Role of the TGF-β/Smad signaling pathway in the transition from acute kidney injury to chronic kidney disease (Review)

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Abstract. The progression from acute kidney injury (AKI) to chronic kidney disease (CKD) has become a focal point of investigation, with the TGF-β/Smad signaling pathway emerging as a key mediator in this process. The present review assesses how TGF-β/Smad contributes to renal fibrosis and the subsequent deterioration of kidney function following AKI. Drawing on recent experimental and clinical findings, this study explores how pathway activation promotes tubular cell injury, inflammation and interstitial fibrosis. By examining these molecular and cellular events, this study offers fresh insights into the complex mechanisms that underlie the AKI-CKD transition and highlights potential therapeutic strategies aimed at interrupting or slowing disease progression.

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Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; Scr, serum creatinine; TGF-β, transforming growth factor-β; TGF-βRI, TGF-β receptor I; R-Smads: receptor-regulated Smads; I-Smads, inhibitory Smads; IRI, ischemia-reperfusion injury; EMT, epithelial-to-mesenchymal transition; ECM, extracellular matrix; GSK3β, glycogen synthase kinase-3β; SIS3, Smad3-specific inhibitor; AS-IV, Astragaloside IV; MAPK, mitogen-activated protein kinases

Key words: acute kidney injury, chronic kidney disease, TGF-β/Smad signaling pathway, renal fibrosis

Contents

1. Introduction

Acute kidney injury (AKI) is characterized by a rapid decline in kidney function, and is typically indicated by an increase in blood serum creatinine (Scr) levels or a decrease in urine output. The global prevalence of AKI is alarming, particularly among hospitalized patients, where it occurs in up to 20% of admissions and contributes to increase morbidity and mortality rates (1). Epidemiological data suggest that the risk factors for AKI include advanced age, diabetes, hypertension and cardiovascular disease, and it is closely associated with prolonged hospital stays, increased healthcare costs and higher mortality rates (2,3). AKI frequently occurs during acute illness. Studies have shown that patients who experience AKI are at a higher risk of progressing to chronic kidney disease (CKD), with the

severity and duration of AKI being critical determinants of this progression (4-8).

The pathophysiological mechanisms linking AKI to CKD are complex and multifactorial. One prominent theory is that renal tubular damage during AKI causes maladaptive repair processes, resulting in kidney fibrosis and scarring in the kidney (9). Such changes can disrupt the normal architecture and function of the kidney, predisposing individuals to CKD. Additionally, systemic factors such as inflammation and oxidative stress during AKI can exacerbate kidney injury and promote the transition to CKD (10-12).

The TGF-β/Smad signaling pathway plays a crucial role in the pathogenesis of both AKI and CKD pathogenesis. TGF-β is a central cytokine that mediates cellular responses to injury by promoting fibrosis and inflammation in the kidney. The activation of this signaling pathway induces the transcription of genes associated with extracellular matrix (ECM) production, resulting in renal fibrosis and the progressive loss of kidney function (13-16). The present review summarized the role of TGF-β/Smad signaling in the AKI-CKD transition, and provided potential therapeutic strategies to prevent this transition.

2. TGF-β/Smad signaling pathway

Structure and function of TGF-β. TGF-β is a multifunctional cytokine that regulates numerous cellular processes, including proliferation, differentiation and immune responses. It exists in three isoforms (TGF-β1, TGF-β2 and TGF-β3), each encoded by distinct genes and exhibiting unique biological activities. Structurally, TGF-β is characterized by a conserved cysteine knot motif, which is crucial for its stability and receptor binding. Upon secretion, TGF-β is typically found in a latent form, bound to latency-associated peptide, and must be activated to exert its biological effects. Activation can occur through various mechanisms, including proteolytic cleavage by matrix metalloproteinases or interaction with integrins, which release the active form of TGF-β from its latent complex (17). Functionally, TGF-β influences various cellular responses, including promoting tissue fibrosis and modulating immune responses, making it a critical player in both normal physiology and pathological conditions such as cancer and fibrosis (18,19). Its dysregulation is often implicated in several diseases, highlighting the importance of understanding TGF-β signaling in therapeutic contexts (20).

