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Review Article

TGF-β-activated kinase-1: New insights into the mechanism of TGF-β signaling and kidney disease

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Abstract

Transforming growth factor-β (TGF-β) is a multifunctional cytokine that regulates a wide variety of cellular functions, including cell growth, cellular differentiation, apoptosis, and wound healing. TGF-β1, the prototype member of the TGF-β superfamily, is well established as a central mediator of renal fibrosis. In chronic kidney disease, dysregulation of expression and activation of TGF-β1 results in the relentless synthesis and accumulation of extracellular matrix proteins that lead to the development of glomerulosclerosis and tubulointerstitial fibrosis, and ultimately to end-stage renal disease. Therefore, specific targeting of the TGF-β signaling pathway is seemingly an attractive molecular therapeutic strategy in chronic kidney disease. Accumulating evidence demonstrates that the multifunctionality of TGF-β1 is connected with the complexity of its cell signaling networks. TGF-β1 signals through the interaction of type I and type II receptors to activate distinct intracellular pathways. Although the Smad signaling pathway is known as a canonical pathway induced by TGF-β1, and has been the focus of many previous reviews, importantly TGF-β1 also induces various Smad-independent signaling pathways. In this review, we describe evidence that supports current insights into the mechanism and function of TGF-β-activated kinase 1 (TAK1), which has emerged as a critical signaling molecule in TGF-β-induced Smad-independent signaling pathways. We also discuss the functional role of TAK1 in mediating the profibrotic effects of TGF-β1.

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Introduction

Regardless of the cause of the initial injury, chronic kidney disease (CKD) frequently progresses to end-stage renal disease with the pathogenesis of fibrosis and complete destruction of functional kidney tissues. CKD has become a major public health concern worldwide as the incidence continues to rise and portends high rates of morbidity and mortality [1]. The hallmark of progressive CKD is the development of renal fibrosis that is thought to be the final common mechanism leading to end-stage renal disease [2–4]. In general, fibrosis is characterized by the continuous production and progressive accumulation of extracellular matrix (ECM) proteins, including collagen and fibronectin, in the tissues. Renal fibrosis shows significant correlation with deterioration of kidney function [4,5]. The growing body of evidence demonstrates that transforming growth factor-β1 (TGF-β1) plays a pivotal role in the pathogenesis of renal fibrosis associated with progressive kidney diseases [6,7]. Therefore, improved and more effective therapies with direct antifibrotic effects are highly potent therapeutic strategies for attenuation or prevention of progressive CKD.

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There are three mammalian isoforms, TGF-β1, TGF-β2, and TGF-β3, of which TGF-β1 represents the predominant isoform and the prototype member of the TGF-β superfamily of multifunctional cytokines. TGF-β1 has been shown to be the key regulator of a variety of cellular functions such as cell growth, cellular differentiation, apoptosis, and wound healing, and is a potent inducer of ECM synthesis [8,9]. In response to tissue injury, upregulation of TGF-β1 expression and consistent activation is a common finding in the pathogenesis of renal fibrosis seen in virtually every type of CKD [6,10,11]. In the acute phase, however, TGF-β1 also triggers cytoprotective effects to mitigate tissue injury through enhancing wound repair and tissue regeneration, as well as anti-inflammatory effects [11–16].

Thus, it seems that TGF-β1 plays a paradoxically dual role in tissue injury response, suggesting that simply inhibiting the function of TGF-β1 receptors or TGF-β1 may not be an appropriate strategy for therapeutic interventions in CKD. In this context, a more detailed understanding of the cellular and molecular mechanisms of TGF-β1 actions will not only provide a more comprehensive knowledge of the pathogenic mechanisms in CKD, but may also guide the development of therapeutic strategies specifically targeting the signaling pathway responsible for the deleterious effects of TGF-β1.

TGF-β receptors

TGF-β1 signals are transmitted through transmembrane serine/threonine kinase receptors, type I (TβRI) and type II (TβRII), to activate intracellular downstream signaling pathways [17]. In the absence of the ligand TGF-β1, TβRI and TβRII exist as homodimers at the cell surface. Upon ligand stimulation, TGF-β1 binds to TβRII, and in turn TβRI and TβRII form heterotetrameric complexes. Since TβRII dimer is a constitutively active kinase receptor, upon ligand binding it phosphorylates serine/threonine residues in the cytoplasmic GS domain of TβRI. However, TβRII signaling in the absence of TβRI has not been reported. The phosphorylation of serine/threonine residues in the GS domain activates TβRI, and this is followed by activation of a number of intracellular signaling molecules in a cell-specific and context-specific manner to mediate the diverse biological functions of TGF-β1.

