Published in final edited form as:
Adv Chronic Kidney Dis. 2014 September ; 21(5): 417–421. doi:10.1053/j.ackd.2014.05.010.

Permeability Factors in Focal and Segmental Glomerulosclerosis

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Abstract

Focal and segmental glomerulosclerosis (FSGS) represents a group of glomerular disorders, identified on kidney biopsy, that progress in the histopathologic pattern of sclerosis in parts of some glomeruli. Damage to podocytes usually marks the beginning of the disease, most evident in primary FSGS. In addition to genetic predisposition, there are many acquired causes that disturb normal podocyte homeostasis and allow for the development of FSGS. The aim of this review is to summarize recent findings of the most relevant circulating permeability factors that may serve as biomarkers of active primary idiopathic FSGS, and aid in the diagnosis and prediction of recurrent FSGS post-kidney transplantation.

Keywords

soluble urokinase receptor; suPAR; permeability factor; recurrent focal and segmental glomerulosclerosis

Introduction

Idiopathic focal and segmental glomerulosclerosis (FSGS) is the most common cause of end stage renal disease (ESRD) caused by primary glomerular disease in the United States in black and white populations[1]. FSGS holds the status of an orphan disease, yet currently more than 5,400 patients are diagnosed with FSGS annually, affecting both children and adults. Today, approximately 20,000 people in the USA live with ESRD due to FSGS. Approximately 1,000 FSGS patients a year receive kidney transplants. However, within hours to weeks after kidney transplantation, FSGS recurs in approximately 30-40% of adult patients and up to 80% in children[2].

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In recent years, our understanding of FSGS has changed dramatically with a major focus on the podocyte as the originating site of the disease pathogenesis. Changes in podocyte phenotype, i.e. the effacement of foot processes, are closely correlated with a loss of function in glomerular permeability and the characteristic clinical hallmark of proteinuria occurring in FSGS. FSGS represents a histopathologic pattern of injury and a clinicopathologic entity classified as: 1) Primary idiopathic FSGS; 2) Genetic or familial FSGS; 3) Secondary FSGS; 4) FSGS caused by infection; 5) FSGS caused by drugs; and 6) FSGS post kidney transplantation. In this review we will focus on the circulating permeability factors that have been investigated and found to have possible roles in the pathogenesis of primary idiopathic FSSG, and may also be the cause of recurrent FSGS following renal transplantation.

Pathogenesis of Podocyte Injury and FSGS

Primary idiopathic FSGS

Changes in podocyte phenotype and function result in proteinuria and may progress to FSGS. The pathogenesis of FSGS starts with podocyte dysfunction but thereafter it involves additional cell types in the glomerulus as well as the tubulo-interstitial compartment. Overall, FSGS progression is an extremely complex process, with new mechanisms still being discovered. Podocyte injury can result from several triggers; however, the first response is simplification of their cellular structure. This is accomplished by retraction of the foot processes and extension of the connecting plasma membrane between two feet resulting in a dedifferentiated podocyte phenotype referred to as foot process effacement[3]. This early stage can be repaired; however, it may become the basis for further aggravating injury resulting in proliferation, cell cycle arrest, apoptosis and necrosis. Loss of podocytes then perpetrates additional glomerular damage, ultimately resulting in loss of the glomerulus with scar formation and eventual irreversible loss of the entire nephron. There are multiple factors, including genetic and acquired abnormalities, that play critical roles in podocyte injury and the progression to FSGS. This includes the recently identified permeability factor soluble urokinase receptor (suPAR)[4]. Herein, we review the most relevant circulating permeability factors that have been investigated thus far and found to have a potential role in primary and recurrent FSGS.

Permeability factors

The presence of circulating permeability factors in the serum of patients with primary FSGS was suggested by cases of rapid recurrence of FSGS post kidney transplantation. Data reported approximately two decades ago suggested the presence of a permeability-circulating factor, identified as a nonimmunoglobulin protein with a molecular weight of approximately 30 to 50 kDa[5]. This alleged permeability factor was present in low levels in normal subjects and was elevated in patients with recurrent FSGS. This study assessed the ability of serum from FSGS patients to increase the permeability of isolated glomeruli to albumin. There was a higher mean value for glomerular permeability using sera from patients with recurrent FSGS compared with normal controls or from those without recurrent FSGS. After plasmapheresis, there was decreased proteinuria and glomerular permeability was reduced in six patients with recurrent FSGS[5]. Additionally, recurrent

FSGS occurred in 86% of patients whose sera caused increase in glomerular albumin permeability compared with only 17% in patients whose sera had no or lesser effect on permeability[5]. This circulating factor bound to protein A and hydrophobic-interaction columns, and had a molecular mass of approximately 50 kDa[6]. Similar findings were observed in a series of 25 children transplanted for FSGS; there was disease recurrence in 85% (11 of 13) of those whose sera induced increased glomerular albumin permeability compared with 33% (4 of 12) of those without an increase[7]. However, these studies were unable to specifically identify the permeability factor(s).

