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Targeting TGF-β/Smad in Chronic Kidney Disease Fibrosis: Mechanisms and TCM Therapeutics

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Abstract: *The pathogenesis of renal fibrosis in chronic kidney disease (CKD) is critically driven by dysregulated transforming growth factor-β (TGF-β) signaling, wherein TGF-β1 activates Smad2/3 phosphorylation to induce epithelial-mesenchymal transition (EMT), stimulate collagen synthesis, and inhibit matrix degradation-processes synergistically amplified through crosstalk with Wnt and MAPK pathways. Smad3 phosphorylation levels correlate positively with fibrosis severity, while Smad7 inactivation disrupts signal regulation, exacerbating pathway hyperactivity. Oxidative stress and angiotensin II (Ang II) further aggravate the fibrotic microenvironment via inflammatory responses and reactive oxygen species (ROS) accumulation. Current therapeutic approaches focus on TGF-β/Smad pathway modulation, including neutralizing antibodies, integrin inhibitors, Smad3-specific antagonists, and non-coding RNA-based interventions, complemented by multitarget regulation through Traditional Chinese Medicine (TCM) components. A central challenge lies in the heterogeneous cellular responses of renal subpopulations to TGF-β/Smad signaling, necessitating integration of single-cell omics to resolve dynamic regulatory networks and development of cell type-specific delivery systems. Future studies must prioritize cross-target synergy to address precision therapy bottlenecks and enhance clinical translation of antifibrotic strategies.*

Keywords: *Chronic kidney disease; TGF-β/Smad signaling pathway; TCM; Therapeutic target*

1. Introduction

Chronic kidney disease (CKD) as a global public health challenge shows persistently increasing incidence and disease burden, with approximately 697 million cases worldwide in 2017[1]. According to the latest national survey, the prevalence of CKD among adults in China is 8.2%, showing a declining trend compared to a decade ago. While this suggests that previous CKD prevention and management strategies in China have demonstrated effectiveness, the challenges we face remain severe[2]. CKD imposes a substantial public health burden on society and creates heavy individual burdens for patients, both physically and economically.

Renal fibrosis represents a common pathological hallmark and ultimate manifestation of CKD progression. Its morphological features include glomerulosclerosis, tubular atrophy, chronic interstitial inflammation with fibrosis, and vascular rarefaction[3]. Fibrosis typically serves to repair tissues subjected to recurrent injury. Upon tissue damage, local fibroblasts and pericytes are activated, accompanied by upregulated secretion of inflammatory mediators and enhanced synthesis of extracellular matrix (ECM) components, facilitating tissue repair[4]. However, when the repair process is recurrently activated in a localized region, sustained proliferation and differentiation of resident cells into myofibroblasts occur, amplifying tissue repair capacity. Notably, the primary drivers of renal fibrosis are the excessive activation of myofibroblasts and subsequent pathological ECM deposition.

The activation and proliferation of myofibroblast precursors are orchestrated by multiple signaling pathways, including transforming growth factor-β (TGF-β), Wnt/β-catenin, Hedgehog, and Notch. Among these, the TGF-β signaling cascade is widely recognized as a classical pathway and plays a pivotal role in the pathogenesis of renal fibrosis[5]. This review provides a comprehensive analysis of the mechanistic contributions of TGF-β signaling to renal fibrosis, with the aim of informing the development of targeted therapeutic strategies to improve clinical outcomes for patients with fibrotic kidney diseases.

ISSN 2706-6819 Vol.7, Issue 2: 82-89, DOI: 10.25236/IJFM.2025.070212

2. The TGF-β Signaling Pathway

The TGF-β/Smad pathway serves as a critical regulator of cellular proliferation, differentiation, and matrix metabolism, playing a central role in fibrogenesis during CKD. The TGF-β family comprises three isoforms-β1, β2, and β3-with TGF-β1 emerging as the predominant driver of renal fibrosis[6,7]. Signaling is initiated when TGF-β1 binds to membrane-associated type II (TβRII) and type I (TβRI) receptors, triggering activation of the downstream Smad protein family. Smad proteins are categorized into receptor-activated Smad2/3, common mediator Smad4, and inhibitory Smad7 subtypes. Phosphorylated Smad3 forms a complex with Smad4, translocates to the nucleus, and regulates the transcription of pro-fibrotic genes. In contrast, Smad7 suppresses signal transduction by competitively inhibiting the interaction between TβRI and Smad2/3[8,9]. Dysregulation of this pathway directly drives excessive ECM deposition, constituting a core mechanism underlying CKD fibrogenesis.

