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Podocyte integrity in proteinuric kidney diseases: Gone with the Wnt

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Abstract

Podocyte dysfunction/injury is one of the major culprits that result in defective glomerular filtration, leading to proteinuria and glomerulosclerosis. However, its underlying mechanism remains poorly understood. Recent studies in our laboratory have shown that Wnt/β-catenin signaling, a developmental signal cascade that is pivotal for nephron formation and kidney development plays a critical role in mediating podocyte injury and proteinuria. 1) Wnt induction and β-catenin activation are evident in a variety of proteinuric kidney diseases such as focal segmental glomerulosclerosis (FSGS) and diabetic nephropathy both in animal models and in humans. 2) Over-expression of Wnt1 gene *in vivo* activates glomerular β-catenin and aggravates the adriamycin-initiated podocyte injury and albuminuria, whereas blockade of Wnt signaling with Dickkopf-1 and Klotho ameliorates podocyte lesions. 3) Mice with podocyte-specific knockout of β-catenin are protected against development of albuminuria after injury. 4) Targeted inhibition of β-catenin with a novel small molecule inhibitor (ICG-001) also protects podocyes from injury and ameliorates proteinuria *in vivo*. 5) Wnt/β-catenin *in vitro* induces Snail1, PAI-1, MMP-7 and multiple genes of the renin-angiotensin system (RAS), leading to podocyte dysfunction. 6) MMP-7, a major transcriptional target of Wnt/β-catenin, specifically mediates the ecto-domain shedding of nephrin in podocytes both *in vitro* and *in vivo*. Altogether, these studies illustrate a pivotal role of hyperactive Wnt/β-catenin signaling in the pathogenesis of podocyte injury and proteinuria.

Biography

Youhua Liu obtained his Ph.D. in cell biology from the Peking Union Medical College in Beijing, China. After receiving his postdoctoral training at NIH and the University of Pittsburgh, he joined the faculty at Brown University as an Assistant Professor of Medicine. He is currently a Professor of Pathology at the University Of Pittsburgh School Of Medicine. His research is focused on dissecting the cellular and molecular pathways that lead to chronic kidney diseases, and exploring novel strategies for therapeutic intervention.