FSP1-specific SMAD2 knockout in renal tubular, endothelial, and interstitial cells reduces fibrosis and epithelial-to-mesenchymal transition in murine STZ-induced diabetic nephropathy.

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Abstract

Extracellular matrix deposition during tubulointerstitial fibrosis (TIF), a central pathological process in patients with diabetic nephropathy (DN), is driven by locally activated, disease-relevant myofibroblasts. Myofibroblasts can arise from various cellular sources, e.g., tubular epithelial cells via a process named epithelial-to-mesenchymal transition (EMT). Transforming growth factor beta 1 (TGF-β1) and its downstream Smad signaling play a critical role in both TIF and EMT. Whereas Smad3 is one central mediator, the role of the other prominently expressed variant, Smad2, is not completely understood. In this study, we sought to analyze the role of renal Smad2 in the development of TIF and EMT during streptozotocin-induced DN by using a fibroblast-specific protein 1 (FSP1)-promotor-driven SMAD2 knockout mouse model with decreased tubular,

endothelial, and interstitial Smad2 expression. In contrast to wild-type diabetic mice, diabetic SMAD2 knockout mice showed the following features: (1) significantly reduced DN and TIF (shown by KIM1 expression; periodic acid Schiff staining; collagen I and III, fibronectin, and connective tissue growth factor deposition); (2) significantly reduced tubular EMT-like changes (e.g., altered Snail1, E-cadherin, matrix metalloproteinase 2, and vimentin deposition); and (3) significantly decreased expression of myofibroblast markers (α-smooth muscle actin, FSP1). As one mechanism for the protection against diabetes-induced TIF and EMT, decreased Smad3 protein levels and, as a possible consequence, reduced TGF-β1 levels were observed in diabetic SMAD2 knockout mice. Our findings thus support the important role of Smad2 for pro-fibrotic TGF-β/Smad3 signaling in experimental DN.

Beteiligte Forschungseinheiten

Mikrobielle Pathogenitätsmechanismen Bernhard Hube Mehr erfahren

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Details

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