Soluble Urokinase Plasminogen Activator Receptor (suPAR)

Recently, Wei and colleagues identified serum soluble urokinase receptor (suPAR) as a possible causal FSGS permeability factor.[4] uPAR is a glycosylphosphatidylinisotol (GPI)-anchored three-domain protein, which has been identified as a cellular receptor for urokinase. It associates with other transmembrane receptors, including integrins, to orchestrate number of signaling effects[8,9]. Following cleavage of the GPI anchor, uPAR can be released from the plasma membrane as a soluble molecule (suPAR)[8]. suPAR can then be cleaved in the linker region between domains DI and DII, releasing fragments DI and DII DIII. suPAR is a circulating protein which ranges from 20 to 50 kDa, depending on the extent of glycosylation and proteolytic cleavage[9]. It is found in low concentrations in human blood under physiologic conditions, and is known to participate in neutrophil trafficking and stem cell mobilization[8].

There is evidence that suPAR may play a significant role in primary FSGS. Wei et al identified elevated serum suPAR in patients with primary FSGS, but not in a control group with other glomerular diseases. They also reported pre-transplant elevated suPAR levels increased risk for recurrence of FSGS post renal transplantation[4]. In support of this, the podocyte urokinase receptor was previously found to play a significant role in glomerular disease[10]. Circulating suPAR has been shown to activate podocyte β(3) integrin in both native and engrafted kidneys, causing foot processes effacement, proteinuria and FSGS-like changes. These findings suggest that the development of renal disease is associated with a certain level of podocyte β(3) integrin activation by suPAR. Conversely, reducing serum suPAR concentrations via plasma exchange, or using antibodies or small molecules to interfering with the suPAR-β(3) integrin interaction by targeting β(3) integrin or uPAR may have promise as therapeutic approaches to FSGS[4]. Using rodent models of glomerular disease, these investigators demonstrated inducible podocyte-specific expression of constitutively active nuclear factor of activated T cells 1 (NFATc1), which increased podocyte uPAR expression. These podocyte uPAR signals affect cell motility via activation of the β(3) integrin, but not through a change in its expression. These changes can be blocked by cyclosporine, NFAT-siRNA, or the cell-permeable NFAT inhibitor[11]. Taken together, these data demonstrate interactions between podocyte β(3) integrin, suPAR, and uPAR which may result in podocyte injury potentially leading to FSGS.

In the clinical setting, circulating suPAR was studied 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[12]. In this study, levels of circulating suPAR were measured in serum obtained from patients in both cohorts at times of disease diagnosis and after therapy. Serum suPAR levels were significantly elevated in patients with FSGS in 84.3% of the CT and in 55.3% of the PodoNet patients, respectively, compared with 6% of controls. Analyses demonstrated lower or reduced suPAR levels associated with higher estimated GFR, male gender, treatment with mycophenolate mofetil, and reduced proteinuria with higher odds for complete remission in the CT cohort after 26 weeks of treatment. Interestingly, patients with an NPHS2 mutation had higher suPAR levels compared to those without a podocyte mutation. A more recent study addressed whether the simultaneous measurement of urinary CD80 and serum suPAR helps differentiate minimal change disease (MCD) and FSGS[13]. Twenty-six children and adolescents with biopsy-proven MCD were evaluated; five patients were studied during relapse, six during remission and 15 were studied in both relapse and remission. The FSGS cohort was composed of 11 children and 15 adults with biopsy proven primary FSGS. The serum suPAR levels were found to be significantly higher in patients with FSGS compared to those with relapsed MCD. Urinary suPAR correlated with proteinuria in those with relapsed MCD and with active FSGS; however, urinary CD80 correlated with proteinuria only in relapsed MCD patients.

