A suPAR circulating factor causes kidney disease

Stuart J Shankland & Martin R Pollak

For many years, investigators have been searching for an elusive circulating factor that could cause the common kidney disease focal segmental glomerulosclerosis (FSGS). The finding that a circulating, soluble form of the urokinase receptor (suPAR) can activate podocyte β_3 integrin, leading to FSGS pathology (pages 952–960), provides new insights into this disease and may have important clinical implications.

The traditional thinking of the mechanisms of glomerular kidney diseases has focused largely on antibody- and cellular-mediated injury and, more recently, intrinsic defects in the structure and function of specialized glomerular epithelial cells called podocytes. FSGS, the commonest pattern of histologic injury seen in adults with nephrotic syndrome in the US, is known to be caused by podocyte damage[1]. The major biological functions of podocytes are to limit the passage of albumin from the circulation into the urine and to maintain overall glomerular integrity. The clinical signatures of podocyte injury include proteinuria and scarring, leading to reduced kidney function.

Until the early 1990s, FSGS was considered either idiopathic (no known cause) or secondary to another kidney insult, such as reflux disease or increased intraglomerular pressures. The field has advanced substantially since then, largely owing to the discoveries that mutations in several proteins that have crucial roles in podocyte structure, function or both can cause FSGS[2]. The identification of a genetic lesion underlying the etiology of an individual's disease can guide the decision to provide or withhold specific forms of therapy[3]. For example, people with causal mutations in *TRPC6* or *NPHS2* do not respond well to immunosuppressive therapies, but, when they receive kidney transplants, disease does not usually recur.

The clinical observations that FSGS frequently develops as a *de novo* disease in transplanted kidneys and can occur immediately after transplant has lead to the speculation that there may be causative circulating factors[4]. However, this factor has remained elusive to investigators since the discovery that something in the plasma of many people with FSGS increases the passage of albumin in isolated glomeruli[3,5]. Thus, in light of previous cumbersome and unsuccessful efforts to identify the circulating factors responsible for FSGS, new findings by Wei *et al.*[6] in this issue of *Nature Medicine* represent an important advance in the FSGS field—the existence of a circulating permeability factor linked to the development of FSGS in humans and mice, suPAR[6]. These findings add substantially to our growing understanding of the etiologies and mechanisms of glomerular injury and may have implications for the clinical management of kidney disease.

Wei *et al.*[6] identified that elevated levels of suPAR were present in the plasma of two-thirds of a sample of people with FSGS, suggesting that suPAR could be the factor responsible for the disease. High blood levels of suPAR were predictive of FSGS recurrence in transplanted kidneys, and lowering the levels of suPAR by plasmapharesis, a common clinical intervention for recurrent FSGS, led to disease remission.

How does a factor circulating in the plasma injure podocytes and lead to FSGS development? Building on their previous work demonstrating that urokinase receptor (uPAR) is required for activation of β_3 integrin signaling within the kidney podocyte[7], Wei *et al.*[6] showed that suPAR also binds and activates this protein. β_3 integrin is one of the main proteins that anchors podocytes to the underlying glomerular basement membrane. Increased podocyte β_3 integrin activation leads to accelerated podocyte foot process dynamics (**Fig. 1**), which dysregulates the shape and

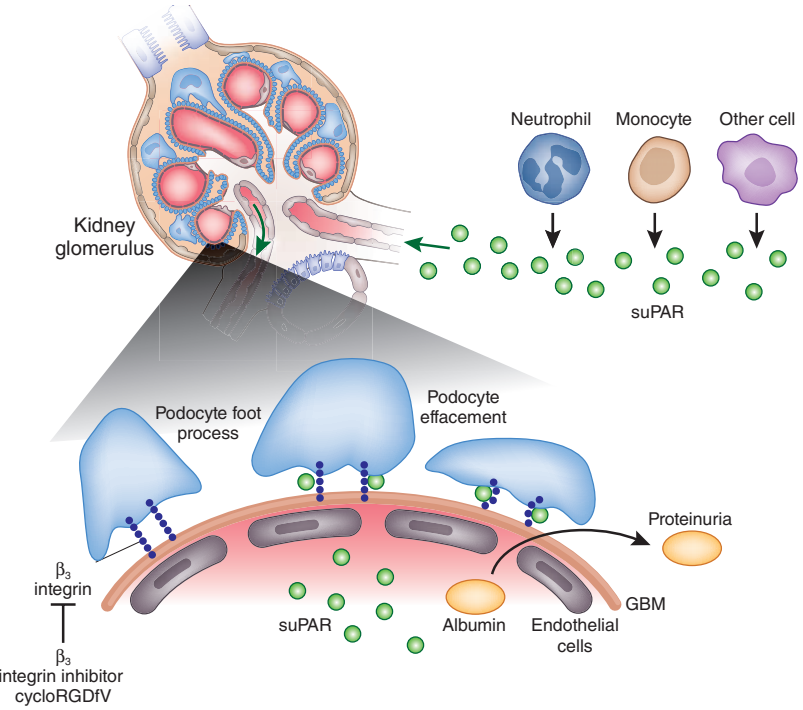

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Figure 1 suPAR is a circulating factor that causes FSGS. Wei *et al.*[6] show that increased levels of the circulating permeability factor suPAR are found in the plasma of people with FSGS and provide mechanistic insights into how increased suPAR can lead to FSGS pathology. They suggest that suPAR is produced by neutrophils, monocytes and perhaps other cells, such as T cells, although the source of suPAR is still to be determined. suPAR enters the kidney glomerulus and binds and activates β_3 integrin, one of the major proteins anchoring podocytes to the underlying glomerular basement membrane (GBM). Increased plasma levels of suPAR lead to increased β_3 integrin activation, thus leading to podocyte dysfunction and effacement and proteinuria characteristic of FSGS.

