Published in final edited form as:

Nat Rev Nephrol. 2017 May ; 13(5): 263–264. doi:10.1038/nrneph.2017.29.

A suPAR kidney connection found in the bone marrow

Lorenzo Gallon and

Northwestern University Feinberg School of Medicine, Division of Nephrology & Hypertension,
303 E. Superior St., Chicago, Illinois 60611, USA

Susan E. Quaggin

Northwestern University Feinberg School of Medicine, Division of Nephrology & Hypertension,
303 E. Superior St., Chicago, Illinois 60611, USA

Abstract

A population of immature myeloid cells in the bone marrow can transfer proteinuric kidney disease from affected to unaffected mice. This new finding highlights a possible central role of bone marrow as the source of the circulating factor(s) that lead to recurrent focal segmental glomerulosclerosis and potentially other kidney diseases.

The circulating factor or factors that cause recurrent focal segmental glomerulosclerosis (FSGS) have eluded investigators for decades. Moving towards this goal, Hahm and colleagues have now identified a subpopulation of immature myeloid cells that can transfer kidney disease from proteinuric to healthy mice¹. They propose that factors produced by the bone marrow, including soluble urokinase plasminogen activator receptor (suPAR), mediate podocyte injury.

Primary recurrent FSGS is a devastating disease of unclear pathogenesis characterized by proteinuria and typical morphologic changes within the glomerulus, including effacement of podocyte foot processes. Clinical observations and various ‘experiments of nature’ strongly support the presence of a circulating factor or factors that can produce rapid and profound podocyte effacement in FSGS^{2–4}. Following renal transplantation, FSGS can recur in a patient shortly or immediately after anastomosis of donor and recipient blood vessels. Remarkably, transplantation of a kidney allograft from a recipient with biopsy-proven recurrent FSGS into a patient with diabetes led to complete resolution of podocyte effacement and proteinuria³. These clinical observations provide strong support for the existence of a circulating factor in a subset of patients with FSGS who relapse rapidly after kidney transplantation.

Numerous inciting factors in recurrent FSGS have been proposed, including suPAR and cardiotrophin-like cytokine-1 (REF. 4). Despite evidence from rodent models and studies showing increased levels of suPAR in patients with recurrent FSGS, reproducibility of findings of elevated suPAR in these patients has not been universal^{5–9}. More recently, suPAR

Correspondence to S.E.Q. quaggin@northwestern.edu.

Competing interests statement

L.G. is a consultant for Alexion. S.E.Q. owns stock in and is a director of Mannin Research.

was identified as an early predictive marker for the development of chronic kidney disease (CKD)¹⁰. In this observational study performed in two disparate cohorts with cardiovascular disease, increased levels of suPAR at baseline correlated with greater loss of estimated glomerular filtration rate during follow-up. Based on these findings, the researchers hypothesized that suPAR may be a key regulator of podocyte health in a variety of renal diseases.

In their study, Hahm and co-workers performed a series of sophisticated experiments showing that bone-marrow-derived cells transferred from proteinuric mice are sufficient to produce proteinuria in wild-type mice, and are a major source of suPAR production in mouse models¹. Using a variety of approaches, including irradiation and bone marrow transplantation, they identified an expanded subpopulation of immature myeloid cells defined by low expression of the molecular markers, Gr-1 and Sca-1 (Gr-1^{lo}Sca-1^{lo}), in the marrow of mice with lipopolysaccharide (LPS)-induced podocyte injury and protein-uria. When stimulated by LPS, transplanted bone marrow cells from wild-type mice, but not from uPAR-deficient mice, could transfer susceptibility to kidney disease, characterized by podocyte foot process effacement and albuminuria, to a healthy mouse. The levels of Sca-1^{lo}Gr-1^{lo} cells in the bone marrow were also increased in other kidney disease models, including diabetic nephropathy, transforming growth factor β -mediated renal fibrosis, and nephrotoxic-serum-induced inflammatory glomerulonephritis. By contrast, direct injury to podocytes via specific activation of Rac1 GTPase did not result in expansion of this myeloid cell population.

What might these seemingly disparate diseases have in common? Hahm and colleagues suggest that expansion of immature myeloid cells that express uPAR on their surface leads to increased levels of circulating suPAR, which may be an important systemic factor leading to podocyte injury (FIG. 1). In keeping with this hypothesis, they showed that the levels of circulating suPAR are indeed increased in all of the models studied, and that bone marrow from uPAR-knockout mice is not able to transfer kidney disease. A previous study from the same research group reported that activation of β 3 integrin on the surface of podocytes leads to cell injury in the presence of elevated suPAR levels⁵. The current study did not report data on integrin activation in the kidney disease models, and this hypothesis would be interesting to investigate in future studies.

