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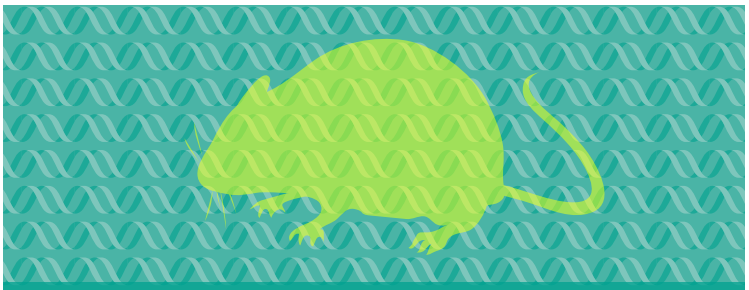

GENETICS

APOL1 risk variants drive kidney disease in mice

> These results offer new therapeutic possibilities for APOL1-associated kidney disease

The G1 and G2 variants of the apolipoprotein L1 gene (*APOL1*) are strongly associated with kidney disease; however, evidence of causality and understanding of the potential underlying mechanisms are lacking. The generation of a new mouse model with inducible, podocyte-specific expression of *APOL1* reference and risk alleles now demonstrates that the G1 and G2 variants are not only associated with disease, but are also likely to cause renal pathology through mechanisms that involve disruption of intracellular vesicle trafficking and autophagy, leading to inflammatory-mediated podocyte death. These findings potentially open new opportunities for therapeutic targeting of *APOL1*-associated kidney disease.

The G1 and G2 variants of *APOL1* are nearly universally found in individuals of recent African ancestry and account for much of the higher risk of nondiabetic kidney disease in African Americans compared to that of European Americans. Studies of causality have been hampered, however, by the fact that APOL1 is present only in humans and some primates, and the finding that the variants are associated with a spectrum of renal phenotypes. To assess whether kidney-specific expression of the risk variants cause kidney disease, Katalin Susztak and colleagues generated mice with podocyte-specific, inducible expression of the *APOL1* reference allele (G0) or each of the risk variants (G1 or G2). They found that podocyte-specific expression of the *APOL1* risk alleles, but not of the G0 allele, caused kidney disease, characterized by albuminuria, azotaemia, glomerulosclerosis and podocyte foot-process effacement. Analysis of the transcriptional changes identified pathways associated with immunity, including genes involved in JAK–STAT and cytokine–cytokine-receptor signalling, and phagosome-related interactions. Expression of the G1 and G2 risk variants in kidney tubules did not result in kidney disease, indicating that the effects are podocyte-specific and not the result of nonspecific toxicity.

To better understand the variation in disease severity associated with *APOL1* variants, the researchers examined the effect of *APOL1* levels on renal function; they observed a strong linear correlation between *APOL1* transcript levels and albuminuria in mice with podocyte-specific expression of the G1 and G2 alleles, but a weaker correlation with no overt proteinuria in mice expressing the G0 allele. Extending these findings to humans, Susztak and colleagues found that *APOL1* transcript levels were significantly higher in glomeruli isolated from biopsy samples of patients with chronic kidney disease compared to levels in glomeruli from control samples.

To investigate the mechanism by which the G1 and G2 alleles induce kidney disease, the researchers first assessed the localization of APOL1 in human kidney tissue samples, showing that APOL1 mostly localizes to the late endosomal compartment within the podocyte. Transfection of HEK293 cells with the G1 and G2 *APOL1* variants led to altered vesicle trafficking and abnormal autophagic flux, which were associated with defective endosome acidification. Similar autophagic defects were identified in human podocytes expressing the risk alleles. "These studies indicate that, in the presence of APOL1 risk variants, there is a defect in autophagosome maturation, which likely results from diminished lysosomal fusion and impaired acidification of the late endocytic compartment, and thus probably leads to reduced autophagy flux," say the researchers. Further experiments indicated that these defects in autophagic flux eventually lead to pyroptosis, an inflammatory form of programmed cell death. Treatment of *APOL1*-transfected HEK293 cells with caspase 1-specific inhibitors reduced APOL1-induced cytotoxicity, supporting a role for pyroptosis in APOL1-induced toxicity. The researchers conclude, "These results offer new therapeutic possibilities for APOL1-associated kidney disease using already approved IL-1 inhibitors or other inflammatory-cell-death inhibitors."

Susan J. Allison

ORIGINAL ARTICLE Beckerman, P. *et al.* Transgenic expression of human *APOL1* risk variants in podocytes induces kidney disease in mice. *Nat. Med.* http://dx.doi.org/10.1038/nm.4287 (2017)