Chapter 9
Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR) in Focal Segmental Glomerulosclerosis

Jochen Reiser and Nada Alachkar

Abstract Focal and segmental glomerulosclerosis (FSGS) is a histopathological entity that identifies a group of glomerular kidney disorders, which manifest by a certain pattern of sclerosis that involves parts of some glomeruli (focal segmental) on light microscopy. In most cases of FSGS, in particular the primary or idiopathic FSGS, the first site of the damage is the podocyte, which marks the beginning of this disease. However, FSGS can be a secondary process to another injury in the glomeruli, giving the definition of secondary FSGS. A large number of pathogenic factors have been identified, which lead to podocyte injury and, thereafter, to FSGS. Several genetic predispositions and mutations have been confirmed, especially in young patients, causing an early onset of primary FSGS. Acquired causes of FSGS constitute a large list of factors that may directly or indirectly injure the podocyte cells. Identifying these factors in the cases of primary or idiopathic FSGS has been the focus of extensive research investigations. For many decades, researchers speculated the presence of circulating factors to be the pathogenic causes of primary FSGS. These factors are thought to be the cause of FSGS recurrence post-kidney transplantation as well. However, not until recently, these factors are being identified. In 2011, soluble urokinase plasminogen activator receptor (suPAR) was suggested to be a circulating factor leading to primary FSGS and post-transplantation FSGS recurrence.

Keywords Focal segmental glomerulosclerosis • suPAR • Permeability factors

J. Reiser, M.D., Ph.D. (✉)
Department of Medicine, Rush University Medical Center, 1735 West Harrison Street, Cohn Building, Suite 724, Chicago, IL 60612, USA
e-mail: Jochen_Reiser@rush.edu

N. Alachkar
Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA

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9.1 Introduction

Primary or idiopathic focal segmental glomerulosclerosis (FSGS) is the most common cause of end-stage renal disease (ESRD) caused by primary glomerular disease in the United States [1], affecting both children and adults. Furthermore, FSGS recurs very commonly post-kidney transplantation in approximately 30–40 % of adult patients and much higher (80 %) in children [2], in many cases very shortly after transplantation, but can recur at any time.

In addition to our understanding of pathogenesis of FSGS that identified the podocyte cell as the originating site of this disease, circulating soluble urokinase plasminogen activator receptor (suPAR) has become the focus of extensive researches, making it the most accepted pathogenic factor that leads to, what we considered in the past, an idiopathic type of FSGS [3]. Podocyte foot process effacement is considered the first mark of injury and closely correlated with a loss of function in glomerular permeability and the characteristic hallmark of proteinuric glomerular disorders resulting in FSGS. Circulating suPAR is thought to bind to a receptor on the podocyte cell membrane leading to cell injury and death, resulting in glomerular hyalinosis, sclerosis, and chronic kidney disease [3].

In this chapter, we will present the current knowledge of suPAR as a pathogenic factor of primary and recurrent FSGS. We will review the recent data on the source of suPAR, the type of pathological suPAR, and its effect on the podocyte cells. Additionally, we will assess the relevant clinical data that support the suPAR role in this complicated disease.

9.2 Circulating Permeability Factors in FSGS

For couple decades, serum circulating permeability factor/s was proposed to exist in patients with primary FSGS and suggestive of the rapid recurrence of the disease after kidney transplantation. An early data indicated that the circulating permeability factor was a non-immunoglobulin protein with a molecular weight of approximately 30–50 kd [4]. A high level of this type of protein was detected in patients with FSGS recurrence post-kidney transplantation compared with much lower levels in normal subjects. To prove that this protein is the possible permeability factor, the researchers showed that serum obtained from patients with primary FSGS increases the albumin permeability of isolated culture glomeruli. Additionally, patients with recurrent FSGS had higher permeability to albumin compared to normal subjects or patients without recurrences, and plasmapheresis resulted in a significant decrease in permeability effect and proteinuria in patients with FSGS recurrence [5]. In a later study, the investigators confirmed that recurrent FSGS after kidney transplantation was much higher in patients whose glomerular albumin permeability sera was substantially higher compared with those whom sera had less permeability activity [4]. Similar to adults' data, researchers showed the same

findings in pediatric patients; recurrence occurred in most of children whose serum increased the glomerular albumin permeability compared with those with negative effect [6].