History of TGF-β and its signaling. Since its initial identification in 1978, TGF-β has been progressively studied and recognized as a regulator of several biological processes (21), including cell proliferation (22), differentiation (23), apoptosis (24) and tissue fibrosis (25). In 1981, Roberts *et al* (26) achieved the isolation and purification of TGF-β from non-neoplastic murine tissues, a milestone paralleled by Moses *et al* (27), who independently characterized this cytokine. An early functional study in 1983 revealed its in wound healing mechanisms (28). A critical breakthrough followed in 1985 when Derynck *et al* (29) determined the amino acid sequence of human TGF-β1 through direct protein sequencing and complementary DNA cloning, establishing it as the prototypical TGF-β isoform. Subsequent discoveries revealed two additional mammalian isoforms: TGF-β2 in 1987 (30) and TGF-β3 in 1988 (31,32). Notably, despite being encoded by distinct genes, these isoforms exhibit high sequence conservation in their mature forms.

The late 1980s and 1990s marked a notable advance in understanding the pathological roles of TGF-β. Its involvement in organ fibrosis was first documented in 1989 (33,34), followed by seminal investigations into its tumorigenic properties in 1995 (35,36). The discovery of SMAD proteins in 1996, homologs of *Caenorhabditis elegans* SMA and *Drosophila melanogaster* mothers against dpp protein, provided mechanistic insights into canonical TGF-β signaling pathways (37,38).

Therapeutic targeting accelerated in the 21st century. Phase I clinical trials of TGF-β antisense-modified tumor vaccines began in 2006 (39). In 2011, fresolimumab, a pan-TGF-β neutralizing monoclonal antibody (targeting β1/β2/β3 isoforms), entered clinical evaluation for primary focal segmental glomerulosclerosis (40). By 2014, pirfenidone, an antifibrotic agent that modulates TGF-β1 expression, received regulatory approval (41), and in 2015, galunisertib (LY2157299), a first-in-class TGF-β receptor I (TGF-βRI) kinase inhibitor, advanced into clinical trials for malignancies (42).

As illustrated in Fig. 1, the evolving understanding of TGF-β signaling has catalyzed the development of targeted therapies across multiple diseases. Ongoing translational research continues to validate TGF-β pathway modulation as a promising therapeutic strategy, particularly in fibrotic disorders.

Role of Smad proteins and their signal transduction process. The Smad proteins are a family of intracellular signaling molecules that mediate TGF-β signaling. Upon TGF-β binding to its receptors, TGF-βRI and TGF-β receptor II (TGF-βRII), the receptor complex undergoes autophosphorylation, resulting in the phosphorylation of receptor-regulated Smads (R-Smads), primarily Smad2 and Smad3 (43). This phosphorylation is a critical step that enables R-Smads to form a complex with Smad4, a common-mediator Smad, facilitating their translocation to the nucleus (44). Once in the nucleus, the Smad complex interacts with various transcription factors and co-factors to regulate the expression of target genes involved in processes such as cell growth, differentiation and apoptosis (45,46). The specificity of the TGF-β/Smad signaling pathway is further modulated by the presence of inhibitory Smads (I-Smads), such as Smad6 and Smad7, which can negatively regulate the pathway by preventing R-Smad phosphorylation or promoting their degradation (47). This intricate regulation underscores the versatility of the TGF-β/Smad signaling pathway in maintaining cellular homeostasis and its potential as a therapeutic target in diseases characterized by aberrant TGF-β signaling, such as fibrosis (48,49). Understanding the detailed mechanisms of Smad signaling is essential for developing strategies to modulate this pathway for therapeutic benefits.