3. The Role of TGF-β1/Smad Signaling in CKD Pathogenesis

3.1. Dominant Role of TGF-β1

TGF-β1 drives fibrosis through multiple mechanisms: (1) Inducing ECM synthesis by activating fibroblasts to secrete collagen I/III and other non-degradable ECM components[10]; (2) Suppressing ECM degradation via upregulation of tissue inhibitors of metalloproteinases-1 (TIMP-1), which inhibit matrix metalloproteinase (MMP) activity[11]; and (3) Promoting epithelial-mesenchymal transition (EMT) by inducing tubular epithelial cells to lose polarity, adopt a mesenchymal phenotype, and secrete ECM[12]. TGF-β1 further synergizes with matricellular proteins in the ECM microenvironment through integrin αvβ6/β8-dependent activation pathways, fostering a pro-fibrotic niche[13].

3.2. Pro-Fibrotic Effects of Smad3

Smad3 serves as the central mediator of TGF-β1 signaling. Phosphorylated Smad3 (p-Smad3) complexes with Smad4, translocates to the nucleus, and directly activates transcription of pro-fibrotic genes. Animal models demonstrate that *Smad3*-knockout mice exhibit significantly attenuated renal fibrosis[9]. Additionally, Smad3 establishes a positive feedback loop by repressing the expression of the anti-fibrotic factor Smad7. Clinical studies confirm that p-Smad3 levels in renal tissue correlate positively with fibrosis severity in CKD patients[14,15].

3.3. Negative Regulation by Smad7

Smad7 competitively binds to TβRI, blocks Smad2/3 phosphorylation, and recruits E3 ubiquitin ligases to degrade receptor complexes[8]. In CKD, Smad7 expression is frequently downregulated due to epigenetic silencing or suppression by pro-inflammatory cytokines, leading to unchecked TGF-β1/Smad3 signaling[16]. Experimental overexpression of Smad7 reduces tubulointerstitial collagen deposition[8]. Moreover, Smad7 indirectly mitigates fibrosis by antagonizing the Wnt/β-catenin pathway[17].

3.4. Dynamic Imbalance and Fibrosis Progression

In CKD, hyperactivation of the TGF-β1/Smad3 pathway and suppression of Smad7 create a self-reinforcing vicious cycle. Accumulation of matricellular proteins within the fibrogenic niche recruits and sequesters TGF-β1, amplifying localized pro-fibrotic signaling[13,18]. Senescent cells exacerbate this process through the senescence-associated secretory phenotype (SASP), which releases TGF-β1, interleukin-6(IL-6), and other profibrotic mediators.

4. Crosstalk Between TGF-β1/Smad and Other Signaling Pathways

TGF-β1 directly activates Wnt ligands via Smad3, promoting β-catenin nuclear translocation and transcription of pro-fibrotic genes. Concurrently, the Wnt pathway upregulates TβRII expression, amplifying TGF-β signaling. Tenascin C, a key matricellular protein within the fibrogenic niche, facilitates Wnt ligand enrichment, synergizing with TGF-β1 to establish a pro-fibrotic axis[19]. Through non-Smad pathways, TGF-β1 activates ERK and JNK, mediating fibroblast migration and EMT. The p38

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MAPK cascade contributes to TGF-β1-induced cell cycle arrest and secretion of pro-inflammatory cytokines[20].

Activation of the PI3K/Akt pathway by TGF-β1 suppresses FoxO transcription factors, diminishing Smad7 expression and derepressing TGF-β signaling[21]. Furthermore, Akt-mediated phosphorylation of GSK-3β stabilizes β-catenin, synergistically enhancing fibrogenesis[22]. TGF-β1 also cooperates with Notch signaling to drive EMT and fibroblast activation. The Notch intracellular domain binds directly to Smad3, potentiating transcriptional activation of pro-mesenchymal genes[23].

