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Regulation of TGF-β signaling in DKD: A therapeutic perspective

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Despite the immense burden of chronic kidney disease, optimal therapies remain limited in impact. Transforming growth factor-β (TGF-β) is the central pathogenic mediator in glomerular and tubulointerstitial injury in diabetic kidney disease (DKD). Elevated expression of TGF-β in DKD had long been observed, and substantial *in vivo* experimental evidence has demonstrated the attenuation of DKD by the inhibition of TGF-β signaling mediators. However, as TGF-β exerts pleiotropic actions in multiple organ systems in a cell type- and context-dependent manner, indiscriminate blockade of its signal transduction may not be optimal. Indeed, while TGF-β signal inhibition has garnered much interest as a therapeutic option for DKD progression, the clinical translation of its blockade by function-blocking anti-TGF-β antibody has been met with less success than anticipated, highlighting the complexities of TGF-β signaling in DKD. Moreover, diverse kidney cell-specific effects of TGF-β continue to emerge, demonstrating both injurious and protective mechanisms and thereby underscoring the strong influence of cell type- and context-dependent regulators and determinants of TGF-β signaling.

The accumulating evidence point to the intricate regulation of potency and specificity of TGF-β signaling by the cell type- and context-specific expression of signaling modulators. These modulators can act at various steps of the signaling cascade, which include cell surface regulators of TGF-β and receptor complex formation that influence the initiation of the signaling cascade or intracellular regulators of regulatory Smad activation and nuclear translocation to alter gene expression. We have demonstrated that the alteration of cell surface molecules that exert context-dependent augmentation or inhibition on TGF-β's interaction with its cognate receptors can have a profound impact on DKD progression in experimental models: We showed that the increased expression of a secreted molecule, leucine-rich-α-2-glycoprotein-1 (LRG1), markedly augments TGF-β signaling to attenuate DKD and that its plasma level is associated with worsened renal outcome in type 2 diabetic patients. In contrast, we also showed that the expression of decoy receptor, BMP and activin membrane-bound inhibitor (BAMBI), can attenuate DKD progression by dampening TGF-β signaling to reduce diabetic podocyte and endothelial cell injury in vivo. At the intersection of Smad3 activation, following the activation of TGF-β receptors, our work also demonstrated a substantial influence by homeodomain interacting protein 2 (HIPK2) on TGF-β/Smad3-responsive gene expression, and that its pharmacological inhibition can attenuate renal fibrosis development and improve renal function. As mice with global genetic deletion of LRG1, BAMBI, or HIPK2 do not have any gross abnormalities, which is in marked contrast to mice lacking the major TGF-β signaling components (*i.e.,* TGF-β ligand, receptors, co-receptors, and Smad proteins), we posit that the specific antagonisms of TGF-β signaling modulators, such as LRG1 and HIPK2, may shift the balance away from excessive pathological signaling in DKD, without a complete systemic blockade of TGF-β signaling that may be associated with unwanted negative effects. Therefore, future therapies aimed toward an effective combination of strategies to block the key modulators of TGF-β signaling potency and duration may lead to a more successful generation of drug therapy for DKD.