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Experimental concerns regarding suPAR-related proteinuria

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We are writing in response to the News & Views commentary by L. Gallon and S. Quaggin (Glomerular disease: a suPAR kidney connection found in the bone marrow. *Nat Rev Nephrol.* **13**, 263–264; 2017)[1], which discusses a recent study by Hahm *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)[2]. We wish to highlight a number of points in response to their commentary.

First, Gallon and Quaggin write that "bone-marrow-derived cells transferred from proteinuric mice are sufficient to produce proteinuria in wild-type mice". However, the study of Hahm and colleagues demonstrates the occurrence of proteinuria after bone marrow transplantation in *Plaur*$^{-/-}$ mice only[1,2]. Previous studies by ourselves and others suggest that soluble urokinase plasminogen activator receptor (suPAR) might induce proteinuria in *Plaur*$^{-/-}$ mice but not in wild-type animals[3–5]. The reason for this discrepancy is unclear, but the possibility exists that lack of uPAR might induce constitutive and secondary changes, such as overexpression of β3 integrins on podocyte membranes, that lead to an explosive response to exogenous suPAR.

Second, we agree that it would be very interesting to show activation of suPAR and β3 integrin in suPAR-supplemented *Plaur*$^{-/-}$ mice. Such a goal presents difficulties, however, because the monoclonal antibody (AP5) used in previous studies by the same research group as the recent study by Hahm *et al.* was designed to detect activation of human β3 integrin[6,7]. This antibody recognizes the human β3 integrin GPINCT sequence, which is absent in mouse β3 integrin[8].

Third, paroxysmal nocturnal haemoglobinuria (PNH) is a rare acquired bone marrow disorder in which suPAR overproduction and/or accumulation is linked to the dysfunction of glycosylphosphatidylinositol anchoring, leading to very high levels of circulating suPAR[9–11]. As the disease occurs in haematopoietic stem cells (at least in early myeloid progenitor cells), PNH might represent the human counterpart of experimental conditions discussed in the commentary (that is, the effects of high levels of circulating suPAR coming from haematopoietic sources). Researchers interested in suPAR-related proteinuria are, therefore, faced with the following conundrum: why do patients with PNH, who do have similar, naturally occurring, very high levels of circulating suPAR, not demonstrate proteinuria or any podocytic disease? We believe that the facts mentioned above should be kept in mind so that the comments by Gallon and Quaggin can be put into perspective.

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Competing interests statement
The authors declare no competing interests.