However, in spite of this long prediction of the presence of circulating permeability factor/s as the most likely causes of primary or idiopathic FSGS and the reason for this disease to recur after kidney transplantation, these early studies were unable to identify the exact molecular type or the mechanism of action of these factors.

9.3 Soluble Urokinase Plasminogen Activator Receptor (suPAR)

In 2011, Wei and colleagues presented the first work on suPAR and its role in FSGS disease. After an extensive work that lasted for more than a decade, the researchers reached a tipping point in identifying the permeability factor; and serum soluble urokinase receptor (suPAR) was the most evident factor. Applying their work in the laboratory to the clinical setting, the investigators found that serum suPAR was indeed elevated in subjects with primary FSGS, but not in control group with other glomerular diseases such as minimal change disease (MCD) or membranous nephropathy (MN). Furthermore, a significantly higher level of suPAR before transplantation was detected in patients who later on developed recurrence of FSGS after kidney transplantation [3]. In Reiser et al's previous work, podocyte urokinase receptor was found to play a significant role in glomerular disease [7]. On the cellular level, uPAR is a glycosylphosphatidylinositol (GPI)-anchored three-domain protein, making up a cellular receptor for urokinase that serves as a versatile signaling orchestrator via association with other transmembrane receptors, including integrins [8–10]. Furthermore, uPAR can be released from the cell membrane forming a soluble molecule (suPAR) by cleavage of the GPI anchor [9]. In the blood circulation or at the cell membrane level, suPAR is further cleaved [11] at the linkage region between domains, releasing three types of fragments: D_I, $D_{I–III}$, and D_{II} $D_{III;}$ the latter is thought to play the major role in the pathogenesis of FSGS (unpublished data). Consistent with the earlier findings of the permeability factors, suPAR was also found to be a protein ranging between 20 and 50 kD molecular weight, depending on the degree of glycosylation and proteolytic cleavage [10]. However, suPAR is present under physiological conditions in low concentrations in non-FSGS human serum, with a known role in neutrophil trafficking and stem cell mobilization [9].

9.4 Source of suPAR

There has been a great interest in identifying the source of the pathological suPAR in FSGS and the cause of its release in the circulation. Long-standing data showed that uPAR is expressed on various types of cells and interacts with ligand urokinase plasminogen activator (uPA). As a result of inflammatory [12] or other stimulations, uPAR is cleaved from the cell surface, such as the monocytes [12], by protease enzymes leading to the formation of the soluble form of the receptor, suPAR, which can be detected via different assays in blood and urine. In addition to the inflammatory cells, endothelial [13], cancerous [14], and other cells are able to release uPAR from the cell membrane. Therefore, low levels of suPAR existed in normal subjects, in contrast to much higher levels that correlate with pathological conditions and associate with worse diseases' prognosis [15, 16].

Although high suPAR levels have been documented in different disorders, such as sepsis and cancers, most of these disorders were not associated with proteinuric or FSGS findings. Therefore, it is possible that the source and the pathological types of suPAR are different in each disorder. Ongoing investigations are focusing on various sites of the immune system as the source of suPAR in FSGS animal models as well as in patients; the results so far have been promising.

9.5 suPAR's Mechanism of Action

In 1996, Harold Chapman's group reported binding of cell membrane-anchored uPAR to integrin [8]. This paper provided the base for bidirectional signaling of uPAR through cell-surface receptors. Our own experiments provided the data that circulating suPAR can bind to and activate podocyte β(3) integrin [3]. Binding of suPAR to podocyte β(3) integrin is causing its activation. This activation depends on the type of suPAR (domain and glycosylation structure) as well as the species in which this binding occurs. A particular soluble form of suPAR is created by alternative splicing of IMAGE cDNA clone 3158012 resulting in a variant of suPAR containing parts of suPAR domains I and II [3]. Expression of this type of suPAR causes foot processes effacement and progressive injury in mice resembling FSGS-like glomerular changes. The short-term effects of three-domain suPAR are accordingly weaker when infused into wild-type mice, establishing the concept that podocyte injury may result from podocyte β(3) integrin activation based on reaching a threshold [3] which relies on the suPAR variant to sufficiently activate this receptor.

