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Circulating factor in FSGS: a black sheep in the suPAR family?

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Sirs

In this edition of *Pediatric Nephrology*, Maas and colleagues summarize recent progress on the role of suPAR in Focal and Segmental Glomerulosclerosis (FSGS) (1)

The observation that total suPAR levels are elevated in the majority of pediatric and adult patients with FSGS as well as in animal models that develop glomerulopathy in response to pathogenic suPAR fragments has sparked innovative research in this important disease with considerable unmet medical need. Indeed, more data have recently been published that evaluated suPAR in FSGS and confirm a link between the circulating molecule in this glomerular disorder.

Why a suPAR idea in FSGS?

A fundamental notion in FSGS is the potential recurrence of disease after renal transplantation. Like FSGS in the native kidney, recurrent FSGS manifests at the level of the podocyte, the presumptive locus of disease in FSGS. Given the rapid onset of recurrent FSGS which can occur within hours after transplantation, a hypothesis was proposed, namely, that a circulating factor was responsible for disease in the allograft. suPAR was noted to be elevated in patients with FSGS in their native kidneys or those with recurrent disease after kidney transplantation (2). This was verified in two additional large follow up cohorts (3). Wei et al documented that 84% of adult and pediatric patients in the FSGS Clinical Trial and 55% of pediatric patients in the PodoNet consortium have elevated suPAR levels (3). Huang and colleagues have also confirmed that the majority of their patients with primary FSGS have increased serum suPAR levels (4).

Which suPAR in FSGS?

Current ELISA tests for suPAR measure total levels of the molecule and may not discriminate well between the isoforms or the variants with post-translational modifications. It is conceivable that the high total suPAR levels measured in FSGS are either a direct measurement of the pathological suPAR molecule that with more specific detection technologies might be measured even higher. In other words, the FSGS-pathogenic suPAR is elevated and represents one or more aberrant molecules among the total suPAR assayed,

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i.e. “the bad versus the conventional suPAR crowd”. Based on published data, certain fragments of suPAR could have stronger podocyte-pathogenic effects than other molecular moieties. For example, total suPAR which can be elevated in inflammation or certain types of cancer as well is not routinely associated with nephrotic-range proteinuria, a common feature of FSGS. While it is likely that all forms of suPAR can bind to $\alpha V\beta 3$ integrin, subsequent activation might vary depending on the specific form of suPAR. In keeping with this hypothesis, Wei et al have shown, that overexpression of D1-D2 suPAR causes a relatively stronger renal phenotype in mice (reference 2, and our unpublished data). This scenario, in which various isoforms of one molecule exert different biological effects, is not unique to suPAR and is a recurrent theme in biology. For example, different splice variants of Vascular Endothelial Growth Factor (VEGF) have distinct biological functions. More refined definition of FSGS-suPAR is likely to yield even better tests to assay this circulating FSGS factor.

Why is suPAR elevated in primary FSGS?

Currently, it is unclear whether suPAR is overproduced or shed at higher levels from the cell membrane into the serum of FSGS patients. There are numerous potential triggers for this and future studies will undoubtedly clarify why and how the circulating suPAR level is elevated in primary FSGS. Modulation of suPAR may represent one example of how a coordinated system that controls glomerular barrier function adjusts an array of serum factors in response to systemic conditions. Perturbations in the regulatory cascade may enable diseases such as primary FSGS to develop if the circulating signal(s) persist(s).

Can the current suPAR test be used in stratifying FSGS patients?

The gold-standard for diagnosing primary and secondary FSGS is a kidney biopsy. However, evaluation of total suPAR serum levels in patients with steady GFR and under non-inflammatory condition (normal CRP level) may be a useful adjunct in the diagnosis of FSGS and enable more accurate risk-stratification with improved clinical management.

Is suPAR the circulating factor?

While suPAR is a circulating factor found in the majority of primary FSGS, it is probably one of several molecules in the serum that act on the glomerulus. The precise contribution of suPAR will require further clinical analysis in prospective studies. Removal of suPAR does not appear to be harmful and doing so may provide a powerful way to test if modification of plasma suPAR levels results in disease modification or resolution of FSGS. We look forward to more investigative work in this area in the hope that better understanding of suPAR will improve outcomes in patients with FSGS and possibly also in other suPAR positive proteinuric disorders.

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