Biomedicine & Pharmacotherapy 101 (2018) 670–681

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Central role of dysregulation of TGF-β/Smad in CKD progression and potential targets of its treatment

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ARTICLE INFO

Keywords:
Transforming growth factor-β
Chronic kidney disease
TGF-β/Smad
Renal fibrosis
Inflammation
MicroRNA
Ubiquitination

ABSTRACT

Chronic kidney disease (CKD) has emerged as a major cause of morbidity and mortality worldwide. Interstitial fibrosis, glomerulosclerosis and inflammation play the central role in the pathogenesis and progression of CKD to end stage renal disease (ESRD). Transforming growth factor-β1 (TGF-β1) is the central mediator of renal fibrosis and numerous studies have focused on inhibition of TGF-β1 and its downstream targets for treatment of kidney disease. However, blockade of TGF-β1 has not been effective in the treatment of CKD patients. This may be, in part due to anti-inflammatory effect of TGF-β1. The Smad signaling system plays a central role in regulation of TGF-β1 and TGF-β/Smad pathway plays a key role in progressive renal injury and inflammation. This review provides an overview of the role of TGF-β/Smad signaling pathway in the pathogenesis of renal fibrosis and inflammation and an effective target of anti-fibrotic therapies. Under pathological conditions, Smad2 and Smad3 expression are upregulated, while Smad7 is downregulated. In addition to TGF-β1, other pathogenic mediators such as angiotensin II and lipopolysaccharide activate Smad signaling through both TGF-β-dependent and independent pathways. Smads also interact with other pathways including nuclear factor kappa B (NF-κB) to regulate renal inflammation and fibrosis. In the context of renal fibrosis and inflammation, Smad3 exerts profibrotic effect, whereas Smad2 and Smad7 play renal protective roles. Smad4 performs its dual functions by transcriptionally promoting Smad3-dependent renal fibrosis but simultaneously suppressing NF-κB-mediated renal inflammation *via* Smad7-dependent mechanism. Furthermore, TGF-β1 induces Smad3 expression to regulate microRNAs and Smad ubiquitination regulatory factor (Smurf) to exert its pro-fibrotic effect. In conclusion, TGF-β/Smad signaling is an important pathway that mediates renal fibrosis and inflammation. Thus, an effective anti-fibrotic therapy *via* inhibition of Smad3 and upregulation of Smad7 signaling constitutes an attractive approach for treatment of CKD.

1. Introduction

Renal fibrosis constitutes a common endpoint of various progressive kidney diseases which leads to the loss of nephrons and impairment of renal function ultimately resulting in end stage renal diseases (ESRD) [1]. Fibrogenesis involves tubulo-interstitial tissues leading to tubulointerstitial fibrosis and glomeruli leading to glomerulosclerosis [2]. Extensive studies have demonstrated that fibrogenesis can be induced

Abbreviations: ACE2, angiotensin-converting enzyme-2; AGE, advanced glycation end-product; AT1R, angiotensin type 1 receptor; BMP, bone morphogenetic proteins; BMP-7, bone morphogenetic protein 7; CKD, chronic kidney diseases; Co-Smads, common mediator Smads; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ERK, extracellular regulated protein kinases; ESRD, end stage renal diseases; FSGS, focal and segmental glomerulosclerosis; HIPK2, Homeodomain interacting protein kinase 2; hRPTEC, human renal proximal tubule epithelial cells; ICAM-1, intercellular cell adhesion molecule-1; IgA, immunoglobulin A; interleukin-1β (IL-1β) I-Smads, inhibitory Smads; Keap1, Kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinase; monocyte chemoattractant protein-1 (MCP-1) NEDD4-2, neural precursor cell expressed developmentally downregulated gene 4; Nrf2, nuclear factor- erythroid-2-related factor 2; PDGF, platelet-derived growth factor; PI3K, phosphatidylinositol-3 kinase; R-Smads, receptor-regulated Smads; Ski, Sloan-kettering institute; Smurf1, Smad ubiquitination regulatory factor-1; Smurf2, Smad ubiquitination regulatory factor-2; SnoN, Ski-related novel protein N; TGF-β, transforming growth factor-β; TGF-β1, transforming growth factor-β1; TGFβR, transforming growth factor-β receptor; TGFβRI, transforming growth factor-β receptor type I; TGFβRII, transforming growth factor-β receptor type II; TNF-α, tumor necrosis factor α; UUO, unilateral ureteral obstruction; WWP1, WW domain containing E3 ubiquitin protein ligase 1; α-SMA, alpha-smooth muscle actin

