University of Zurich[UZH]

Zurich Center for Integrative Human Physiology (ZIHP)

ZIHP Special Seminar

Monday, September 25, 2017, 11:00 h
University of Zurich, Irchel
Seminar room Y23 K52

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Deleting the TGF-β Receptor Impairs Proximal Tubule Response to Chronic Injury

TGF-β is arguably the most potent fibrotic factor in chronic kidney disease (CKD); though its effect depends on the targeted cell type and microenvironment. Epithelial TGF-β signaling plays important roles in chronic injury; however, the intrinsic TGF-β´s effect on renal epithelia response to chronic injury is not well studied. To investigate how TGF-β signaling in the proximal tubule (PT), a key target and mediator of CKD, alters the response to chronic kidney injury, we injured mice lacking the TGF-β type II receptor specifically in this epithelial segment. Mice lacking the proximal tubular TGF-β receptor had significantly increased tubular injury and tubulointerstitial fibrosis compared to littermate controls in two different models of CKD. Deleting the TGF-β receptor in PT cells modulated many different growth factor pathways, and RNAseq indicated that Wnt/β-catenin signaling was the pathway most affected by genetic deletion of the type II TGF-β receptor. We validated that deleting the proximal tubular TGF-β receptor impaired β-catenin activity in vitro and in vivo. Genetically restoring β-catenin activity in PT lacking the TGF-β receptor strikingly improved the tubular response to chronic injury. This study demonstrated the role of TGF-β signaling in PT adaptive response to chronic injury, partly through β-catenin activation. Cellular mechanisms underlying this TGF-β´s protective effect are still unknown and will be addressed in future studies.

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