Additionally, using rodent models of glomerular disease suggested that inducible podocyte-specific expression of the constitutively active nuclear factor of activated T cells 1 (NFATc1) which represent a downstream target of calcium signaling may increase podocyte uPAR expression by binding to the urokinase-type plasminogen activator receptor (Plaur) gene promoter (which encodes uPAR).

Such an increase in podocyte uPAR expression may favor podocyte cell dynamics/motility via activation of β(3) integrin, all independent of T cells, causing foot process effacement [7, 17]. These changes can be blocked by cyclosporine use and NFAT-siRNA or cell-permeable NFAT inhibitors [18].

Recently, data emerged that linked the podocyte-protective effects of rituximab to the stabilization of podocyte SMPDL3b, a molecule participating in plasma membrane lipid composition [19]. In a follow-up paper, Yoo et al. have shown that SMPDL3b may bind suPAR to allow for modulation of podocyte function in conditions with high or low podocyte SMPDL3b expression [20].

Finally, Kobayashi et al. suggested a PAI-1/uPA complex to mediate uPAR-dependent podocyte β1-integrin endocytosis and introduce a novel mechanism of glomerular injury, leading to progressive podocytopenia [21].

9.6 The Pathological Type/s of suPAR in FSGS

As indicated above, three types of suPAR fragments have been identified, depending on the cleavage sites of the molecule. Clinical data showed that different suPAR sub-domains are associated with different disorders, e.g., levels of $suPAR_{I–III}$ and $suPAR_{II–III}$ are higher in ovarian cancer [22] and not $suPAR_{I}$; however, data beyond the total suPAR level that would systematically assess the potential involvement of suPAR sub-types that correlate with FSGS pathology is not available yet. Therefore, identifying suPAR sub-domain/s that particularly strongly activate podocyte β(3) integrin and thus may lead to FSGS has been the focus of ongoing work by several investigators. This examination of pathological sub-type/s of suPAR in comparison to the full length of suPAR will be important and will probably explain the differences of phenotypes between different suPAR forms utilized in various animal models [3, 23, 24] and some of the open questions when measuring suPAR with commercial ELISA [25].

9.7 Clinical Data of suPAR in Primary FSGS

Since the discovery of the suPAR's active role in FSGS, cumulative clinical data have emerged to confirm this role.

Circulating suPAR was investigated in two well-characterized cohorts of children and adults with biopsy-proven primary FSGS: 70 patients from the North America-based FSGS clinical trial (CT) and 94 patients from PodoNet, the Europe-based consortium studying steroid-resistant nephrotic syndrome [26]. The investigators measured the level of circulating suPAR levels in the serum obtained from these cohorts at time of disease diagnosis and after therapy. Serum suPAR levels were elevated in 84.3 % and 55.3 % of patients with FSGS patients in the CT and PodoNet cohorts, respectively, compared with 6 % of controls ($P < 0.0001$).

In multiple regression analysis, the investigators found that lower suPAR levels were associated with higher estimated GFR, male gender, and treatment with mycophenolate mofetil. In the PodoNet cohort, patients with a nephrosis 2, idiopathic, steroid-resistant (podocin) (NPHS2) mutation had higher suPAR levels than those without a mutation [26].