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https://doi.org/10.1016/j.biopha.2018.02.090
Received 13 December 2017; Received in revised form 5 February 2018; Accepted 20 February 2018

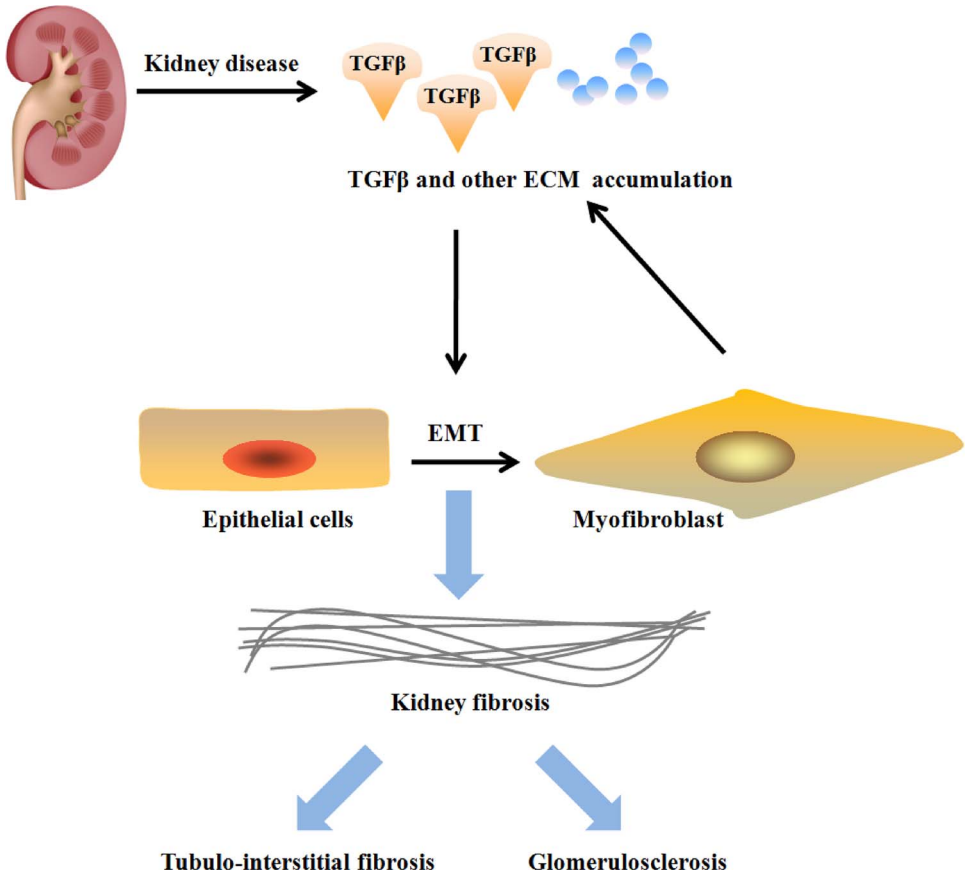

Fig. 1. Hypothesis of progression of fibrosis by EMT in the interstitium or in the glomerulus.