Although TGF-β1 binds efficiently to TβRI–TβRII complexes, TGF-β type III receptor (TβRIII), also known as betaglycan, which lacks a signaling domain, serves as a co-receptor to promote the binding of TGF-β ligands to TβRII in certain cells [18]. This function of TβRIII appears to be particularly important for TGF-β2. In contrast to TGF-β1 and TGF-β3, affinity of TGF-β2 for TβRII is much weaker and requires betaglycan for high-affinity binding to TβRII [19].

Signaling pathways induced by TGF-β1

A comprehensive overview of TGF-β-activated Smad-dependent and Smad-independent signaling pathways is shown in Fig. 1. The first member of the Smad family, Mad [mothers against *dpp* (decapentaplegic)], was identified in a genetic screen in *Drosophila* [17,20], and followed by cloning of sma-2, sma-3 and sma-4 (Small body size) in *Caenorhabditis elegans* [21,22].

Phosphorylation in the GS domain of TβRI resulting in its receptor kinase activity recruits and activates receptor-regulated Smads (R-Smads). In addition to the phosphorylation in the GS domain [23], the nine-amino-acid L45 loop [24] of TβRI is thought to be crucial for its interaction with R-Smads. The recruitment of R-Smads to the receptor complex is mediated by auxiliary proteins, such as Smad anchor for receptor activation (SARA) [25]. R-Smads, Smad2 and Smad3, are phosphorylated by kinase activity of TβRI and rapidly dissociate from TβRI. Subsequently, the phosphorylated R-Smads interact to form complexes with the common mediator (Co-Smad) Smad4, leading to nuclear translocation and transcriptional activity [26]. Transcriptional activation of Smad complexes leads to cooperate with other co-activators, such as p300 and CREB-binding protein (CBP), which possess histone acetyl transferase activity [27]. On the other hand, the inhibitory Smads (I-Smads), Smad6 and Smad7, inhibit TGF-β signaling through binding of their MAD homology (MH) 2 domains to TβRI, thus preventing the recruitment and phosphorylation of R-Smad [17,28].

The Smad signaling pathway is widely accepted as a canonical pathway induced by TGF-β1 [29], and the role of Smads in kidney diseases has been a topic of several previous reviews [30,31]. Nevertheless, it has become quite evident that the Smad signaling pathway does not explain all of the diverse actions of TGF-β1. A large body of evidence demonstrates that TGF-β1 also induces the activation of various Smad-independent signaling pathways, with or without direct crosstalk with the Smad [32,33].

The Smad-independent TGF-β signaling pathways, as illustrated in Fig. 1, include the mitogen-activated protein kinases (MAPKs), namely extracellular signal-regulated kinases 1/2 [34,35], c-Jun N-terminal kinase (JNK) [36–38], and p38 MAPK [39–42], phosphatidylinositol-3-kinase (PI3K)/AKT [43–46], Rho-like GTPases (RhoA) [47,48], and protein phosphatase 2A (PP2A) [49]. Recent studies have demonstrated the role of p38 MAPK signaling pathway in the development of glomerular and tubulointerstitial fibrosis [50,51] in animal models and in human kidney disease such as diabetic nephropathy [50,52]. We and others have demonstrated that TGF-β-activated kinase 1 (TAK1) is a major upstream signaling molecule in TGF-β1-induced type I collagen and fibronectin expression through activation of the MAPK kinase (MKK) 3–p38 and MKK4–JNK signaling cascades, respectively (Fig. 2) [53–55]. Here, we review recent progress toward understanding the molecular mechanisms of Smad-independent signaling pathway via TAK1 and its role in mediating the cellular effects of TGF-β1.

TAK1 in TGF-β signaling

TAK1, a serine/threonine kinase, was originally identified as a member of the MAPK kinase kinase (MAP3K) family, named as MAP3K7, and is rapidly activated by TGF-β1 [56,57]. To date, TAK1 is the only MAP3K family member that has been directly implicated in TGF-β1 signaling. In addition to TGF-β1, TAK1 can also be activated by various stimuli including proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) [58] and interleukin-1 (IL-1) [59], lipopolysaccharides [60], and environmental stress [61]. Phosphorylation of Thr-187 and Ser-192 in the activation loop of TAK1 induces TAK1 activation [62,63] and subsequently triggers the activation of several downstream signaling cascades, including MKK4/7–JNK, MKK3/6-p38 MAPK, and nuclear factor-kappa B (NF-κB)-inducing kinase-IκB kinase (Fig. 2) [58–60].

Recent investigations also indicate a role for TAK1 in the regulation of Smad function. TAK1 interacts with the MH2 domain in Smad proteins, via which TAK1 dramatically

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