Another study sought to identify the role of suPAR in predicting the response to the main therapy for FSGS steroid. Li and colleagues enrolled 109 patients with biopsy-proven primary FSGS between 2011 and 2013; the patients were treated with prednisone and followed up for 6–24 months. These patients were compared with control groups that consist of 96 healthy volunteers, 20 MCD patients, and 22 patients with MN. Using ELISA methods, suPAR levels were measured in all patients and controls. Patients with FSGS had significantly higher suPAR levels (median, 3512 [interquartile range (IQR), 2232–4231] pg/ml) than healthy controls (median, 1823 [IQR, 1563–2212] pg/ml; $P < 0.001$), patients with MCD (median, 1678 [IQR, 1476–2182] pg/ml; $P < 0.001$), and patients with MN (median, 1668 [IQR, 1327–2127] pg/ml; $P < 0.001$). When the investigators used a level of 3000 pg/ml as a cutoff, they found that suPAR was elevated in 48.6 % of patients with FSGS, in contrast to 5 % of patients with MCD and 4.5 % of those with MN. Additionally, when using a level of 3400 pg/ml as the threshold, the investigators found that suPAR level was independently associated with steroid response in patients with FSGS (odds ratio, 85.02; $P = 0.001$); patients who were responsive to steroids had significantly higher suPAR levels than nonsensitive patients (median, 3426 [IQR, 2670–5655] pg/ml versus 2523 [IQR, 1977–3460] pg/ml; $P = 0.001$). Interestingly, patients who had initially suPAR levels ≥ 3400 pg/ml had a significant decrease in these levels (median, 4553 [IQR, 3771–6120] pg/ml), compared to those with levels <3400 pg/ml, in whom the level did not change after therapy [27].

Other investigators also confirmed that suPAR was higher in FSGS compared to other glomerular diseases. In this study, 74 patients with primary FSGS were compared to healthy participants and patients with MCD, MN, and secondary FSGS. The suPAR levels of patients with primary FSGS (median: 2923, interquartile range 2205–4360 pg/ml) were significantly higher than those of patients with MCD (median 2050 pg/ml), MN (median 2029 pg/ml), and healthy subjects (median 1739 pg/ml). However, in this study, there was no significant difference in suPAR levels between the primary and secondary FSGS. Additionally, in primary FSGS, suPAR level was negatively correlated with creatinine clearance at presentation but positively correlated with crescent formation on the biopsies [28].

In children with primary nephrotic syndrome, suPAR was also evaluated to address the correlation between levels and clinical features and the value of the plasma suPAR level in predicting steroid-resistant nephrotic syndrome. In this study from China, 176 children were enrolled in a 6-month study to assess suPAR levels before and after treatments. The authors found that there was a significant difference in plasma suPAR levels between steroid-resistant and steroid-sensitive nephrotic syndrome groups ($3{,}744.1 \pm 2{,}226.0$

vs. 2,153.5 ± 1,167.0, $p < 0.05$). The area under the curve was 0.80, with $p < 0.001$ using suPAR to predict steroid-resistant nephrotic syndrome [29]. In patients who had biopsies to confirm the diagnosis, the investigators found that suPAR levels were much higher in the active phase of FSGS (4,674.0 ± 1,915.4) compared to those with non-FSGS (2,974.5 ± 1,544.9, $p < 0.05$) and controls ($p < 0.05$). Interestingly, and in contrast to FSGS cases, patients with steroid-resistant MCD had much higher suPAR levels than those in the steroid-sensitive group (3,228.8 ± 1,543.2) vs. (2,264.9 ± 810.2, $p < 0.05$), respectively, or controls ($p < 0.05$) [29].

Because of these conflicted results between the suPAR levels in MCD versus FSGS, investigators sought to address whether the simultaneous measurement of urinary CD80 and serum suPAR can help differentiate MCD and FSGS. Twenty-six children and adolescents with biopsy-proven MCD were enrolled, five during relapse, six were in remission, and 15 were assessed in both relapse and remission. This MCD group was compared to biopsy-proven primary FSGS group that is composed of 11 children and 15 adults. The investigators found that serum suPAR levels were significantly higher in patients with FSGS compared with patients with relapsed MCD. Urinary suPAR correlated with proteinuria in MCD in relapsed cases and in FSGS patients, whereas urinary CD80 correlated with proteinuria only in MCD patients in relapse [30].

