FSGS is a podocyte-derived glomerular disease characterized by marked proteinuria, often coupled with steroid resistance, hypertension, and high probability for progression to renal failure. It is a heterogeneous disorder that can present as a primary disorder of unknown etiology. A number of genetic mutations in various proteins have been linked to the development of FSGS. Finally, the glomerulopathy can represent an adaptive response that is secondary to a variety of insults such as HIV infection, obesity, or reduced renal mass (1). Moreover, the disease recurs in approximately 30% of patients who receive a kidney transplant. Recent studies have shown that the disease recurs in approximately 30% of patients who receive a kidney transplant (1). Moreover, the disease recurs in approximately 30% of patients who receive a kidney transplant (1)

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The term permeability refers to the effects of the factor causing leakiness of the filter which can occur before and after kidney transplantation. Rodents injected with whole or fractionated serum from patients with recurrent FSGS develop proteinuria (3). Sera from patients with FSGS increase albumin permeability in isolated glomeruli and transient nephrotic syndrome has been transmitted to a newborn from a mother with FSGS [reviewed by Sharma et al. (3)]. The presence of permeability factors has provided the rationale to treat FSGS with plasmapheresis (3). Current candidate molecules are cardiotrophin-like cytokine-1 (which was proposed as a putative FSGS permeability factor), heparin, and vascular endothelial growth factor [reviewed by McCarthy et al. (4)]. Studies from our laboratory suggest that the permeability factor in both native and recurrent FSGS is suPAR.

The identification of suPAR as a FSGS factor might appear counterintuitive to some because suPAR levels are elevated in other diseases, including cancer and infection, that do not routinely present with proteinuria. In addition, some patients present with normal suPAR serum levels and still develop recurrent FSGS (5,6).

suPAR is the cleaved molecule derived from Urokinase-type plasminogen activator receptor (uPAR), which is a glycosyl-phosphatidylinositol anchored membrane protein present on multiple cells, including podocytes. Both uPAR and suPAR activate αvβ3 integrin signaling (6,7). Using multiple animal models, we showed that acute induction of suPAR in uPAR null mice as well as chronic suPAR overexpression of the suPAR variant (GenBank accession number BC010309) in wild-type mice caused features of FSGS such as foot process effacement, proteinuria, and segmental lesions, all of which could be ameliorated with the addition of a uPAR-specific Ab or by expression of suPAR deficient in integrin β3 binding (6).

Using a commercially available ELISA assay kit, we demonstrated that suPAR levels were increased in two thirds of pediatric and adult patients with biopsy-proven FSGS, including both native and recurrent FSGS cases (n=78) (6). We confirmed these findings in patients with FSGS from two well characterized cohorts: the FSGS Clinical Trial (FSGS CT) (n=70, pediatric and adult patients, eGFR >40 ml/min per 1.73 m²) and the PodoNet European FSGS consortium (n=94, pediatric patients, normal eGFR) (8). Using 3 ng/ml as a cut-off value, we demonstrated that suPAR levels were elevated in 84% and 55% of patients in the two cohorts, respectively. Importantly, the elevation of suPAR in these FSGS patients was not related to inflammation because concurrent C-reactive protein (CRP) levels were not elevated. Huang et al. also showed elevation of suPAR in the majority of serum samples from adult patients with primary FSGS in a cohort from Beijing (9). Most recently, Franco Palacios et al. suggested the use of urinary suPAR as a pretransplantation biomarker for recurrent FSGS (10).

The hypothesis that circulating suPAR drives the disease in a subset of FSGS is directly challenged by Bock et al. (2) in this issue of CjASN. They report that suPAR levels were not significantly different in children with primary FSGS (n=20), non-FSGS glomerular disease (n=240), nonglomerular CKD (n=26), and healthy controls (n=29). It should be noted that although the authors assert that they performed the first evaluation of suPAR in pediatric patients with FSGS, 42 of the 70 patients enrolled in the FSGS CT were aged <18 years and were included in the random subset selected for assay of plasma suPAR levels. Moreover, the PodoNet cohort included children and adolescents with FSGS (8). However, it is worth exploring potential differences that might explain the disparate
findings. The most obvious question is whether suPAR levels in adults with FSGS who have a later onset of disease are indicative of suPAR-driven FSGS compared with children who have earlier-onset glomerulopathy. It is theoretically possible that the molecular mechanisms that lead to late-onset FSGS are distinct from those that drive early onset of FSGS. This appears to be unlikely on the basis of our findings in the FSGS CT and PodoNet cohorts, which included children and adolescents with FSGS.

