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Molecular control of podocyte differentiation and maintenance: What can we learn from zebra-fish pronephros?

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Abstract

Proteinuria usually indicates damage to the glomerular filtration barrier. Clinically, proteinuria is the hallmark of chronic kidney disease (CKD) leading to end-stage renal disease and is also an independent risk factor for cardiovascular disease. Glomerular podocytes play a central role in establishing and maintaining the complex cellular architecture of glomeruli. Dysfunction of podocytes contributes to development of CKD. To address the molecular basis of podocyte development and function, we first validated the phenotypic marker for zebra-fish pronephric podocyte injury by assessment of pericardial edema together with loss or decline of podocyte-specific GFP expression driven by the nphs2 promoter. Using this model, we further identified a podocyte-specific enhancer motif present in the nphs2 proximal promoter as well as its binding proteins. This finding allowed us to predict genome-wide a number of genes potentially co-expressed with Nphs2. Podocin encoded by Nphs2 is a key component of the slit diaphragm protein complex and is constitutively expressed in differentiated/mature podocytes. Accordingly, the predicted genes utilizing the same regulatory element as nphs2 are implicated in controlling podocyte differentiation and maintenance. Currently, four genes (Ccnc, Meis2, Ankrd6 and Slc16a9) have shown that their enhancer motifs predicted can drive reporter expression in zebrafish podocytes and their expression is detectable in mouse glomeruli. Ankrd6 is known to be involved in inhibition of Wnt/ß-catenin signaling, coincident with the absence of Wnt signaling in mature podocytes. Knockdown of zebra-fish homolog of Ankrd6 led to defect of glomerular development associated with up-regulation of active ß-catenin. The Wnt-dependent signaling inhibitor IWR suppressed increased Wnt signal activity in zebra-fish. These data suggest that Ankrd6 is required for podocyte terminal differentiation and maturation by silencing Wnt/ß-catenin signaling. Thus zebra-fish provides an excellent avenue towards revealing fundamental signal pathways controlling glomerular development and maintenance.

Biography

Bing He received his MD from Wuhan University School of Medicine, China and PhD from Karolinska Institute, Stockholm, Sweden. He is a senior researcher at Matrix Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institute, Sweden. He has published more than 50 papers in the peer-reviewed scientific journals. His major research interests include molecular genetics of diabetic nephropathy, podocyte biology and molecular control of glomerular development.