5. Additional Factors in CKD Fibrosis

5.1. Enzymes and Cytokines

Multiple enzymes and cytokines exacerbate CKD fibrosis by dysregulating apoptosis and ECM metabolism. Caspase-3 activation induces DNA damage and irreversible tubular cell death, while studies by He et al. demonstrate that Caspase-3 downregulation attenuates oxidative stress and fibrosis[24]. Imbalanced MMPs and tissue inhibitors of metalloproteinases (TIMPs) drive pathological ECM deposition. John et al. report significant TIMP upregulation in CKD renal tissues, which suppresses MMP degradation activity[25]. Angiotensin II (Ang II) exacerbates fibrosis by not only inducing glomerular hypertension through hemodynamic effects but also activating fibroblasts and monocytes, thereby promoting oxidative stress and inflammatory signaling pathways[26,27]. Aldosterone further stimulates TGF-β1 and connective tissue growth factor (CTGF) production while activating the NF-κB pathway, disrupting renal cell proliferation and differentiation[28,29]. The synergistic actions of these enzymes and cytokines directly compromise renal architecture, accelerating fibrosis.

5.2. Oxidative Stress and Chronic Inflammation

A vicious cycle between oxidative stress (OS) and chronic inflammation exacerbates CKD progression. Excessive reactive oxygen species (ROS) damage lipids, proteins, and nucleic acids, impairing tubular cell function. Su et al. highlight ROS as a persistent contributor to interstitial fibrosis across disease stages[30]. OS disrupts redox balance, triggering overexpression of inflammatory cytokines, which dysregulate MMPs and promote ECM accumulation[31]. Macrophage and mast cell infiltration amplifies inflammation; these cells release basic fibroblast growth factor (bFGF) and tryptase to directly induce fibrosis. Wang et al. confirm that macrophages interact with the ECM via paracrine mechanisms, exacerbating endothelial injury and interstitial fibrosis[32,33].

6. Therapeutic Advances Targeting the TGF-β/Smad Pathway in CKD Fibrosis

6.1. TGF-β Signaling Pathway Blockade Strategies

Targeted therapeutic approaches for the TGF-β pathway focus on two key directions: direct inhibition of the ligand-receptor axis and precise blockade of latent complex activation. For direct suppression of TGF-β signaling, neutralizing antibodies, antisense oligodeoxynucleotides, soluble TGF-β type II receptor (TGF-βRII), and small-molecule receptor kinase inhibitors have all demonstrated efficacy in reducing renal interstitial fibrosis (RIF) in preclinical CKD models[34]. However, clinical trials reveal that systemic TGF-β suppression may impair critical physiological functions. For example, Fresolimumab, a pan-TGF-β neutralizing antibody, failed to significantly improve serum creatinine (Scr), estimated glomerular filtration rate (eGFR), or proteinuria in patients with diabetic nephropathy or focal segmental glomerulosclerosis (FSGS), while also disrupting normal anti-inflammatory and immunomodulatory responses[35,36].

Integrin αv subtypes, particularly αvβ6 and αvβ1, play a pivotal role in the spatiotemporal regulation of TGF-β activation, with dual-pathological relevance demonstrated in pulmonary fibrosis[37]. Decaris et al. reported that αvβ6 and αvβ1 cooperatively enhance TGF-β activation in fibrotic lung tissues. Dual inhibition of these integrins reduces collagen I and other fibrotic gene expression more effectively than single-target inhibition or pan-αv blockade. Mechanistic studies implicate integrin-ECM mechanosignaling and Smad pathway modulation within the pulmonary microenvironment as key drivers.Tissue-specific dual αvβ6/αvβ1 inhibitors-such as those currently in Phase II clinical trials (NCT04396756, NCT04072315)-are pharmacologically advantageous by locally inhibiting TGF-β

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activation without systemic pathway disruption, potentially mitigating adverse effects associated with conventional antifibrotic therapies[38,39].