3. TGF-β/Smad signaling activation in AKI, AKI-CKD transition and CKD

TGF-β/Smad signaling activation in AKI. In models of AKI, TGF-β expression increases significantly and correlates with

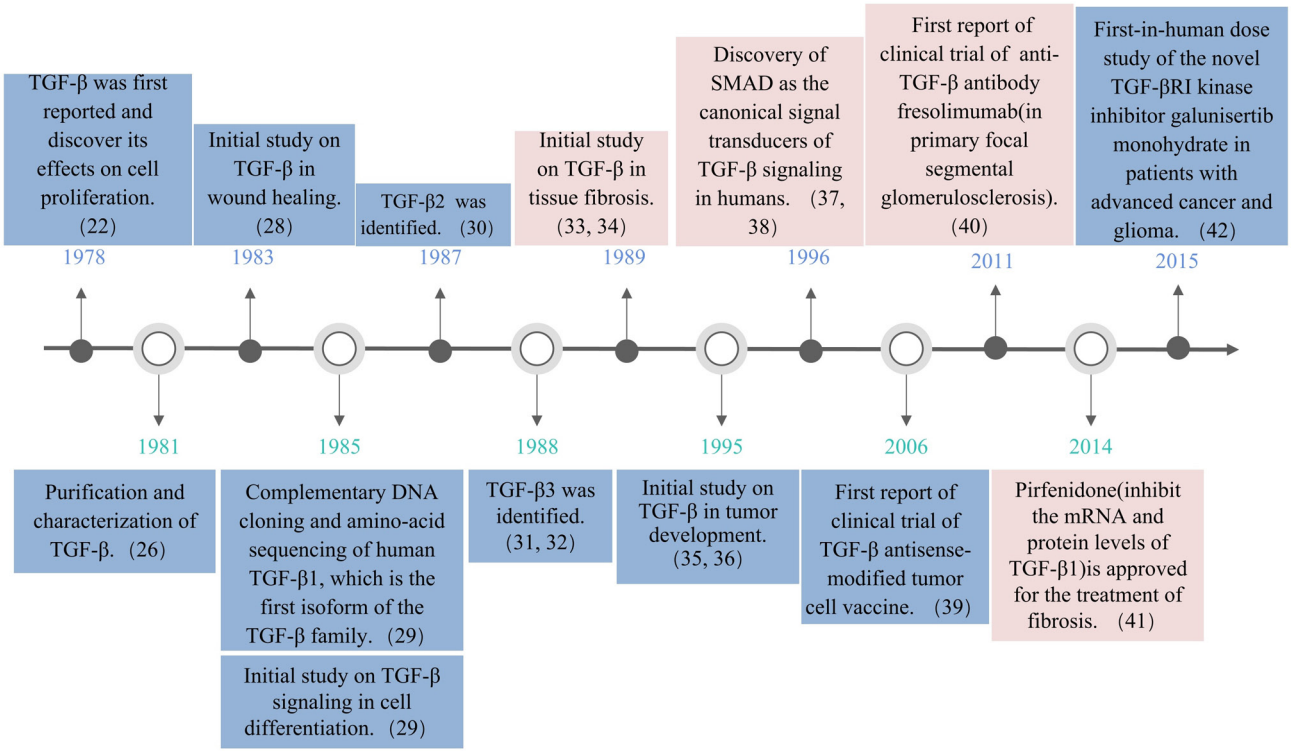

Figure 1. Timeline of milestones in TGF-β signaling research.

injury severity (50). Conditional knockout of TGF-βRII in experimental models confers protective effects against acute renal injury, underscoring the role of TGF-β in promoting inflammation and necroptosis during AKI (51). In tubular epithelial cells, TGF-β triggers the Smad2/3 phosphorylation and nuclear translocation, driving epithelial-to-mesenchymal transition (EMT) characterized by fibronectin and type I/III collagen upregulation, which is activation of the TGF-β/Smad pathway and early fibrotic progression in AKI phase. Specifically, upon TGF-β stimulation, renal tubular epithelial cells undergo morphological and functional changes, causing them to lose epithelial characteristics and acquire mesenchymal traits. This transition is characterized by the upregulation of fibronectin and collagen types I and III, which contribute to ECM deposition and fibrosis (52). TGF-β-induced EMT is mediated through the activation of Smad2/3 signaling pathways, which interact with various transcription factors to promote fibrogenic responses (53). Accordingly, the complex role of TGF-β in renal tubular cell dynamics presents a promising area of future research aimed at mitigating renal injury and fibrosis.

