Soluble Urokinase-Type Plasminogen Activator Receptor in FSGS: Stirred but Not Shaken
Jochen Reiser† and Harold Chapman‡

†Department of Medicine, Rush University Medical Center, Chicago, Illinois; and ‡Department of Medicine, University of California, San Francisco, California

doi: 10.1681/ASN.2014030257

The soluble urokinase-type plasminogen activator receptor (suPAR) has been proposed as a candidate circulating factor causing FSGS.1 In this issue of JASN, Cathelin et al. further examine the short-term effects of two different types of suPAR on the kidney filtration barrier.2 Although the authors show deposition of suPAR in the glomerular capillary wall of their experimental models, they do not find changes in albumin permeability. The activation of the suPAR target on podocytes, αvβ3 integrin, is not examined, leaving the question of target engagement unanswered. Nevertheless, this study provides some additional insights into the complexity of suPAR-derived signals in kidney disease and offers a potential explanation as to why patients with elevated acute phase–associated suPAR may not readily develop nephrotic syndrome.

The debate regarding the existence of a serum factor that causes FSGS is certainly glorified, heated, and polarizing. Since Shalhoub first suggested the existence of such a factor in 1974,3 the quest to find such molecules is ongoing and is in line with the ever-growing need for definitive treatments that eradicate pretransplant and post-transplant FSGS. Savin et al. are credited for demonstrating that serum and plasma from patients with FSGS induce kidney filter permeability changes.4 Savin et al. also proposed that the FSGS factor is a protein with a molecular mass between 20 and 50 kD.4 Studies in our laboratory showed that suPAR is a permeability factor in native and recurrent FSGS.5 suPAR is a multidomain protein that is heavily glycosylated and precisely fits the suggested size range expected for the putative circulating factor. The proposed pathogenic role of suPAR is based on three observations: (1) variants of suPAR produced proteinuria in several mouse models, (2) total levels of glycosylated suPAR were elevated in the majority of patients with FSGS, and (3) suPAR can bind to and activate podocyte β3 integrins allowing for activation of Rac-1 and podocyte motility (a surrogate for podocyte foot process effacement).

Several follow-up studies confirmed increased total suPAR serum levels in FSGS, which were validated in patients with normal or mildly reduced renal function compared with other glomerular diseases5 but not necessarily in advanced renal failure in which suPAR accumulation may occur.6 Furthermore, it should be noted that in certain recent studies, serum suPAR did not differentiate FSGS from other glomerulopathies in the setting of relatively preserved renal function.7 However, healthy control patients in this study also had elevated suPAR levels at baseline, which is atypical and might be a confounder of the cohort. Nevertheless, these discrepancies around single-value suPAR testing in different cohorts with the current ELISA imposes an obstacle for bulk suPAR measurements in clinical practice.6 Development of a more specific FSGS-suPAR ELISA and/or cell-based testing systems that can detect different forms of suPAR with strong podocyte integrin activation capacities is needed.8

suPAR is the cleaved product of the cell-bound urokinase-type plasminogen activator receptor (uPAR), a multifunctional receptor that binds both the protease urokinase and the adhesion protein vitronectin.9 uPAR also functionally and physically interacts with integrins both directly and indirectly through signaling, with the latter in some circumstances due to uPAR vitronectin binding.10 suPAR is normally heavily glycosylated and can be cleaved into various shorter molecules that determine variability in suPAR’s cell-surface function and stability in body fluids, including serum. Cathelin et al.

---

See related article, “A Patient-Centered Vision of Care for ESRD: Dialysis as a Bridging Treatment or as a Final Destination?,” on pages 1647–1651.

---


---

See related article, “A Patient-Centered Vision of Care for ESRD: Dialysis as a Bridging Treatment or as a Final Destination?,” on pages 1647–1651.

---


---

See related article, “A Patient-Centered Vision of Care for ESRD: Dialysis as a Bridging Treatment or as a Final Destination?,” on pages 1647–1651.