6.2. Targeting Smad Signaling for Antifibrotic Therapy

To circumvent the systemic toxicity of global TGF-β inhibition, downstream Smad signaling and non-coding RNAs have emerged as alternative therapeutic targets. Smad3, a core effector of TGF-β signaling, can be selectively inhibited by the phosphorylation blocker SIS3. Preclinical studies show that SIS3 attenuates RIF in unilateral ureteral obstruction (UUO) models and reduces ECM production in TGF-β1-stimulated scleroderma fibroblasts by suppressing Smad3 nuclear translocation[40,41]. Bone morphogenetic protein-7 (BMP-7) competitively antagonizes Smad3 phosphorylation, inhibiting EMT and pathological ECM deposition across multiple kidney disease models[42]. BT173, a small-molecule inhibitor of homeodomain-interacting protein kinase 2 (HIPK2), suppresses TGF-β1-induced Smad3 phosphorylation and target gene transcription in UUO mice, ameliorating renal fibrosis and ECM accumulation[43]. Niclosamide mitigates doxorubicin-induced kidney injury by blocking HIPK2-Smad3 promoter binding and inhibiting Smad/NF-κB pathway activation[44]. Smad7, an endogenous negative regulator of Smad3, exhibits significant therapeutic potential. Asiatic acid, for instance, upregulates Smad7 to restore Smad3/Smad7 equilibrium, thereby improving RIF[45].

Non-coding RNA interventions offer novel antifibrotic strategies. Smad3-dependent miRNAs exhibit dysregulated expression during fibrosis; modulating these molecules can reverse ECM synthesis. Ultrasound microbubble-mediated delivery of miR-29b mimics or miR-21 inhibitors suppresses collagen deposition in obstructive nephropathy models[46]. Long non-coding RNAs, such as lncRNA-TSI, competitively bind the MH2 domain of Smad3, preventing its phosphorylation and nuclear translocation, which downregulates fibrotic markers[47].

6.3. Therapeutic Potential of TCM Targeting the TGF-β/Smad Pathway in Renal Fibrosis

TCM, as a cornerstone of disease management in Chinese medical practice, demonstrates well-documented therapeutic efficacy. Modern research highlights that the multicomponent nature of TCM enables multidimensional and multitarget clinical effects. Active compounds from TCM have been shown to modulate the TGF-β/Smad signaling system, playing a pivotal role in the prevention and treatment of RIF. For example, hirudin, a bioactive component derived from leeches (Hirudo medicinalis), significantly downregulates TGF-β1 expression and suppresses phosphorylation of Smad2/3 in UUO rat models. It concurrently inhibits the NF-κB pathway by reducing levels of P65, phosphorylated P65 (p-P65), and phosphorylated IκB kinase-α (p-IκBα) while enhancing IκBα expression, thereby ameliorating renal injury and fibrosis[47]. Panax notoginseng saponins (PNS), the primary active constituents of Panax notoginseng (Araliaceae family), reduce TGF-β1 expression and Smad2/3 phosphorylation, while enhancing Smad6 activity through transcriptional and translational regulation. This dual modulation alleviates renal hyperplasia, fibrotic pathology, and microcirculatory dysfunction[48,49]. Naringenin, a dihydroflavonoid derived from citrus plants, demonstrates cross-pathway regulatory capacity through bidirectional modulation of the TGF-β/Smad system. It suppresses Smad2/3/Smad4 complex formation and HMGB1/AP-1/NF-κB signaling cascades while markedly upregulating Smad7 expression. These integrated effects significantly reduce pathological deposition of extracellular matrix components, including collagen I (COL1A1) and collagen III (COL3A1), and mitigate expression of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and IL-6[50,51]. Ursolic acid further attenuates renal fibrosis in UUO mice by downregulating TGF-β1 and its downstream phospho-Smad2/3[52]. Additionally, triterpenoids from Poria cocos exhibit unique antifibrotic properties by competitively binding the TGF-β type I receptor, thereby blocking Smad3 interaction and inhibiting TGF-β1/Ang II-mediated Smad3 phosphorylation. This inhibition subsequently disrupts Wnt/β-catenin signaling, as validated in HK-2 renal tubular cell models[53].

