Accelerated suPAR mediated kidney disease in the solitary functioning kidney

Xuexiang Wang, Sudhini Yashwanth, Shuangxin Liu, Jing Li, Ke Zhu, Beata Samelko, Michael Garrett, Changli Wei and Jochen Reiser

Rush University Medical Center, Department of Medicine

Objective: Kidney mass and number of functioning nephrons are determinants of renal long-term health. Single functioning kidney (SFK) is a rare disease (1:1500 at birth) resulting in early onset chronic kidney disease (CKD) in over 50% of those affected. Similarly, kidney donors may have an increased risk for future CKD. The underlying mechanisms are not clear. The soluble urokinase receptor (suPAR) is an immune-derived circulating factor implicated in pathogenesis and prediction of CKD incidence and progression. We **hypothesized** that SFK condition could be more sensitive to increased suPAR levels and examined three different rodent models of SFK.

Methods: Uninephrectomy and sham surgeries were performed on C57B/6 mice, suPAR transgenic/knockout models or littermate controls. The minipumps with three different concentrations of LPS were implanted subcutaneously. Proteinuria and suPAR were followed weekly for 4 weeks. In congenital SKF rat model (HSRA), the recombinant human suPAR protein was injected intravenously into HSRA single kidney rats (HSRA-S) and two-kidney controls (HSRA-C). Proteinuria was measured 24 hours after. The activity of beta3 integrin in podocytes was assessed.

Results: Urinary protein slowly increased in nephrectomized suPAR transgenic mice, while the littermate controls with nephrectomy showed no change. LPS infusion resulted in increased level of serum and urine suPAR in C57B/6 mice. Interestingly, SFK models had a higher serum suPAR and substantially higher proteinuria, compared to the sham two-kidney groups. In contrast, uPAR deficient SFK mice were protected from LPS induced proteinuria. HSRA-S rats revealed an increase of proteinuria compared to HSRA-C after the recombinant human suPAR injection. Moreover, the activity of the suPAR receptor beta3 integrin was significantly increased in the kidney of HSRA-S rats following administration of suPAR.

Conclusions: In conclusion, increased circulating suPAR levels, either induced by LPS, or from suPAR transgenic models or extrinsically injected, induce proteinuria in uninephrectomized mice or congenital SFK rats, when compared to their two-kidney controls. These findings suggest an important role of suPAR in SFK kidney, possibly in kidney donors and support other findings on increased suPAR levels causing renal function decline. Monitoring circulating suPAR levels might be important in understanding the pathogenesis and risk-control for patients who are born with or remain having only one functional kidney.