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function of the kidney filter—the glomerulus—characteristic of what happens in FSGS.

Wei *et al.*[6] provide several lines of evidence to support the role of suPAR as a biologically active circulating factor. These include showing that increasing suPAR levels in mice induces podocyte abnormalities similar to those seen in human FSGS, reducing suPAR levels in individuals with recurrent FSGS using plasmapharesis reduces disease and blocking suPAR actions with a monoclonal antibody improves kidney morphology in mice. Overall, one might expect that inhibiting the suPAR-integrin signaling cascade might therefore afford protection from FSGS.

The data of Wei *et al.*[6] are paradigm shifting for our understanding of the pathogenesis of FSGS. Like all major breakthroughs, this study raises many questions, and, until further data become available, one can only speculate what the answers may be. What is the source of increased suPAR? Wei *et al.*[6] suggest that neutrophils and monocytes may be responsible, but another possibility is circulating T cells, as there is an association between systemic T cell activation and proteinuria. Determining the answer to this question is important, as limiting the source of increased suPAR would be an ideal therapeutic strategy.

The identification of biomarkers is crucial for the diagnosis and monitoring of FSGS. Although the current study shows an association between increased suPAR abundance and disease, we need to better understand what levels of suPAR can be considered 'diagnostic' and what levels we should aim for when using plasmapheresis as therapy. One can easily envision using an ELISA for testing people with FSGS. As with making a genetic diagnosis in some subsets of individuals with FSGS, determination of suPAR abundance in other subsets may prove to be helpful in guiding therapy choices.

It is intriguing that not all people with idiopathic FSGS have increased suPAR levels. This is further confirmation that FSGS is not a disease but rather a form of kidney injury that can result from many primary insults. Some of these may be genetic defects, others may be responses to circulating factors and others might represent responses to common insults such as reduced nephron mass, diabetes and hypertension. In some of the cases of idiopathic FSGS, other yet-to-be identified circulating factors may be involved. Genetic variation in the circulating apolipoprotein ApoL1 predisposes to FSGS in African Americans, although the underlying mechanisms are unknown[8,9].

Do other FSGS circulating factors still await identification? The probable answer is yes, based in part on recent observations that podocyte-secreted angiopoietin-like 4 and vascular endothelial growth factor can mediate other forms of proteinuric glomerular injury such as minimal change disease, suggesting the existence of additional extracellular factors that can operate via autocrine and paracrine mechanisms[10,11]. Despite the future studies that need to be performed to resolve these issues, the work of Wei *et al.*[6] provides the hope and promise of improved diagnostics and perhaps the development of new therapies for people with FSGS.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Killing the messenger to maintain control of HIV

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Certain human leukocyte antigen (HLA) alleles are associated with vigorous human immunodeficiency virus (HIV)-specific CD8$^+$ T cell responses and good clinical outcomes. A new study suggests that CD8$^+$ T cell–mediated killing of regulatory CD4$^+$ T cells may partially explain how people with these protective alleles control HIV-1 replication (pages 989–995).

HIV-1 infection usually results in progressive depletion of CD4$^+$ T cells and consequent immunosuppression. However, in a small group of HIV-infected individuals known as HIV controllers, elite controllers, elite suppressors or long-term nonprogressors (LTNPs), viral replication is suppressed to the point where the level of viremia is below the limit of detection of clinical assays[1]. The mechanisms responsible for this remarkable control are not fully understood, but many studies have shown that the *HLA-B*57* and *HLA-B*27* alleles are overrepresented in LNTPs[1]. Furthermore, in a recent large genome-wide association study (GWAS), the single nucleotide polymorphisms (SNPs) most associated with control of viral replication in LTNPs were related to these alleles and other HLA class I alleles[2]. HLA class I molecules on infected cells present antigen to CD8$^+$ T cells, and there is growing evidence that HIV-1–specific CD8$^+$ T cells in people with protective HLA alleles are very effective at controlling viral replication *in vitro*[3–6]. However, it is still unclear why certain HLA alleles are more closely associated with effective HIV-specific CD8$^+$ T cell responses and virologic control than others.

In this issue of *Nature Medicine*, Elahi *et al.*[7] provide new insights into this phenomenon of elite HIV control. They focus on regulatory T cells (T_{reg} cells), a subset of CD4$^+$ T cells that are involved in modulating the immune system by inhibiting effector T cell responses, thereby preventing chronic inflammation. Imbalances in T_{reg} cell function have been implicated in the pathogenesis of some autoimmune diseases, and the role of these cells in HIV-1 infection is of particular interest because, as CD4$^+$ T cells, they can be infected by the virus[8,9] and are depleted to an extent in primary HIV-1 infection[10]. T_{reg} cells express galectin-9, which is a ligand for Tim-3, an inhibitory molecule found on effector T cells. The authors show that HIV-specific CD8$^+$ T cells that recognize antigens presented (or restricted) by protective HLA alleles are much more resistant to suppression by T_{reg} cells than CD8$^+$ T cells that recognize antigens presented by other HLA alleles[7] (**Fig. 1**). This may be partly because HLA-B*27– or

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