Multifaceted Regulatory Effects of Herbal Formulations on TGF-β/Smad Signaling in RIF.Herbal formulations exhibit multifaceted regulatory effects on TGF-β/Smad signaling to ameliorate RIF. For instance, the Astragalus membranaceus–Angelica sinensis herb pair, a classic combination in TCM for replenishing Qi and activating blood circulation, extends its therapeutic scope by improving metabolic dysregulation while synergistically rebalancing the TGF-β1/Smad pathway. This dual action provides experimental evidence for multitarget antifibrotic strategies[54]. The Shenning I Formula, comprising Poria cocos and Cinnamomum cassia, exerts multitarget therapeutic effects. Preclinical studies demonstrate its ability to reduce serum biomarkers of renal dysfunction, including blood urea nitrogen

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(BUN) and Scr, in UUO models, while delaying RIF progression via suppression of Smad2 and TGF-β1 signaling[55]. Shenfu Decoction, a renowned formula for invigorating Qi and warming Yang, significantly suppresses aberrant expression of TGF-β1 and its downstream effectors-phosphorylated Smad2/3 (p-Smad2/3), CTGF, and tumor necrosis factor-α (TNF-α)-while upregulating Smad7 in adenine-induced nephropathy models. This bidirectional modulation underscores its antifibrotic potential[56].

The Shenshuaixiezhuo Decoction demonstrates cross-pathway regulatory advantages, reducing transcriptional and protein levels of Smad3 and Smad4 in the TGF-β1/Smad axis while disrupting the Wnt4/β-catenin cascade. It further stabilizes epithelial cell phenotypes by enhancing E-cadherin expression[57]. Shen Di Bushen Capsule demonstrates multidimensional regulatory effects in UUO models, alleviating tubular endoplasmic reticulum stress and collagen deposition through downregulation of TGF-β1/p-Smad2/3 signaling and suppression of interstitial fibrosis markers such as collagen I (Col I) and α-smooth muscle actin (α-SMA)[58]. Modern formulations like Shenkang Injection reveal novel mechanisms via in vitro and in vivo studies. It promotes nuclear translocation of Smurf1/2, triggering ubiquitin-mediated degradation of TβRII and Smad2, thereby destabilizing the TβR-I/TβR-II and TβR-I/Smad2/3 receptor complexes and halting EMT[59].

7. Conclusion and Future Perspectives

The progression of fibrosis in CKD is critically linked to dysregulation of the TGF-β/Smad pathway, characterized by functional aberrations across renal cell subpopulations. TGF-β1 exerts cell type-specific effects via Smad2/3 phosphorylation: in tubular epithelial cells, TGF-β1/Smad3 signaling drives EMT, leading to polarity loss and aberrant ECM secretion; in pericytes and fibroblasts, integrin αvβ6/β8 activation mediated by this pathway promotes myofibroblast differentiation and synthesis of non-degradable matrix components such as collagen I; in macrophages, aberrant TGF-β/Smad3 activation amplifies pro-inflammatory cytokine release, including IL-6 and TNF-α, exacerbating fibrogenic niche damage. Smad7 suppression displays context-dependent heterogeneity, with epigenetic silencing predominating in tubular epithelial cells and fibroblast Smad7 downregulation associated with microRNA-21 dysregulation, collectively potentiating global TGF-β signaling hyperactivity.

Current therapies increasingly target this heterogeneity: αv integrin inhibitors disrupt pericyte-ECM mechanosignaling to block TGF-β activation, small molecules such as SIS3 selectively inhibit fibroblast-specific Smad3 phosphorylation, and TCM formulations like Shenshuaixiezhuo Decoction modulate multicellular crosstalk, exemplified by macrophage-fibroblast paracrine interactions, to achieve cross-target effects. However, critical challenges remain. Dynamic intercellular networks, notably senescent cell-activated pericyte interactions mediated by TGF-β/Smad, are incompletely mapped. Additionally, existing agents struggle to concurrently address functional disparities across cell types, such as inhibiting fibroblast ECM overproduction while restoring tubular epithelial regenerative capacity. Future efforts must integrate spatial transcriptomics and single-cell proteomics to delineate TGF-β/Smad regulatory landscapes at cellular resolution and advance cell type-specific, promoter-driven delivery systems for microenvironment-tailored interventions.

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