TGF-β/Smad Signaling in Kidney Disease

Hui Y. Lan, MD, PhD, and Arthur C.-K. Chung, PhD

Summary: Chronic progressive kidney diseases typically are characterized by active renal fibrosis and inflammation. Transforming growth factor-β1 (TGF-β1) is a key mediator in the development of renal fibrosis and inflammation. TGF-β1 exerts its biological effects by activating Smad2 and Smad3, which is regulated negatively by an inhibitory Smad7. In the context of fibrosis, although Smad3 is pathogenic, Smad2 and Smad7 are protective. Under disease conditions, Smads also interact with other signaling pathways, such as the mitogen-activated protein kinase and nuclear factor-κB pathways. In contrast to the pathogenic role of active TGF-β1, latent TGF-β1 plays a protective role in renal fibrosis and inflammation. Furthermore, recent studies have shown that TGF-β/Smad signaling plays a regulating role in microRNA-mediated renal injury. Thus, targeting TGF-β signaling by gene transfer of either Smad7 or microRNAs into diseased kidneys has been shown to retard progressive renal injury in a number of experimental models. In conclusion, TGF-β/Smad signaling plays a critical role in renal fibrosis and inflammation. Advances in understanding of the mechanisms of TGF-β/Smad signaling in renal fibrosis and inflammation during chronic kidney diseases should provide a better therapeutic strategy to combat kidney diseases.

Keywords: Chronic kidney disease, TGF-β/Smad signaling, renal fibrosis, renal inflammation

Matrix deposition and inflammatory cell infiltration within the glomerulus and interstitium accompanied with a loss of functioning nephrons are common pathologic features of progressive kidney diseases.[1,2] Transforming growth factor-β1 (TGF-β1) has been recognized as a powerful multifunctional cytokine that plays roles in cell proliferation, differentiation, migration, immunomodulation, and extracellular matrix (ECM) turnover in the kidney.[1] Increasing evidence suggests that dysregulation of TGF-β1 may be a pathogenic mechanism in the progression of chronic kidney diseases.[1-4]

TGF-β1 and its isoforms (TGF-β2 and TGF-β3) are synthesized and secreted as latent precursors (latent TGF-β1) complexed with latent TGF-β binding proteins (latent TGF-β binding proteins−1, −3, and −4).[1,4] TGF-β1 becomes active when TGF-β1 is liberated from the latency-associated peptide and dissociated from latent TGF-β binding protein via proteolytic cleavage by plasmin, reactive oxygen species, thrombospondin-1, and acid.[1,4] Active TGF-β then participates in many biological functions in both autocrine and paracrine manners.

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TGF-β1 exerts its biological and pathologic activities via Smad-dependent and -independent signaling pathways. Of them, the Smad-dependent mechanism has been well studied and considered to be a major pathway in many pathophysiological processes associated with TGF-β1. As shown in Figure 1, the binding of TGF-β1 to its receptor II (TβRII) activates the TGF-β receptor type I (TβRI) kinase. Then TβRI phosphorylates Smad2 and Smad3. Subsequently, phosphorylated Smad2 and Smad3 bind to Smad4, the common Smad, and form the Smad complex. This complex then translocates into the nucleus to regulate the target gene transcription, including Smad7. Smad7 is an inhibitory Smad that negatively regulates Smad2 and Smad3 activation and functions. This review focuses on the molecular basis and the role of TGF-β/Smad signaling in chronic kidney diseases, particularly on renal fibrosis and inflammation. A therapeutic targeting on the TGF-β/Smad signaling pathway using ultrasound-microbubble–mediated gene transfer of Smad7 and TGF-β/Smad-dependent microRNAs in renal fibrosis and inflammation also is described.

ROLE OF TGF-β1 IN RENAL FIBROSIS AND INFLAMMATION

TGF-β1 has long been known as a key mediator in the pathogenesis of renal fibrosis in both experimental and human kidney diseases because of its ability to promote ECM production and to inhibit its degradation.[1,3,4] In addition, TGF-β1 also mediates renal fibrosis by inducing the transformation of tubular epithelial cells (TECs) to myofibroblasts through epithelial mesenchymal transition.[5] On the other hand, a blockade of TGF-β with neutralizing TGF-β antibodies, decorin, and antisense oligonucleotides prevents or ameliorates renal fibrosis.[6] Furthermore, mice overexpressing an active form of