Translating the results from mouse models to a mechanism in patients is not straightforward. A challenge faced by Hahm *et al.* is the absence of expression of Sca-1 and Gr-1 in human myeloid cells, making it impossible to determine if the myeloid subpopulation identified in mice also has a role in human diseases. As a first step to overcome this obstacle, the researchers performed xenograft experiments using human CD34⁺ haematopoietic stem progenitor cells. Nude mice that received CD34⁺ cells from patients with recurrent FSGS, but not those that received CD34⁺ cells from a healthy individual, developed proteinuria — albeit very mild. The patient CD34⁺ cells stimulated expansion of Sca-1^{lo}Gr-1^{lo} immature myeloid cells in the murine bone marrow, suggesting that a similar mechanism to that found in mice may have a role in human FSGS. The possibility exists that CD34⁺ cells from patients with recurrent FSGS produce a unique set of cytokines that promote expansion of

Gr-1⁺ immature myeloid progenitor cells within the bone marrow, but further studies are needed to confirm this hypothesis.

An important question remains: what is the initiating factor (the LPS equivalent) in patients with recurrent FSGS? This chronic disease can relapse many years after kidney transplantation and some patients have multiple recurrences with associated graft failures. These relapses suggest that if bone-marrow-derived myeloid cells are responsible for FSGS, they must somehow remain expanded over the long-term. As the LPS model is an acute renal injury, it would be interesting to know for how long the population of immature myeloid cells remains expanded after stimulation, and if these cells are still able to transfer kidney disease in the mouse model at later time points. If this population is short-lived, other mechanisms will need to be identified to explain FSGS recurrence in the long-term. In addition, efforts to identify the 'responsible' cell and the mechanism by which it becomes stimulated in individual patients are important as they might pave the way to identification of novel treatments.

Hahm *et al.*'s study highlights a possible central role of bone marrow cells and derived factors in the pathogenesis of recurrent FSGS and perhaps other kidney diseases. Although additional studies are needed to determine if suPAR is the causative FSGS factor produced by immature dysfunctional myeloid cells, the new findings represent an important advance in our understanding of the pathogenesis of these diseases and identify cells within the bone marrow as potential therapeutic targets.

References

1. Hahm E, et al. Bone marrow-derived immature myeloid cells are a main source of circulating suPAR contributing to proteinuric kidney disease. *Nat Med.* 23:100–106.2017; [PubMed: 27941791]
2. Savin VJ, et al. Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. *N Engl J Med.* 334:878–883.1996; [PubMed: 8596570]
3. Gallon L, Leventhal J, Skaro A, Kanwar Y, Alvarado A. Resolution of recurrent focal segmental glomerulosclerosis after retransplantation. *N Engl J Med.* 366:1648–1649.2012; [PubMed: 22533598]
4. Fogo AB. Causes and pathogenesis of focal segmental glomerulosclerosis. *Nat Rev Nephrol.* 11:76–87.2015; [PubMed: 25447132]
5. Wei C, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med.* 17:952–960.2011; [PubMed: 21804539]
6. Cathelin D, et al. Administration of recombinant soluble urokinase receptor per se is not sufficient to induce podocyte alterations and proteinuria in mice. *J Am Soc Nephrol.* 25:1662–1668.2014; [PubMed: 24790179]
7. Sinha A, et al. Serum-soluble urokinase receptor levels do not distinguish focal segmental glomerulosclerosis from other causes of nephrotic syndrome in children. *Kidney Int.* 85:649–658.2014; [PubMed: 24429405]
8. Meijers B, et al. The soluble urokinase receptor is not a clinical marker for focal segmental glomerulosclerosis. *Kidney Int.* 85:636–640.2014; [PubMed: 24402090]
9. Bock ME, Price HE, Gallon L, Langman CB. Serum soluble urokinase-type plasminogen activator receptor levels and idiopathic FSGS in children: a single-center report. *Clin J Am Soc Nephrol.* 8:1304–1311.2013; [PubMed: 23620441]
10. Hayek SS, et al. Soluble urokinase receptor and chronic kidney disease. *N Engl J Med.* 373:1916–1925.2015; [PubMed: 26539835]

Figure 1. Hypothetical model for the role of bone-marrow derived factors in the pathogenesis of focal segmental glomerulosclerosis and other proteinuric renal diseases

Initiating factors can stimulate the expansion of Gr-1^{lo} immature myeloid cells, which produce soluble urokinase plasminogen activator receptor (suPAR) and other factors. Increased levels of circulating suPAR are proposed to promote podocyte remodelling, foot-process effacement and proteinuria, via β 3-integrin signalling. Modified with permission from Macmillan Publishers Limited © Shankland S. J. & Jefferson, J. A. *Nat. Med.* 23, 13–14 (2017).