguish FSGS from these other histopathological forms.
2019	Shuai et al. [29]		A meta-analysis of 29 studies on serum suPAR	2992.6 to 5500	suPAR concentration of 3000 pg/ml may be the best threshold for the diagnosis of primary FSGS (sensitivity = 0.72; specificity = 0.88; the area under the curve (AUC) = 0.85).

Table 3 Summary of studies on suPAR related to treatment response in nephrotic syndrome

Year	*Study*	*N. cases*	*Patient population*	*suPAR (pg/ml)*	*Comments*
2014	Peng et al. [30]	176	176 children (69.3% male). Mean age: 19–191 months old. 108 steroid-sensitive NS (SSNS), 68 steroid-resistant NS (SRNS)	Serum suPAR in SSNS was 3744.1 ± 2226.0 compared with SRNS was 2153.5 ± 1167.0	(i) There is a significant difference in serum suPAR between SSNS and SRNS, $p < 0.05$. (ii) AUC was 0.80, with p <0.001 to predict SRNS. The suPAR concentration to predict SRNS was estimated to be 1907.0 pg/ml to 3043.5 pg/ml ($\chi^2 = 14{,}775$, p=0.001).
2018	Mousa et al. [31]	75	Mean age: 7.9 ± 4.2 years old 25 SSNS, 25 steroid-dependent NS (SDNS) and 25 SRNS and 40 controls	SRNS: (66.52 ± 9.7 ng/mL), SDNS: (56.82 ± 11.09 ng/L), SSNS: (26.22 ± 3.86 ng/mL), and controls: (20.29 ± 0.69 ng/mL).	(i) There was a significant difference between the treatment response groups of NS with p<0.01 (ii) AUC of suPAR in predicting SDNS was 0.99 with p <0.001. A suPAR concentration > 32.4 ng/mL was the best cutoff for 96% sensitivity and specificity. Meanwhile, the AUC of suPAR in predicting SRNS was 1.00 with p <0.001. A suPAR concentration >33.17 ng/mL was the best cutoff with a sensitivity and specificity of 100%.

Table 4 Summary of studies on suPAR in relation to progression of renal failure

Year	*Study*	*N. cases*	*Patient population*	*suPAR (pg/ml)*	*Comments*
2017	Schaefer et al. [32]	898	The mean age was 11.9 years old, 62.4% male. Follow-up of the study for 7.9 years, mean 3.1 years. The end of follow-up when glomerular filtration rate decreases by more than 50% for more than 1 month, or <10ml/min/1.73m^2, or start renal replacement.	5658	The 5-year renal survival rate was 64.5% (95% CI, 57.4–71.7) in children with suPAR concentration in the lowest quartile compared with 35.9% (95% CI, 28.7–43.0) of suPAR concentration in the highest quartile ($p < 0.001$).
2020	Weideman et al. [22]	556	Age from 1 to 16 years old. 6-month follow-up	3204	(i) Patients with suPAR in the highest quartile had a 54% faster progression than the group in the lowest quartile ($p < 0.001$) (ii) No change in plasma suPAR level in 6 months (iii) The higher the suPAR concentration, the faster progression to chronic kidney disease.
2020	Iversen et al. [23]	25,497	Mean age: 58 years old, 52.5% female		Serum suPAR was a risk factor for acute and chronic renal failure. suPAR was a potential marker to classify the risk of renal injury with the intention of early intervention.
2021	Jhee et al. [33]	751	Mean age: 61.4± 11.4 years old with 52.6% male	1439	suPAR concentration was an independent factor associated with progression of chronic kidney disease.
2020	Roca et al. [34]	152	Mean age: 46–50 years old	3160–4347	There was an inverse relationship between glomerular filtration rate with serum suPAR (rs= −0.39, p<0.01).
2021	Jehn et al. [35]	100	Kidney transplant patients after 1 year follow-up		suPAR concentration above 6212 pg/ml were associated with a reduction of glomerular filtration rate >30% and occurred almost twice as rapidly as in patients with suPAR ≤6212 pg/ml ($p < 0.001$).

must pass through the glomerular membrane, so the quantification of suPAR in the urine will reflect more clearly the relationship between suPAR and glomerular damages [20, 21, 26].

Relationship between urinary suPAR and serum suPAR

In healthy people, suPAR concentrations in the blood and urine were quite stable, and the urinary suPAR/creatinine ratio is strongly positively related to serum suPAR [36].

A study by Palacios et al. [20] in 86 patients after kidney transplantation found that serum suPAR and urinary suPAR were correlated (r=0.41, p=0.01).

Sinha et al. [37] reported that urinary suPAR and serum suPAR in 61 pediatric patients with NS were not correlated (p=0.37).

Huang et al. in 2014 commented that urinary suPAR and serum suPAR were correlated in the FSGS group (r=0.43, p=0.001) but no correlation in the MCD group (r=0.12, p=0.69) [21].

Sun's study showed that there was no correlation between urinary suPAR and serum in 52 patients with secondary FSGS [38].

At present, the number of parallel studies of urinary suPAR and serum suPAR is limited, and the correlation between serum and urinary suPAR concentrations is unclear. Therefore, urinary suPAR is hypothesized to help clarify the correlation between suPAR and the pathogenesis as well as the level of treatment response, while the result of the studies in serum suPAR was unclear.

Studies on urinary suPAR

Palacios et al. [20] researched on 86 kidney transplantation patients and concluded that there was an increase of urinary suPAR in FSGS patients recurred after kidney transplantation compared to the other groups of kidney diseases, and they suggested that suPAR played a role as a predictor of kidney disease progression, besides proteinuria.