---
Table 1. Effects of various suPAR types on podocyte integrin activation and kidney filter function

<table>
<thead>
<tr>
<th>suPAR Type</th>
<th>Source</th>
<th>Accession</th>
<th>Recipient</th>
<th>Route</th>
<th>Dose (µg)</th>
<th>Time</th>
<th>Glomerular β3 Integrin Activity</th>
<th>Kidney Phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full length, isoform 1, Drosophila S2 cells</td>
<td>NM_01111</td>
<td>B6 or 129 mice</td>
<td>Intravenous</td>
<td>Up to 100</td>
<td>24 h</td>
<td>Not studied</td>
<td>No proteinuria, no podocyte FP effacement</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Full length, isoform 1, Mouse N50 cells</td>
<td>Q545X5</td>
<td>B6 or 129 mice</td>
<td>Intravenous</td>
<td>Up to 100</td>
<td>24 h</td>
<td>Not studied</td>
<td>No proteinuria, no podocyte FP effacement</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Full length, isoform 1, Mouse N50 cells</td>
<td>Q545X5</td>
<td>uPAR KO mice 129/B6</td>
<td>Intravenous</td>
<td>20</td>
<td>24 h</td>
<td>Increased</td>
<td>Proteinuria</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Endogenous</td>
<td>LPS induced</td>
<td>—</td>
<td>B6 mice</td>
<td>Endogenous</td>
<td>N/A</td>
<td>24 h</td>
<td>Increased</td>
<td>Serum and urinary suPAR increased, proteinuria, podocyte FP effacement</td>
<td>1</td>
</tr>
<tr>
<td>Secreted, isoform 2</td>
<td>Plasmid DNA</td>
<td>BC010309</td>
<td>B6 mice</td>
<td>Intradermal electroporation</td>
<td>80 DNA weekly</td>
<td>1 mo</td>
<td>Increased</td>
<td>FSFS-like changes, proteinuria</td>
<td>1, 11</td>
</tr>
</tbody>
</table>

S2, Schneider 2; KO, knockout; FP, foot process.

suPAR, which is structurally well characterized, 11 and recombinant mouse myeloma protein A (sucPAR), which is produced monoclone and three-domain suPAR, which is produced monoclone.
The removal of all suPAR forms in patients very interesting questions to answer. From a clinical perspective, circ in human FSGS. From a scientific perspective, these will be very interesting questions to answer. From a clinical perspective, the removal of all suPAR forms in patients’ circulation using a specific suPAR-immunoadsorption device may provide an approach in addressing the relevance of suPAR for human FSGS, and, if successful, may suggest a therapeutic consideration in this and potentially other suPAR-mediated disorders.

DISCLOSURES
J.R. has pending or issued patents on novel kidney protective drug therapies. He stands to gain royalties from their commercialization.

REFERENCES

Cytomegalovirus and Anemia: Not Just for Transplant Anymore

Michael E. Seifert*† and Daniel C. Brennan‡
*Division of Pediatric Nephrology, Southern Illinois University School of Medicine, Springfield, Illinois; and ‡Division of Pediatric Nephrology, Department of Pediatrics, and §Renal Division, Department of Medicine, Washington University at St. Louis, St. Louis, Missouri

Cytomegalovirus (CMV) is one of the most important viruses in renal transplantation that causes significant morbidity and mortality, even in the current era of effective prophylaxis and treatment. The CMV syndrome is characterized by fever, malaise, and transplant dysfunction that manifests as AKI, leukopenia, monocytopoiesis, and anemia. Less than 20 years ago, in the absence of effective prophylactic or treatment agents, immunosuppression reduction was the only treatment and was commonly associated with reduction of death and/or transplant failure. The introduction of effective antiviral medications, such as

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Daniel C. Brennan, Renal Division, Department of Medicine, Washington University 660 S. Euclid Ave., Campus Box 8208, St. Louis, MO 63110. Email: dbrennan@dom.wustl.edu

Copyright © 2014 by the American Society of Nephrology