by multiple stimuli or mediators including growth factors, cytokines, toxins and lipid disorders as well as stress molecules *via* multiple mechanisms and signaling pathways [3–13]. Fibrosis is primarily driven by inflammatory cytokines including members of the transforming growth factor-β (TGF-β) superfamily [14,15], various interleukins [16] and oxidative stress [17–20]. Among them, transforming growth factor-β1 (TGF-β1) has served as an important and crucial mediator in the pathogenesis of progressive renal fibrosis. TGF- β1 has been demonstrated to transform tubular epithelial cells into extracellular matrix (ECM) producing fibroblasts or myofibroblasts and to induce epithelial-to-mesenchymal transition (EMT) (Fig. 1). TGF-β is a multi-functional mediator that regulates proliferation, differentiation, apoptosis, adhesion and migration in various cells such as macrophages, activated T and B cells, immature haematopoietic cells, neutrophils and dendritic cells [21].

The TGF-β superfamily is characterized by six conserved cysteine residues. It is encoded by forty-two open reading frames in humans and more than thirty related members in mammals including activins, inhibins, growth factors, differentiation factors and bone morphogenetic proteins (BMP) and anti-mullerian hormone [22,23]. Although the different TGF-β ligands induce very different cellular activities, they share a set of common sequence and structural features [24]. The three mammalian isoforms including TGF-β1 and its isoforms (TGF-β2 and TGF-β3) share 70–82% amino acid homology. Despite their structural similarities, the three TGF-β isoforms induce distinct biological responses. Based on their cell/tissue-specific expression they interact with specific inhibitory molecules and unique combinations of receptors [25]. The active form of TGF-β is a dimer stabilized by hydrophobic interactions. TGF-β evokes intracellular signaling by binding to receptor complexes that contain two distantly related transmembrane serine/threonine kinases called transforming growth factor-β receptor type I (TGFβRI) and transforming growth factor-β receptor type II (TGFβRII) [21,23]. TGFβRII is a constitutively active kinase, whereas TGFβRI kinase needs to be activated by TGFβRII kinase [21,26]. TGF-β directly binds to TGFβRII in most cell types. The TGFβRII bound TGF-β is then recognized by TGFβRI, which is recruited into the complex and becomes phosphorylated by TGFβRII [14]. The intracellular mediators of TGF-β signaling are known as Smad-dependent and Smad-independent signaling pathways. Three classes of Smads including receptor-regulated Smads (R-Smads), common mediator Smads (Co-Smads) and inhibitory Smads (I-Smads) have been identified in biological system. The R-Smads including Smad1–Smad3, Smad5 and Smad8 are directly activated *via* phosphorylation by TGFβRI forming a hetero-oligomeric complex with the common mediator Smad4. The Smad complex translocate into the nucleus where it is recruited into DNA by specific DNA-binding transcription factors and modulates target gene transcription [23,27,28]. Smad2 and Smad3 are activated by the TGF-β subfamily and Smad1, Smad5 and Smad8 respond to signaling by BMP subfamily [27,29]. I-Smads including Smad6 and Smad7 antagonize the R-Smads' activity by interacting with TGFβRI to prevent the docking and phosphorylation of R-Smads and diverting them for degradation *via* the ubiquitin proteasome degradation mechanisms [23,27] (Fig. 2). In addition to Smad-mediated transcription, TGF-β could activate other signal transduction pathways including mitogen-activated protein kinase (MAPK), phosphatidylinositol-3 kinase (PI3K) and Rho-like GTPases pathways [14,30]. Since the Smad-dependent signaling pathway plays a critical role in pathogenesis of various forms of chronic kidney disease (CKD) [14], TGF-β1 has emerged as an attractive target of novel therapeutic interventions.

This review focuses on the molecular mechanisms of TGF-β/Smads-mediated renal fibrosis and inflammation and its role in the progressive kidney injury. The new therapies against renal fibrosis by targeting the downstream Smad3 and Smad7 as well as TGF-β/Smad3-mediated microRNAs are also summarized and discussed.