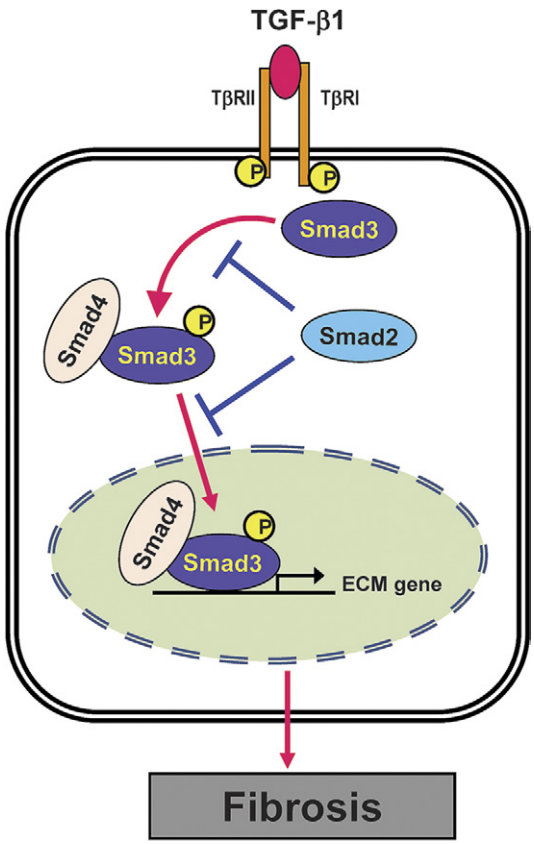

Figure 1. Diverse roles of Smad2 and Smad3 in renal fibrosis. Smad3 is a critical mediator of TGF-β/Smad signaling in fibrosis whereas Smad2 plays a protective role in renal fibrosis by either inhibiting Smad3 phosphorylation or blocking phosphorylated Smad3 nuclear translocation.

TGF-β1 in liver develop progressive liver and renal fibrosis, showing the essential function of TGF-β1 in renal fibrosis.[7,8]

Although the critical role of TGF-β1 and its signaling pathways in renal fibrosis has been well recognized, little attention has been paid to the role of TGF-β1 in renal inflammation. TGF-β1 also is known as an anti-inflammation cytokine.[9] Deletion of TGF-β1 in mice results in lethal multi-organ inflammation and death at 3 weeks of age.[10] Similarly, conditional deletion of TβII or TGF-β1 gene from T cells in mice develops autoimmune diseases.[11,12] These findings suggest a vital role for TGF-β1 in anti-inflammation. This is confirmed further by the findings that application of TGF-β1 improves autoimmune diseases, including allergic encephalomyelitis, collagen-induced arthritis, and experimental colitis.[13-15] These findings show the importance of TGF-β1 as a useful therapeutic agent in inflammation and immune diseases.[16-18] However, signaling mechanisms by which TGF-β1 exerts its anti-inflammatory properties remain unclear, although the TGF-β/Smad7-nuclear factor-κB (NF-κB) cross-talk mechanism recently was considered.[2]

Diverse Roles of Smad2 and Smad3 in Renal Fibrosis

It is now well accepted TGF-β/Smad signaling is a major pathway for renal fibrosis. The biological effects of TGF-β1 are mediated by two downstream mediators: Smad2 and Smad3[4,19] (Fig. 1). In the context of renal fibrosis, Smad2 and Smad3 are strongly activated in experimental and human kidney diseases, including diabetic nephropathy, ob-

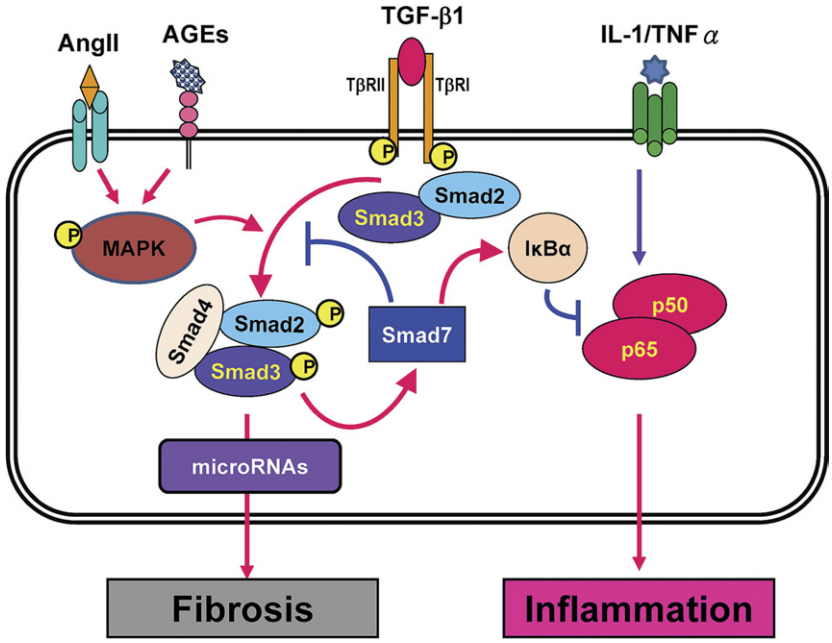

Figure 2. TGF-β/Smads and its cross-talk pathways in renal fibrosis and inflammation. Binding of TGF-β1 to TβRII activates TβRI kinase, which phosphorylates Smad2 and Smad3. The phosphorylated Smad2 and Smad3 then bind to Smad4 and form the Smad complex, which translocates into the nucleus and regulates the target gene transcription, including microRNAs and Smad7. Smad7 is an inhibitory Smad that blocks TGF-β/Smad-dependent fibrosis and inhibits NF-κB–driven inflammatory response by inducing nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IκBα). Note that AngII and AGEs can activate Smads directly via the ERK/p38/mitogen-activated protein kinase (MAPK) cross-talk pathway.