Huang et al. [21] studied suPAR in 62 patients with FSGS and found that the urinary suPAR concentration in FSGS patients was higher than that in the MCD, MN, and other kidney disease groups, and it associated with the severity of the disease.

The study of Fujimoto et al. [39] found that serum and urinary suPAR concentration in the control group was lower than that in primary NS patients. The urinary and serum suPAR concentration was a useful indicator of therapeutic responsiveness in primary NS patients, and they distinguished MCD from FSGS in the post-treatment period. In addition, serum and urinary suPAR were

associated with a long-term therapeutic responsiveness in primary NS [39].

In 2020, Fujimoto et al. published a study in 36 NS patients (18 MCD, 7 FSGS, and 9MN) with the conclusion that suPAR urinary was an independent predictor of proteinuria compared to serum suPAR and suggested the possibility of activating the β3 integrin pathway of suPAR [40].

The study of Sun et al. [38] observed that the urinary suPAR/creatinine ratio in the secondary FSGS group was 500pg/μmol, significantly higher than that of the MCD, MN, and control groups.

The study of Burscar in 2021 in patients with lupus nephritis showed that urinary suPAR, but not serum suPAR, was associated with kidney disease activity [41].

Studies of urinary suPAR in renal disease have not been as numerous as those of serum suPAR, because the role of serum suPAR remains in the study. However, the conclusions of urinary suPAR still confirm its value in the glomerular disease. More clinical studies of urinary suPAR is needed because urinary suPAR still has advantages over serum suPAR in renal disease [20, 21, 39, 41].

suPAR and therapeutics

The fact that researchers are actively investigating the relationship between new biomarkers and the pathogenesis of glomerular diseases is aimed at finding better targeted therapies is preventing or slowing progression to end-stage kidney disease (Fig. 3).

Currently, there are several trials of targeted therapy with suPAR in renal disease to reduce suPAR concentration by plasma filtration or immunosorbent:

A clinical case study in Germany on FSGS with chronic renal failure—not on hemodialysis, plasma dialysis, and immunosorbent (Cytosorb) suPAR, was performed, and the results showed that serum suPAR concentration decreased by 27.3% after 1 session of Cytosorb and by 25.2% after 3 times of plasma exchange. However, at the start of Cytosorb therapy, the patient required parallel hemodialysis because of high blood urea, so the effect of delaying renal replacement could not be assessed in this patient. However, it is also a new research direction for FSGS patients [43].

In 2018, a study result of 34 FSGS patients after renal transplantation in American, quantified serum suPAR concentration before and after plasma exchange and rituximab infusion showed that a decrease in suPAR concentration was associated with a decrease in proteinuria after therapy. Therefore, quantification of suPAR concentration before and after treatment is considered as a useful method to assess the treatment response [44].

Conclusions

Researching on circulating permeability factors in kidney disease is a current trend, which opens new avenues in targeted diagnosis and treatment. The identification of circulating permeability factors by FSGS is elusive, and scientists suggest suPAR is a promising candidate. Over the past 10 years, there have been many studies on the role of suPAR in the FSGS, but the later results differ

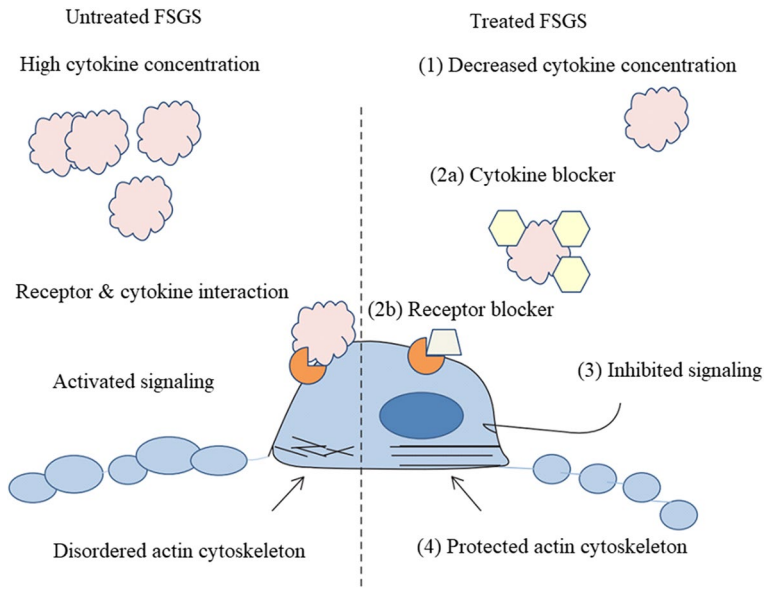

Fig. 3 Targeted therapies with circulating factors [42]

from the initial studies. Serum suPAR is related to the severity of glomerular disease; however, summarizing the studies on the role of suPAR in diagnosing FSGS is uncertain. And urinary suPAR has shown advantages over serum suPAR; therefore, more research on this issue is needed in the future.

Abbreviations
suPAR: Soluble urokinase plasminogen activator receptor; FSGS: Focal segmental glomerulosclerosis; CLCF1: Cardiotropin-like cytokine factor 1; TRPC6: Transient receptor potential cation channel subfamily C member 6; ROS: Reactive oxygen species; MN: Membranous nephritis; AUC: Area under the curve; NS: Nephrotic syndrome; SSNS: Steroid-sensitive NS; SRNS: Steroid-resistant NS; SDNS: Steroid dependent.

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Authors' contributions
LTPA and TKH were involved in the concept, design, and data collection of the study. LTPA, HTTY, TKH, and NHS carried out the critical evaluation and interpretation of the data. LTPA and TKH wrote the first draft of the manuscript, and all authors contributed to the subsequent drafts. The authors revised the manuscript and approved the final version for submission.

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Competing interests
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