해외연수발표

TGF-b-Activated Kinase 1 Is Crucial in Podocyte Differentiation and Glomerular Capillary Formation

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TGF-b-activated kinase 1 (TAK1) is a key intermediate in signal transduction induced by TGF-b or inflammatory cytokines, such as TNF-a and IL-1,which are potent inducers of podocyte injury responses that lead to proteinuria and glomerulosclerosis. Nevertheless, little is known about the physiologic and pathologic roles of TAK1 in podocytes. To examine the in vivo role of TAK1, we generated podocyte-specific Tak1 knockout mice (Nphs2-Cre+:Tak1fx/fx; Tak1Δ/Δ). Targeted deletion of Tak1 in podocytes resulted in perinatal lethality, with approximately 50%of animals dying soon after birth and 90%of animals dying within 1 week of birth. Tak1Δ/Δ mice developed proteinuria from P1 and exhibited delayed glomerulogenesis and reduced expression of Wilms' tumor suppressor 1 and nephrin in podocytes. Compared with Tak1fx/fx mice, Tak1Δ/Δ mice exhibited impaired formation of podocyte foot processes that caused disruption of the podocyte architecture with prominent foot process effacement. Intriguingly, Tak1Δ/Δ mice displayed increased expression of vascular endothelial growth factor within the glomerulus and abnormally enlarged glomerular capillaries. Furthermore, 4- and 7-week-old Tak1Δ/Δ mice with proteinuria had increased collagen deposition in the mesangium and the adjacent tubulointerstitial area. Thus, loss of Tak1 in podocytes is associated with the development of proteinuria and glomerulosclerosis. Taken together, our data show that TAK1 regulates the expression of Wilms' tumor suppressor 1, nephrin, and vascular endothelial growth factor and that TAK1 signaling has a crucial role in podocyte differentiation and attainment of normal glomerular microvasculature during kidney development and glomerular filtration barrier homeostasis.