Although suPAR was shown in many studies to correlate strongly with primary FSGS, other investigators failed to show similar findings. An early analysis from the ongoing NEPTUNE study using samples from 241 patients with glomerular diseases (including 95 with FSGS) indicated that changes in suPAR levels were associated with the changes in estimated glomerular filtration rate (eGFR), but there was no difference in the levels between patients with FSGS and other nephrotic diseases which is a consequence of the reduced GFR of this patient cohort [23]. Overall, there is strong experimental and clinical evidence suggesting causality of suPAR in FSGS. However, further prospective multicenter clinical studies are still needed to clarify the precise contribution of GFR to suPAR plasma levels as well as the potential role of suPAR in other kidney diseases.

9.8 The Role of suPAR in Post-transplant FSGS Recurrence

Recurrence of primary FSGS is very common in kidney transplant recipients with chronic kidney disease or ESRD due to primary FSGS. The recurrence rate is estimated to be as high as 30–40 % of patients with primary FSGS [31]. The recurrence rate can be as high as 70–80 % in second kidney transplants if the first kidney transplant failure was due to recurrence of FSGS [32] and in pediatric patients [33].

The majority of the recurrence happens early post-transplantations due to the circulating permeability factors [3]; however, later recurrence has also been documented. High level of suPAR was found in many studies to play a major role in recurrent FSGS.

In their first data on suPAR, Wei et al. showed that patients with recurrent FSGS have significantly higher levels of suPAR before transplant compared to those who did not have recurrence. These results suggested that suPAR is a predictive biomarker for recurrent FSGS post-kidney transplantation [3].

Recently, the authors found that the degree of podocyte foot process effacement correlates significantly with the suPAR levels at the time of diagnosis in patients with preserved renal function. Response to therapy resulted in significant reduction of suPAR levels and complete or significant improvement of podocyte effacement; these findings support the role of suPAR as a disease marker for primary and recurrent FSGS after kidney transplant [34].

Others showed that in recurrent FSGS patients, urine suPAR was significantly elevated compared to those who did not have recurrence. Pre-transplant serum and urine-stored samples were analyzed for suPAR from 86 kidney transplant recipients and 10 healthy controls [35]. Causes of native kidney disease were primary FSGS, diabetic nephropathy, membranous nephropathy, IgA nephropathy, and autosomal dominant polycystic kidney disease. The investigators found that both serum and urine suPAR correlated with proteinuria and albuminuria. Serum suPAR was found to be elevated in all pre-transplant sera in those patients with advanced renal disease compared with healthy controls and could not differentiate the diagnosis of the native kidney disease. However, urine suPAR was elevated in cases of recurrent FSGS compared with all other causes of ESRD [35].

Another exciting development is the cooperation of suPAR with preformed antibodies relevant for the development of recurrent FSGS. In a recent publication, Delville and colleagues suggested that some patients with recurrent FSGS developed autoantibodies against CD40 antigen, possibly reacting with CD40 on podocytes. Mice that received purified autoantibodies had only mild proteinuria, but co-injection of anti-CD40 antibody derived from recurrent FSGS patients together with three-domain suPAR (usually with mild effects on podocytes) into wild-type mice caused substantial proteinuria [36].

9.9 Toward suPAR's Targeted Therapy

Steroid and other immunosuppressant therapies have been the treatment of choice for primary FSGS. The mechanisms of action of these drugs in this disease are not fully understood and in most part not specific. Therefore, the response rate is not optimal and in best cases can reach 50–60 %; and in many cases multiple relapses occur.

Although suPAR level was found to decrease by steroid [26] and other immunosuppressant drugs, such as mycophenolate mofetil (MMF), these drugs are not

well suited to lower suPAR substantially and in addition have significant systemic side effects.

