BASIC RESEARCH

CD151—role in strengthening podocyte–GBM binding

Podocytes adhere tightly to the glomerular basement membrane (GBM) to maintain a functional filtration barrier in the presence of considerable mechanical stress. A new study has revealed an important role for the tetraspanin CD151 in mediating podocyte–GBM binding strength and suggests that dysfunctional CD151 might increase susceptibility to hypertension-induced nephropathy.

Arnoud Sonnenberg and colleagues used immunohistochemistry and an *in situ* proximity ligation assay to show that CD151 and the integrin $\alpha 3$ colocalize in glomerular epithelium and that these proteins interact in podocytes from healthy human kidneys. They then investigated the role of CD151 in $\alpha 3\beta 1$ -mediated adhesion to laminin by generating glomerular epithelial cell lines with and without *Cd151*. Cells lacking *Cd151* adhered weakly to an $\alpha 3\beta 1$ ligand and had reduced tolerance to shear stress compared with cells that expressed *Cd151*. Moreover, the researchers found that the

distribution of $\alpha 3$ varied depending on the presence of *Cd151*. “CD151 forms complexes with the main podocyte adhesion receptor *in vivo* and regulates $\alpha 3\beta 1$ binding to laminin in the GBM, not by converting to a high affinity state, but by changing its localization at the basal plasma membrane”, explains Sonnenberg.

“CD151 ... regulates $\alpha 3\beta 1$ binding to laminin ... by changing its localization at the basal plasma membrane”

Global deletion of *Cd151* does not induce nephropathy in BL6 mice; however, since glomerular epithelial cells that lack *Cd151* have reduced resistance to shear stress, the researchers hypothesized that *Cd151*-knockout mice on a BL6 background might be susceptible to increases in transcapillary filtration pressure. They found that inducing hypertension by unilateral nephrectomy,

administering deoxycorticosterone acetate and replacing drinking water with saline induced nephropathy in *Cd151*-knockout mice but not in control mice. Conversely, treatment of nephropathy-susceptible *Cd151*-knockout FVB mice with the angiotensin-converting-enzyme (ACE) inhibitor enalapril delayed nephropathy and improved median survival by 70%. By contrast, the calcium-channel blocker verapamil had no effect. “If the findings in mice can be translated to humans, it would suggest that patients who suffer from kidney damage due to impaired podocyte adhesion, such as is caused by the absence of CD151, should be given drugs that primarily decrease intraglomerular filtration pressure, such as ACE inhibitors,” states Sonnenberg.

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Original article Sachs, N. *et al.* Blood pressure influences end-stage renal disease of *Cd151* knockout mice. *J. Clin. Invest.* 122, 348–358 (2012)