Hot Off the Press

Matthew Sparks, MD

Assistant Professor, Associate Program Director, Nephrology Fellowship, Director of Medical Student Research, Department of Medicine, Duke University School of Medicine, USA

Podocyte specific APOL1 risk variant overexpression in mice induces proteinuric kidney disease

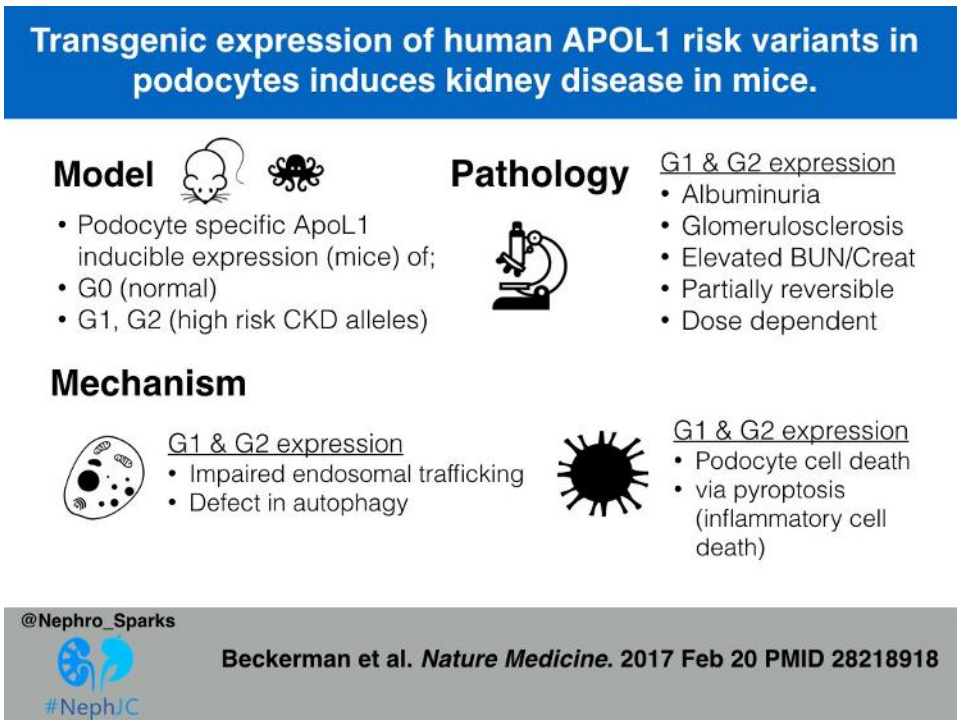
Beckerman *et al.* (2017) *Nature Medicine*

The presence of 2 APOL1 risk alleles (risk alleles termed G1 and G2, with G0 being normal) emerged as a huge story back in 2010 after Genovese et al reported their findings in *Science* that the presence of these risk alleles were associated with FSGS and hypertension attributed ESKD in African Americans. Interestingly, they described how the high risk alleles function as a serum lytic factor for *Trypanosoma brucei rhodesiense*. This is important because this particular subspecies is able to evade lysis from the G0 allele. Since the seminal observation a number of investigations have associated these risk alleles with several kidney diseases in African Americans (HIVAN, FSGS, hypertension associated ESKD, and Lupus).

This paper from Beckerman et al, reported in the journal *Nature Medicine,* examines the effect of APOL1 risk alleles specifically in the podocyte using a mouse model. First, it is important to note that mice and rats do not have APOL1, nor do they have an analog. Therefore, it was necessary to not only overexpress the risk alleles (G1 and G2) but also the normal allele (G0) in order to examine their function in vivo. This group of investigators overexpressed all 3 alleles only in podocytes with a doxycycline inducible system (Nephrin-rtTA).

They report in the supplemental data that nephron specific APOL1 risk allele expression does not induce kidney alterations. After verification of podocyte specific expression they examined the kidney for signs of pathology. After inducing podocyte specific APOL1 transgene expression in adult mice they found a higher amount of albuminuria, glomerulosclerosis, and elevated BUN/Creatinine in G1/G2 mice compared to G0. They also demonstrated that albuminuria was partially reversible after stopping APOL1 G1/2 transgene expression (by withholding doxycycline). The degree of albuminuria also correlated nicely with APOL1 G1/2 expression and not with APOL1 G0. The mechanism of G1/G2 induced kidney disease was linked to impaired podocyte endosomal trafficking. Thus, this defective trafficking results in altered autophagy, and ultimately podocyte cell death via pyroptosis.

These data demonstrate the central role of the podocyte to kidney disease and could provide important avenues targeting these pathways in APOL1 associated kidney disease. To read more about this paper and view the online discussion go to NephJC.



- Matthew Sparks