NEPHROTIC SYNDROME

The *KANK* family in podocyte function

Monogenic mutations in any one of 27 genes account for 30% of cases of steroid-resistant nephrotic syndrome (SRNS), but the cause of disease in the remaining 70% of patients is often unknown. New research has identified mutations in *KANK* family genes as a previously unrecognized cause of nephrotic syndrome. Friedhelm Hildebrandt and colleagues show that *KANK* family members regulate RHO GTPase activity in podocytes and that this activity is required for proper podocyte function. “Our findings confirm the role of RHO-like GTPase signalling in the pathogenesis of human SRNS and point to the possibility of targeting RHO-like GTPase for treatment of this disease,” says Hildebrandt.

To identify additional mutations that cause nephrotic syndrome, Hildebrandt and coworkers used homozygosity mapping and whole-exome sequencing in families with nephrotic syndrome of unknown cause, identifying recessive mutations in *KANK1*, *KANK2* and *KANK4*. “To validate whether *KANK* mutations

cause SRNS, we reproduced the nephrosis phenotypes in *Drosophila* and zebrafish,” explains Hildebrandt. Knockdown of the *KANK* orthologue, *dKank*, in *Drosophila* reduced nephrocyte function. Likewise, knockdown of the *KANK2* orthologue in zebrafish resulted in oedema, proteinuria and histologic changes typical of nephrotic syndrome. Injection of wild-type *KANK2* mRNA partially rescued the oedema phenotype whereas injection of mutated *KANK2* mRNA had no effect.

The researchers also found that *KANK2* interacts with ARHGDI1, a regulator of RHO GTPase that is dysfunctional in some forms of nephrotic syndrome. Knockdown of *KANK2* in cultured podocytes increased active GTP-bound RHOA and decreased podocyte migration, suggesting that *KANKs* regulate RHO GTPase activity and podocyte function.

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