The single-center data presented by Bock et al. differ from our larger multicenter studies and those conducted in China. Specifically, there is a much broader range of suPAR levels in all patient subgroups in the Bock report. Whereas Huang et al. report suPAR levels for minimal change disease and membranous nephropathy to be 2050 pg/ml and 2029 pg/ml, respectively, Bock et al. report suPAR levels of 3075 pg/ml for glomerular non-FSGS and 3385 pg/ml for non-glomerular CKD. Both of these values are higher than those for the FSGS patients described by Huang et al. (median 2923 pg/ml). Indeed, several samples in patients with non-FSGS glomerular CKD and patients with nonglomerular CKD exhibited very high suPAR levels (>5000 pg/ml), which were not documented by Huang et al. These high levels of suPAR may reflect systemic inflammation and immune activation. Indeed, suPAR is elevated in HIV (11) and one of the glomerular non-FSGS samples in the Bock series was from a patient with HIV nephropathy. Thus, it would have been valuable if Bock et al. reported the status of inflammation as reflected by CRP levels to verify the specificity of the suPAR measurements as we did in the FSGS CT study.

Another obvious difference between this study and previous reports is the protocol for sample collection. In our studies, peripheral venous blood was drawn into rapid serum tubes, which contain prothrombotic gel to facilitate clotting. After immediate spinning of the sample, we collected serum. In contrast, Bock et al. mainly used plasma collection tubes that contained EDTA or heparin. Moreover, the plasma was obtained in the past and stored for future use. There are no differences between serum or EDTA-plasma suPAR concentrations when whole blood samples are kept for a few hours. However, suPAR is significantly increased when kept for 72 hours at 20°C (12). In the series by Bock et al., timing of specimen collection was not uniform among the patients and occurred at varying time points of the disease course. The latter is important as children with FSGS can have serum suPAR levels that are normal during remission (13). Without delineation of the number of patients in remission, this might explain the lower suPAR values in the FSGS cohort of the study by Bock et al. A few samples were collected from the same patient and presumably those samples were collected as the patient’s nephrotic syndrome status changed. It would be informative to know whether changes in nephrotic syndrome status correlated with changes in suPAR levels. Huang et al. (9) found that plasma suPAR levels decreased significantly in FSGS patients who were in complete remission. In contrast, plasma suPAR levels remained unchanged or even rose in patients with partial remission or treatment failure.

Similarly, patients with a kidney transplant are included in the Bock series. Without detailed information on recurrent disease, it is impossible to assess whether those patients had stable graft function, a lower risk of recurrent FSGS, and predictably lower levels of suPAR. Finally, some of FSGS patients had low-grade proteinuria (Up/e <1), which suggests that they were responsive to their treatments and had low levels of suPAR.

Taking into consideration all of these factors that might explain the discrepancy between the findings of Bock et al. and previous studies, we suggest that measuring suPAR levels with currently available ELISA kits and deploying the result in clinical practice should not be used as a single decisive test in the evaluation of patients with FSGS. Our own unpublished data suggest the existence of additional forms of suPAR that are relevant in FSGS and for which better tests need to be developed. These highly pathogenic forms may be more prevalent and relevant in children with FSGS.

However, if one views all of the available preclinical and clinical information about suPAR in FSGS in perspective, it is reasonable to conclude that suPAR plays a role in the podocytopathy that characterizes FSGS. There is clinical value in using currently available assay kits to measure suPAR levels in FSGS. However, the measurement needs to be done using serum and the result must be viewed in the full clinical context that includes the disease presentation, biopsy findings, results of genetic testing, medication use and response based on the level of proteinuria eGFR status, presence of infection/inflammation, and, if possible, the podocyte integrin activation profile.

The National Institute of Diabetes and Digestive and Kidney Diseases recently solicited applications to establish a large cohort (n=2400) of prevalent patients with primary glomerular disease including FSGS. In the request for applications, suPAR was one of the key mediators singled out as a worthy focus for scientific investigation. We look forward to the creation of this prospective cohort and performance of a well designed clinical investigation to definitively ascertain the role of suPAR as a contributing factor in the development and potential treatment of FSGS and the other primary glomerulopathies. Although these patient cohorts will surely be created, a suPAR removal trial in recurrent FSGS patients is feasible now and may provide the best proof of principle to test the causative nature of suPAR in FSGS.

Disclosures

S.S., C.W., and J.R. have pending patents, and S.S. and J.R. have issued patents regarding novel and anti-proteinuric technologies. They stand to gain royalties from future commercialization.

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