Permeability Factors in Focal and Segmental Glomerulosclerosis

Jochen Reiser, Cynthia C. Nast, and Nada Alachkar

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 was 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 after kidney transplantation.

Key Words: Soluble urokinase receptor, suPAR, Permeability factor, Recurrent focal and segmental glomerulosclerosis

Introduction

Idiopathic focal and segmental glomerulosclerosis (FSGS) is the most common cause of 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 5400 patients are diagnosed with FSGS annually, affecting both children and adults. Today, approximately 20,000 people in the United States live with ESRD because of FSGS. Approximately 1000 FSGS patients a year receive kidney transplants. However, within hours to weeks after kidney transplantation, FSGS recurs in approximately 30% to 40% of adult patients and up to 80% in children.[2]

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, that is, 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 after 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 after kidney 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 and the tubulointerstitial 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 2 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, which play critical roles in podocyte injury and the progression to FSGS. This includes the recently identified permeability factor serum-soluble urokinase receptor (suPAR).[4] Here, 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 after kidney transplantation. Data reported approximately 2 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

From Department of Medicine, Rush University School of Medicine, Chicago, IL; Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, CA; and Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD.

Financial Disclosure: J.R. is an inventor on pending and issued patents related to the modification of suPAR. He stands to gain royalties from their commercialization. N.A. has a sub-grant from Terumo BCT to study suPAR changes with plasmapheresis.

Address correspondence to Jochen Reiser, MD, PhD, Rush University Medical Center, 1735 West Harrison Street, Cohn Building, Suite 724, Chicago, IL 60612. E-mail: jochen_reiser@rush.edu

1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2014.05.010

those without recurrent FSGS. After plasmapheresis, there was decreased proteinuria, and glomerular permeability was reduced in 6 patients with recurrent FSGS.[5] Additionally, recurrent FSGS occurred in 86% of patients whose sera caused increase in glomerular albumin permeability (P(alb)) 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 P(alb) compared with 33% (4 of 12) of those without an increase.[7] However, these studies were unable to specifically identify the permeability factors.

Soluble Urokinase Plasminogen Activator Receptor

Recently, Wei and colleagues identified serum-soluble urokinase receptor (suPAR) as a possible causal FSGS permeability factor.[4] uPAR is a glycosylphosphatidylinisotol-anchored 3-domain protein, which has been identified as a cellular receptor for urokinase. It associates with other transmembrane receptors, including integrins, to orchestrate the number of signaling effects.[8,9] After cleavage of the glycosylphosphatidylinisotol (GPI) anchor, urokinase receptor (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, DII, and DIII. suPAR is a circulating protein that 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 and colleagues identified elevated serum suPAR in patients with primary FSGS but not in a control group with other glomerular diseases. They also reported that pre-transplant elevated suPAR level increased the risk for recurrence of FSGS after kidney 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 kidney 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 interfere 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-short interfering RNA (siRNA), or the cell-permeable NFAT inhibitor.[11] Taken together, these data demonstrate interactions between podocyte β(3) integrin, suPAR, and uPAR that may result in podocyte injury potentially leading to FSGS.

In the clinical setting, circulating suPAR was studied in 2 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 glomerular filtration rate, 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 with 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; 5 patients were studied during relapse, 6 during remission, and 15 were studied in both relapse and remission. The FSGS cohort 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 with 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

CLINICAL SUMMARY

- Circulating permeability factors may be pathogenic in primary and recurrent focal and segmental glomerulosclerosis.
- Serum-soluble urokinase receptor may play a causal role in focal and segmental glomerulosclerosis via interactions between podocyte β(3) integrin, serum-soluble urokinase receptor, 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 receptor.