β-catenin Signaling and Podocyte Dysfunction

Youhua Liu

Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Podocyte dysfunction is one of the major causes of proteinuria that leads to glomerulosclerosis and end stage kidney failure. However, its underlying mechanism remains poorly understood. Studies in our laboratory show that β-catenin signaling plays a critical role in mediating podocyte injury and proteinuria. Wnt and integrin-linked kinase (ILK), major upstream activators of β-catenin, were induced and active β-catenin was upregulated in glomerular podocytes in experimental and human proteinuric kidney diseases. Over-expression of Wnt1 gene in vivo activated glomerular β-catenin and aggravated the adriamycin-initiated nephrin suppression and albuminuria, whereas blockade of Wnt signaling with Dickkopf-1 ameliorated podocyte lesions. Similarly, inhibition of ILK with small molecule inhibitor also prevented podocyte dysfunction and proteinuria. Mice with podocyte-specific knockout of β-catenin were protected against development of albuminuria after injury. Moreover, pharmacologic activation of β-catenin was able to induce albuminuria in wild-type mice, but not in β-catenin knockout littermates. Ectopic expression of Wnt1, ILK or stabilized β-catenin in vitro induced Snail transcription factor and suppressed nephrin expression, leading to podocyte dysfunction. We observed that paricalcitol protected against the development of proteinuria and kidney injury in mouse model of adriamycin nephropathy primarily by inhibiting β-catenin signaling. These studies uncover a cascade of pathogenic pathway and illustrate a pivotal role of hyperactive β-catenin signaling in the pathogenesis of podocyte dysfunction and proteinuria. Targeting this signal pathway may represent a novel strategy for treatment of proteinuric kidney diseases.