The identification of suPAR as an FSGS factor may be brought into question as there are patients who develop recurrent FSGS in the absence of high circulating suPAR levels[14]. Additionally, suPAR serum levels are increased in association with a variety of illnesses that are not primarily associated with proteinuria. These include paroxysmal nocturnal hemoglobinuria, infectious diseases such as HIV-1, TB sepsis, and bacterial and viral CNS infections, and malignancies[15] which can present with high serum suPAR. This may be a consequence of systemic inflammation and immune activation[14]. There are studies of FSGS patients with small sample sizes that could not validate the specificity of high suPAR levels for primary FSGS[16, 17]. While the small samples sizes of these studies prevent drawing firm conclusions, and the difficulties of differentiating primary and secondary FSGS using clinical and histologic criteria may play a role, these reports indeed question the clinical usefulness of high suPAR levels as the sole measure of FSGS status and/or disease activity[18.] Recent studies of suPAR have reported conflicting data, highlighting inconsistencies among the various study cohorts and sampling conditions[19 20 21 22]. Given the many pathways that may cause FSGS and the presence of suPAR in various health and disease states, accurate measuring of suPAR requires a reliable assay platform, defined and uniform specimen types (plasma, serum, storage conditions), a larger sample size and a defined time of sampling. The current suPAR test should not be used as a single value for FSGS screening alone but rather in combination with clinical parameters and in conjunction with a kidney biopsy. Serial suPAR tests in the same patient can be very helpful, yet a single test value in a patient with FSGS and severely reduced eGFR is of unknown value. Sample size must be large enough to control variations especially when a single center cohort is analyzed. While suPAR itself is relatively stable in the blood, values differ in different forms of samples, with serum levels usually higher than plasma levels. Even with plasma, the use of EDTA or heparin can generate different suPAR readings. Unfortunately, it is not uncommon for serum and plasma to be used interchangeably in clinical studies. When

evaluating the role of suPAR in FSGS or other glomerular disorders, one needs to first identify whether other conditions associated with high suPAR levels co-exist, for example infections or tumors. With the former, concurrently analyzing serum CRP level can be helpful. Additionally, ESRD patients may accumulate suPAR which contributes to increased suPAR levels[19 20 21]. As current suPAR test kits measure bulk suPAR and cannot sufficiently differentiate pathological or aberrant suPAR fragments, evaluation of suPAR induced podocyte β(3) integrin activity can provide further specificity related to glomerular injury and the presence of FSGS; studies are underway to address this issue.

Other Possible Biomarkers of FSGS

Active proteases

Another possible serum circulating factor was investigated by Harris et al. in patients with biopsy proven primary FSGS in active and remission phases and in recurrent FSGS patients.[23] These investigators confirmed that vasodilator-stimulated phosphoprotein (VASP) became phosphorylated in response to plasma from 10 patients with relapsed FSGS, but not in response to plasma from FSGS patients in remission and non-FSGS controls. VASP is an organizer of the actin cytoskeleton, with multiple roles affecting dynamic cell morphology. Furthermore, the inhibition of proteases in the plasma of patient in relapse leads to the loss of VASP phosphorylation. By the use of siRNA technology, in active FSGS it was demonstrated that plasma proteases signal to VASP predominantly via protease activated receptor-1 (PAR1); thus, podocyte motility is increased by plasma from patients with FSGS, and this is dependent on VASP phosphorylation[23].

Protein tyrosine phosphatase receptor-O antibodies

Protein tyrosine phosphatase receptor-O (PTPro) is a transmembrane protein expressed on the apical surface of podocyte foot processes. To determine whether PTPro activity is required to maintain glomerular permeability, albumin permeability (P(alb)) was investigated by incubation of glomeruli from normal animals with a series of monoclonal and polyclonal antibodies to this receptor[24]. Monoclonal 4C3 antibodies specific to the amino acid core of PTPro were found to decrease its phosphatase activity and increase P(alb) of normal rabbit glomeruli. Pre-incubation of 4C3 with a PTPro extracellular domain fusion protein blocked glomerular binding and inhibited its permeability activity. Additionally, P(alb) of rat glomeruli was increased by two monoclonal antibodies and a polyclonal anti-rat PTPro. However, how PTPro phosphatase activity is involved in glomerular filtration and the identities of the PTPro ligand and substrate remain unclear.

Cardiotrophin-like cytokine-1 (CLC-1)

Another possible circulating permeability factor is cardiotrophin-like cytokine-1 (CLC-1). CLC-1, a member of the IL-6 family, was the only cytokine found in the active fraction following galactose affinity chromatography of sera from patients with recurrent FSGS, in whom the concentration may be up to 100 time greater than in normal subjects[25]. It has been suggested that CLC-1 may be the permeability factor in recurrent FSGS, as it mimics the effects of FSGS plasma on albumin permeability and is present in plasma from patients with active disease. Additionally, CLC-1 decreases nephrin expression by cultured podocytes and

glomeruli. The albumin permeability effect of FSGS sera has been reported to be blocked by a monoclonal antibody against CLC-1. Work on CLC-1 and FSGS is still in its early stages and requires more investigations into the role of this potentially interesting circulating factor.

