CHRONIC KIDNEY DISEASE

Mechanisms of *APOL1*-associated renal disease

Mutations in *APOL1* are associated with an increased risk of renal disease and are found at a high frequency in people of African ancestry. Two recent studies used transgenic *Drosophila melanogaster* models to investigate the molecular mechanisms that underlie *APOL1*-associated renal disease.

Karl Skorecki and colleagues showed that expression of *APOL1-G1* or *G2* risk variants in *Drosophila* nephrocytes — which are homologous to human podocytes — resulted in the accumulation of an endocytic tracer, followed by nephrocyte loss in older flies. Further investigations in *Saccharomyces cerevisiae* provided evidence that *APOL1* risk alleles impair endosomal trafficking and vacuole acidification.

Similarly, Zhe Han and colleagues found that nephrocyte-specific expression of *APOL1* or *APOL1-G1* in *Drosophila* resulted in increased endocytic activity and reduced organelle acidification, followed by a loss of function, increase in size and premature death of nephrocytes as the flies aged. The phenotype was most severe in flies that expressed *APOL1-G1* and was similar to that of cultured mammalian podocytes that overexpress this risk allele.

“To observe fly renal cell dysfunction as a result of expressing *APOL1* in nephrocytes, and to be able to relate the resulting phenotypes to *APOL1*-associated pathology of human podocytes, is a major advance for the use of *Drosophila* as a biomedical model with clinical relevance,” says Han.

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“The findings also tell us some very important things about *APOL1* protein function. I am confident that genetic screening in *Drosophila* will unveil interaction networks of proteins and pathways with *APOL1* that will significantly advance our understanding of the mechanisms by which *APOL1* causes kidney disease.”

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ORIGINAL ARTICLES Fu, Y. et al. *APOL1-G1* in nephrocytes induces hypertrophy and accelerates cell death. *J. Am. Soc. Nephrol.* <http://dx.doi.org/10.1681/ASN.2016050550> (2016) | Kruzel-Davila, E. et al. *APOL1*-mediated cell injury involves disruption of conserved trafficking processes. *J. Am. Soc. Nephrol.* <http://dx.doi.org/10.1681/ASN.2016050546> (2016)