Sustained TGF-β/Smad signaling activation during the AKI-CKD transition. During the AKI-CKD transition, TGF-β1 signaling remains persistently activated, contributing to decreased kidney function. In this context, sustained TGF-β1/Smad signaling maintains Smad2/3 phosphorylation and Smad4 complex formation, driving the continuous transcription of ECM genes. Inhibiting TGF-β signaling can reduce renal fibrosis and improve renal function in models of AKI-CKD transition models (54,55). Therefore, targeting the TGF-β/Smad pathway is a promising therapeutic approach to mitigate CKD progression following AKI.

Crosstalk between TGF-β/Smad and other pathways in AKI-CKD transition. In addition to the TGF-β/Smad pathway, several other signaling pathways interact and influence AKI-CKD transition. For instance, the PI3K/Akt signaling pathway has been implicated in renal cell survival and apoptosis. Dysregulation of this pathway during AKI can exacerbate tubular injury and promote fibrosis (56-58). The Wnt/β-Catenin signaling pathway is also involved, mediating processes related to inflammation and fibrosis. Its activation is associated with poor outcomes in renal injury models (59-61). Furthermore, the interplay between inflammatory cytokines and pathways such as NF-κB and mitogen-activated protein kinases (MAPK) contributes to the persistent post-AKI inflammation, ultimately facilitating the progression to CKD (62-66).

Notably, as a central hub in the regulation of fibrosis, the TGF-β/Smad pathway exhibits extensive crosstalk with these other pathways (Fig. 2) (67). Specifically, in the PI3K/Akt pathway, TGF-β promotes Smad3 stabilization via Akt-mediated phosphorylation, thereby enhancing profibrotic gene transcription (68,69). Concurrently, TGF-β suppresses GSK-3β activity within the Wnt/β-catenin pathway, leading to β-catenin stabilization and its synergistic interaction with Smad3 to drive fibrogenesis (53,70). In parallel, MAPK signaling, primarily through Erk and p38, phosphorylates the linker regions of Smad proteins, modulating their transcriptional activity and fine-tuning the fibrotic response (71). Moreover, NF-κB activation interacts with TGF-β/Smad signaling to sustain inflammation, which further exacerbates fibrosis (72,73). Collectively, these integrated signaling networks emphasize the complex molecular interplay underlying fibrotic pathology and highlight potential targets for therapeutic intervention.

