Nature Reviews Nephrology | Published online 30 Oct 2017; doi:10.1038/nrneph.2017.153

PODOCYTES

ShcA regulates nephrin turnover

> podocyte injury led to upregulation of ShcA and a corresponding decrease in the cell surface expression of nephrin

Nephrin is a core component of the podocyte slit diaphragm and its expression at the cell surface is critical to maintain the glomerular filtration barrier. Now, Nina Jones and colleagues report that the adaptor protein ShcA regulates nephrin endocytosis in podocytes.

"Nephrin mislocalization often accompanies kidney diseases, including focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD) and IgA nephropathy (IgAN)," explains Jones. "Phosphorylation has been implicated in nephrin trafficking, but the binding partner that facilitates these phospho-dependent mechanisms had not been identified."

Using a binding prediction model, the researchers have now identified ShcA as a novel binding partner of phosphorylated nephrin. They show that ShcA is expressed in podocytes and interacts with tyrosine-phosphorylated sites on nephrin via its SH2 domain. "We found that ShcA induces internalization of phosphorylated nephrin and acts in a feedforward mechanism to amplify this signal," says lead author Claire Martin.

In a rat model of MCD, podocyte injury led to upregulation of ShcA and a corresponding decrease in the cell surface expression of nephrin. ShcA was also overexpressed, and colocalized with nephrin, in renal biopsy samples from patients with FSGS or MCD compared with those from healthy individuals. Moreover, analysis of gene expression data showed that *ShcA* is one of the most overexpressed genes in FSGS, MCD and IgAN. "This finding makes ShcA an intriguing lead in the quest for a better understanding of some of the common and distinct pathomechanisms of human diseases," comments Jones.

The researchers conclude that ShcA regulates nephrin turnover at the plasma membrane of podocytes. They suggest that upregulation of ShcA disrupts steady-state recycling of nephrin, potentially leading to slit diaphragm disassembly and proteinuric kidney disease.

Ellen F. Carney

ORIGINAL ARTICLE Martin, C. E. *et al.* ShcA adaptor protein promotes nephrin endocytosis and is upregulated in proteinuric nephropathies. *J. Am. Soc. Nephrol.* http://dx.doi.org/10.1681/ASN.2017030285 (2017)