Molecular Mechanisms and Therapeutic Implications of TGF-beta/Smads in Kidney Diseases

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It is now well accepted that TGF-β/Smad signaling is a major pathway leading to progressive renal fibrosis, a major pathological feature of CKD. We recently found under hypertensive and diabetic conditions, angiotensin II and advanced glycation end products (AGE) are able to activate the TGF-β/Smad signaling pathway via both TGF-β-dependent and independent mechanisms. Under disease conditions, renal Smad7, an inhibitor of Smad2/3, is lost, which is mediated by Smurf2-dependent ubiquitin proteasome degradation mechanisms. Because Smad7 is also capable of inducing IκBa, an inhibitor of NF-κB, mice lacking Smad7 promote, but overexpressing Smad7 inhibits renal fibrosis and inflammation. Thus, Smad7 acts as a therapeutic agent for kidney diseases, which is validated in a number of experimental kidney disease models.

More excitingly, we also found that Smad2 and Smad3, two key downstream mediators of TGF-β signaling, differentially regulate renal fibrosis. While Smad3 is pathogenic, Smad2 plays a protective role in renal fibrosis. This new finding suggests that targeting Smad3 may have therapeutic effect on renal fibrosis. However, deletion of Smad3 gene from mice impairs immunity, leading to the development of massive inflammation in the gut. Thus, strategies aimed to prevent or treat fibrosis need to precisely target the Smad3-specific regulatory gene(s) related to fibrosis. We recently found that Smad3-mediated renal fibrosis was associated with a loss of miR-29 but upregulation of miR-21. Thus, we hypothesize that overexpression of miR-29 or downregulation of miR-21 may have therapeutic effect on renal fibrosis. This hypothesis was confirmed in vitro in both kidney cells and fibroblasts lacking Smad3 or and in vivo in a mouse model of obstructive kidney disease (UUO) by overexpressing miR-29 or knocking down miR-21. Indeed, TGF-β-induced renal fibrosis is associated with a loss of miR-29 but upregulation of miR-21, which was prevented in cells or mice lacking Smad3. In contrast, cells overexpressing the miR-29b or knocking down miR-21 are able to prevent TGF-β-induced collagen I and III expression. Importantly, ultrasound-microbubble-mediated overexpression of miR-29b or knockdown of miR-21 within the kidney before or after established obstructive nephropathy is capable of preventing and intervening renal fibrosis, demonstrating that targeting TGF-β/Smad3-dependent miRNAs that are specifically related to fibrogenesis may represent a novel and specific therapy for renal fibrosis.