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CHRONIC KIDNEY DISEASE

Role of suPAR in *APOL1*-associated kidney disease

> suPAR is … a modifiable target to combat renal disease in carriers of *APOL1* risk alleles

Researchers report that soluble urokinase plasminogen activator receptor (suPAR) synergizes with the apolipoprotein L1 (APOL1) risk variants G1 and G2 to activate $\alpha_v\beta_3$ integrin on podocytes. "Our findings provide an epidemiological and mechanistic explanation for renal disease in *APOL1* risk carriers," says lead researcher Jochen Reiser.

In two separate cohorts of African Americans (comprising >1,000 individuals), Reiser and colleagues show that suPAR levels modify the association between *APOL1* genotype and annual decline in estimated glomerular filtration rate. "*APOL1* high-risk carriers had an attenuated decline in kidney function with lower levels, and increased decline with higher levels of plasma suPAR," explains Reiser.

Using surface plasmon resonance assays, the researchers identified high-affinity interactions between suPAR, APOL1 and $\alpha_v\beta_3$ integrin. All three APOL1 variant proteins bound suPAR with very high affinity; however, the risk variants APOL1 G1 and G2 bound suPAR-activated $\alpha_v\beta_3$ integrin with substantially higher affinity than did the reference variant APOL1 G0.

In human podocyte cultures, addition of suPAR plus APOL1 G1 or G2, but not of suPAR plus APOL1 G0, resulted in substantial activation of β_3 integrin and cell detachment, suggesting toxic effects on podocytes. Similarly in wild-type mice, but not in mice deficient in *Plaur*, which encodes uPAR and suPAR, expression of human APOL1 G1 or G2, but not of APOL1 G0, resulted in β_3 integrin activation, podocyte foot-process effacement and substantial proteinuria.

The researchers conclude that synergy of circulating suPAR and APOL1 G1 or G2 on $\alpha_v\beta_3$ integrin activation is a mechanism of chronic kidney disease. "SuPAR activates $\alpha_v\beta_3$ integrin to enable binding of APOL1, but only binding of the risk variants produces pathological integrin activation beyond that which is achieved by suPAR alone," says Reiser. "SuPAR is therefore a modifiable target to combat renal disease in carriers of *APOL1* risk alleles."

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ORIGINAL ARTICLE Hayek, S. S. *et al.* A tripartite complex of suPAR, APOL1 risk variants and $\alpha_v\beta_3$ integrin on podocytes mediates chronic kidney disease. *Nat. Med.* http://dx.doi.org/10.1038/nm.4362 (2017)