In the above-mentioned CT and PodoNet cohort study, the authors noted the effect of treatment on serum suPAR levels. Samples were analyzed in patients who were randomly assigned to either cyclosporine A (CSA) or MMF/dexamethasone arms. When using univariate analysis, there was no difference between the patients in the two treatment arms, at baseline, with regard to age at disease onset, age at sampling, sex, race, urine protein-creatinine ratio (UPCR), serum creatinine, eGFR, serum albumin, as well as circulating suPAR levels. However, after 26 weeks of treatments, the mean suPAR level was significantly higher in patients assigned to CSA compared with the MMF arm. Furthermore, compared to baseline, suPAR levels increased in the CSA arm and decreased in the MMF arm after 26 weeks [26]. Additionally, multiple regression analysis showed that the relative changes of serum suPAR from baseline to week 26 correlated positively with the absolute change ($P = 0.01$) and percentage reduction ($P = 0.003$) in the UPCR. When controlled for age, sex, race, and eGFR, the study showed that UPCR and suPAR at baseline indicated greater odds for complete remission (UPCR $\leq$0.2 g/g) with each 10 % reduction in suPAR concentration (odd ratios, 1.44; 95 % CI, 1.02–2.03; $P = 0.04$) [26].

In recurrent FSGS, plasmapheresis/exchange and immunoadsorption have been the treatment of choice for a long time. In these patients who are already on large amount of immunosuppression therapy, the target is to remove the circulating factors by removing the patients' plasma that contains these factors. However, data on suPAR response to these therapies is limited. Serum suPAR levels were assessed in a case of recurrent FSGS in which investigators also analyzed the effect of removing suPAR on podocyte β(3) integrin activation. The authors found that suPAR significantly decreased after one apheresis treatment to levels considered slightly above normal (median of 3878 pg/mL); however, it rebounded after few days to median pretreatment level of 6437 pg/mL. Furthermore, even short-term suPAR reduction (median of 3878 pg/mL) due to intensified apheresis resulted in a significant reduction of podocyte β(3) integrin activation as measured by AP5 staining to a normal mean fluorescence intensity. This decrease in podocyte β(3) integrin activation was associated with a decrease in proteinuria to 3.6 g/d from much higher concentration and partial recovery of podocyte foot process effacement [37].

We previously showed that suPAR levels decrease significantly with plasmapheresis; this decrease is associated with decreasing in proteinuria and improving in podocyte foot processes effacement [3, 33].

Interestingly, immunoadsorption to protein A columns was found by Beaudreuil et al to be ineffective in removing suPAR in patients with recurrent FSGS. In this study, the authors measured suPAR in the eluates of protein A columns from seven patients with recurrent FSGS, and in the serum of 13 patients with recurrent FSGS and 11 hemodialysis (HD) patients used as control. Plasma suPAR levels were higher in patients with recurrent FSGS than control; however, they remained similar before and after the therapy for the recurrent FSGS and HD samples.

Surprisingly, suPAR levels were very low in the eluates from protein A columns incubated with plasma from both HD and recurrent FSGS patients [38], suggesting that immunoadsorption was an ineffective therapy in removing suPAR from the plasma.

Although plasmapheresis has been effective in decreasing proteinuria and achieving total or partial remissions in the majority of recurrent FSGS patients, more than 30 % of patients fail to respond to these therapies in most published data. In addition to the significant side effects, such as bleeding, severe anemia, infection, and allergic reactions, these treatments need strong experienced facilities and staff familiar with managing recurrent FSGS. Therefore, there has been a great interest in identifying specific therapies that directly target suPAR, by removing either this molecule only or antibodies that block its effects. Works are undergoing to manufacture targeted suPAR removal methods that adsorb/remove suPAR only without removing patients' plasma. Additionally, some have succeeded in making antibodies against suPAR that have been used in vivo but still to be trialed in humans.

9.10 Conclusion

Primary FSGS is a common glomerular disorder that manifests in proteinuria, leads to ESRD in the majority of patients, and recurs commonly after kidney transplantation. Identifying the circulating permeability factors that lead to the primary FSGS in native kidneys and to the recurrent disease post-transplant has been an ongoing effort for a couple of decades. Although data thus far have shown that suPAR is the most evident circulating permeability factor for FSGS, more validating clinical data is still required, along with the need to confirm the specific pathological type/s of suPAR and how these types are relevant to FSGS and other renal diseases.

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