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GLOMERULAR DISEASE

A "DOUBLE HIT" CAN INJURE PODOCYTES

Gain-of-function mutations in the transient receptor potential channel C6 (TRPC6) are associated with familial forms of focal segmental glomerulosclerosis (FSGS). New research by Robert Spurney and colleagues suggests that targeting Gq protein-dependent activation of TRPC6 might be a promising therapeutic strategy to ameliorate glomerular disease.

In previous research, the investigators generated a doxycycline-inducible transgenic mouse line that expresses a constitutively active Gq α-subunit (GqQ>L) specifically in podocytes. These mice did not develop albuminuria or exhibit indicators of kidney injury. In the present study, GqQ>L mice were administered puromycin aminonucleoside (PAN), to determine whether this additional challenge to the podocyte could promote glomerular injury.

"PAN-treated GqQ>L mice developed robust albuminuria, exhibited histologic features of FSGS, and had a decreased number of glomerular podocytes compared to similarly treated wild-type animals," explains Spurney. "Gq induction also stimulated calcineurin activation and an upregulation of *Trpc6* and cyclooxygenase 2." Administration of a calcineurin inhibitor (FK506) attenuated PAN-induced albuminuria, and genetic deletion of *Trpc6* in PAN-treated GqQ>L mice prevented both FSGS and podocyte loss.

In the Akita mouse model of type 1 diabetes, constitutive activation of GqQ>L enhanced albuminuria, mesangial expansion, and increased glomerular basement membrane width, compared with normal mice. On the basis of these data, the researchers propose that the adverse effects of Gq activation could be generalized to other glomerular diseases.

"Our data support the concept that podocyte injury requires a 'second hit', such as activating mutations in *TRPC6,* in some familial forms of FSGS," says Spurney. "An important implication of this possibility is that, while we often study mediators of glomerular damage as individual entities, it is likely that the biological outcome represents the net effect of multiple hits." The researchers now hope to determine whether inhibition of TRPC6 or Gq signalling has a beneficial effect in other glomerular disease processes.

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Original article Wang, L. *et al.* Gq signaling causes glomerular injury by activating TRPC6. *J. Clin. Invest.* doi:10.1172/JCI76767