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GLOMERULAR DISEASE

Saving the podocyte—Notch 2 to the rescue

The neurogenic locus notch homologue (Notch) proteins have wide ranging functions in cell biology, from cell–cell communication to the determination of cell fate. Researchers have now shown that Notch 2 has a role in protecting damaged podocytes from apoptosis, ameliorating the effects of nephropathy in a model of focal segmental glomerulosclerosis (FSGS).

> “...activating the Notch 2 pathway might ... have a protective effect...”

Previous reports had implicated Notch 2 in glomerular disease, but its precise role remained unclear. In this study, researchers administered agonistic Notch 2 antibodies to mice with adriamycin-induced nephropathy, a model of podocyte injury. Activation of the Notch 2 pathway decreased the severity of proteinuria in these animals. Conversely, blockade of Notch 2 with antibodies against its ligand Jagged1 exacerbated proteinuria. These effects were also reflected histologically, with Notch 2 activation leading to less glomerular change, less sclerosis and higher numbers of WT1-positive cells than in the untreated mice with nephropathy.

“Since other renal diseases—such as diabetic nephropathy, IgA nephropathy and lupus nephritis—express podocyte injury, it is possible that activating the Notch 2 pathway might also have a protective effect in these glomerular diseases,” explains investigator Katsuhiko Asanuma.

The researchers also showed that Notch 2 activation likely exerts its protective effects by activating Akt, which ultimately saves damaged podocytes from apoptosis. Akt (also known as protein kinase B) is involved in cellular survival pathways, and in this case phosphorylates and deactivates the proapoptotic protein Bcl2 antagonist of cell death. Inhibition of Akt enhanced the rate of apoptosis in damaged podocytes *in vitro*, and negated the protective effects of Notch 2 agonism.

When examining renal biopsy samples from patients with FSGS, the research team found fewer podocytes and lower expression of Notch 2 than in samples from patients with minimal change disease. Importantly, the number of podocytes with activated Notch 2 positively correlated with the total number of residual podocytes in the glomerulus, reinforcing the purported protective role of Notch 2 in nephropathy.

“We are planning to investigate the protective effect of Notch 2 agonistic antibodies in other renal disease models as a novel strategy for treatment,” Asanuma concludes.

Mina Razzak

Original article Tanaka, E. *et al.* Notch2 activation ameliorates nephrosis. *Nat. Commun.* doi:10.1038/ncomms4296