Permeability Factors in Recurrent and De Novo FSGS in Renal Transplants suPAR

Recurrence is very common in kidney transplant recipients whose original disease was primary FSGS. The recurrence rate is estimated to be as high as 30%-40% of patients with primary FSGS[26, 27], and may reach 70%-80% in second kidney transplants when the first allograft failed due to recurrent disease[28]. Most recurrent FSGS occurs early post-transplantation, likely due to the same pathogenetic mechanisms causing disease in the native kidney[4]. A recent study by Alachkar, et al examining podocyte injury and suPAR established that the first site of injury in recurrent or de novo post-transplant FSSG is the podocyte[29]. At the time FSGS is diagnosed in a renal allograft, they identified a significant correlation of suPAR levels with the degree of foot process effacement, suggesting a role for suPAR in disease initiation. Upon investigating the impact of treatment, they found therapeutic response associated with reduction in foot process effacement, significant reductions in suPAR levels, and improvement in renal function.

Apolipoprotein A-I

A recent study used proteomic analysis of plasma and urine samples from transplanted FSGS patients with and without recurrent disease to identify candidate proteins related to recurrence[30]. A high molecular weight form of apolipoprotein A-I (ApoA-1b) was found in 93% of those with recurrent FSGS compared to in <5% of those without recurrence, transplanted for familial FSGS or with proteinuria unrelated to FSGS. Urinary ApoA-1b had a sensitivity of 92.8% and a specificity of 98.1% for identifying an FSGS relapse. This study demonstrates the potential of circulating and urinary factors to serve as biomarkers for the early detection and treatment of recurrent FSGS.

Angiotensin II type 1 (AT1) receptor

Although recurrent disease is the most common cause of FSGS in the renal allograft, transplant kidneys in patients who did not have FSGS as the original disease may develop de novo FSGS[31, 32]. While there is limited information regarding the causes of de novo FSGS, we believe this entity may be the outcome of mechanisms similar to those in primary FSGS. In support of this, de novo collapsing FSGS one month after transplantation has been reported in association with antibodies to the angiotensin II type 1 (AT1) receptor[33]. In this case report, antibodies to the AT1-receptor were significantly elevated in association with new onset proteinuria and preserved renal function. Renal biopsy disclosed de novo collapsing FSGS and extensive podocyte foot process effacement. Treatment with plasmapheresis, intravenous immunoglobulin, and angiotensin receptor blocker resulted in undetectable AT1- receptor antibodies, and resolution of proteinuria and the glomerular lesion. This suggests a mechanism for primary podocyte injury and de novo FSGS in renal allografts. However, when FSGS occurs later (months to years) following transplantation, it is considered by some investigators to be a secondary form of FSGS due to glomerular hyperfiltration, vascular disease, calcineurin inhibitor injury, or related to rejection[32, 34].

Summary

Primary FSGS is a common glomerular disorder clinically manifesting with proteinuria and posing a risk for development of ESRD. Following renal transplantation, FSGS not infrequently recurs, sometimes within hours or day post-engraftment, and may result in allograft failure. There is evidence suggesting that circulating permeability factors play a pathogenetic role in primary and recurrent FSGS. suPAR is a likely candidate as a key permeability factor; however, the specific pathologic type of suPAR inducing podocyte injury and FSGS is yet to be identified. In addition, there may well be other circulating proteins or lipids that initiate or promote podocyte dysfunction in FSGS and other glomerular disorders. The quest for circulating permeability factors is an important ongoing effort, as they present attractive diagnostic, prognostic and therapeutic targets.

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Clinical Summary

- Circulating permeability factors may be pathogenic in primary and recurrent focal and segmental glomerulosclerosis.
- Serum soluble urokinase receptor (suPAR) may play a causal role in focal and segmental glomerulosclerosis via interactions between podocyte β(3) integrin, suPAR, and uPAR.
- Other possible permeability factors affecting native kidneys include vasodilator-stimulated phosphoprotein, protein tyrosine phosphatase receptor-O, and cardiotrophin-like cytokine-1
- Transplant focal and segmental glomerulosclerosis has been associated with apolipoprotein A-I and antibodies to the angiotensin II type 1 (AT1) receptor