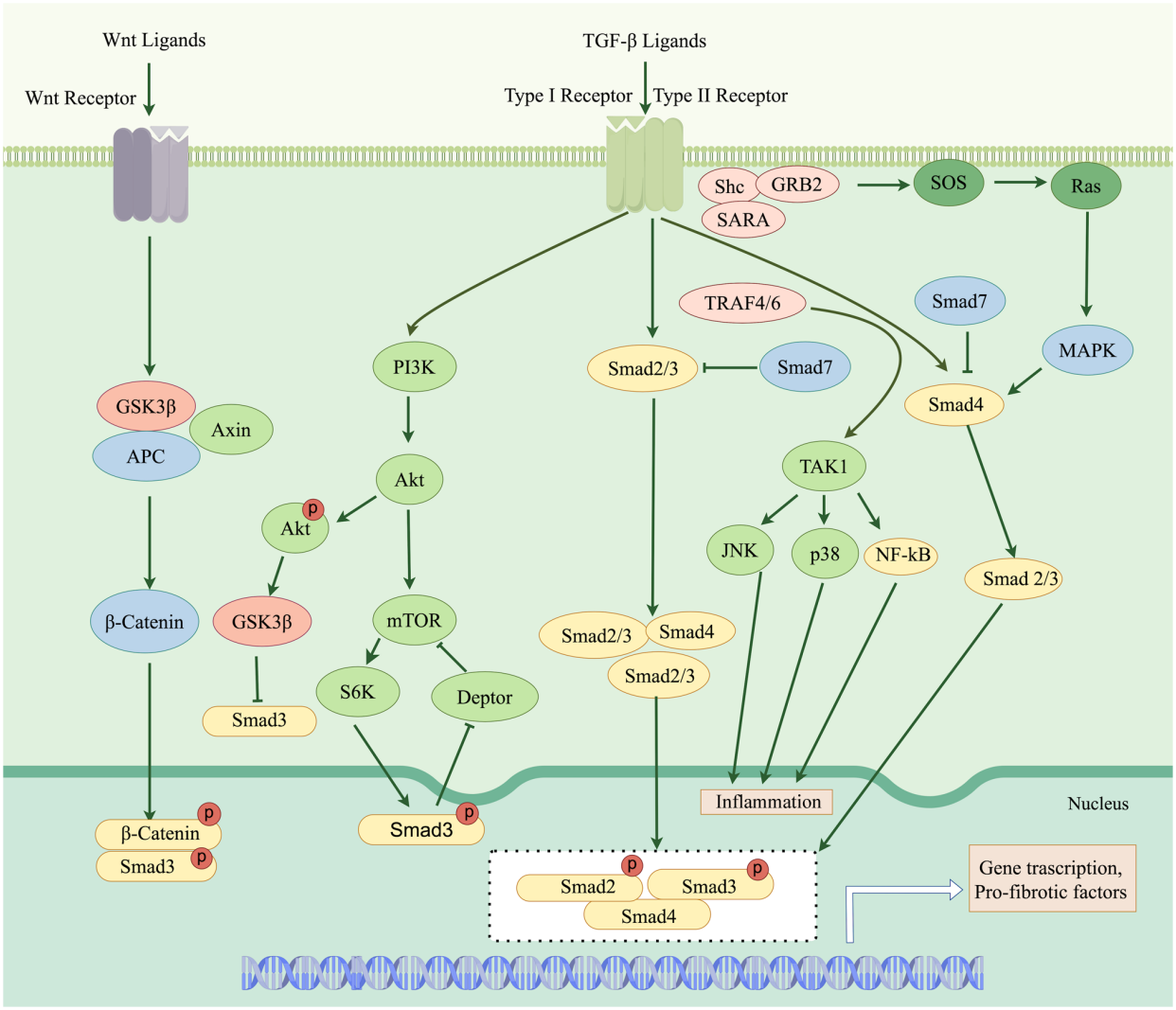

Figure 2. Biological processes of AKI-CKD and its relationship with TGF-β/Smad signaling. The Figure was created by Figdraw 2.0 (https://www.figdraw.com). AKI, acute kidney injury; CKD, chronic kidney disease; GSK-3β, glycogen synthase kinase-3β; TGF-β, transforming growth factor-β; MAPK, mitogen-activated protein kinases; Shc, SHC adaptor protein; SARA, SMAD anchor for receptor activation; SOS, son of sevenless (a guanine nucleotide exchange factor); TAK1, TGF-beta-activated kinase 1; APC, adenomatous polyposis coli.

TGF-β/Smad signaling pathway activation and regulation in CKD. Renal fibrosis is the main pathological characteristic of CKD (74,75). TGF-β promotes renal interstitial fibrosis through autocrine and paracrine mechanisms. Elevated TGF-β levels are commonly observed in various kidney diseases, including diabetic nephropathy (76), hypertensive nephropathy (77) and focal segmental glomerulosclerosis (78), each representing distinct etiologies of CKD. Elevated TGF-β1 expression and downstream Smad signaling contribute to progressive interstitial fibrosis and glomerulosclerosis in established CKD (79,80). MicroRNAs (miRNAs/miRs), including miR-21 and miR-155-5p modulate this axis by targeting Smad7 and suppressor of cytokine signaling proteins, respectively, thereby enhancing Smad2/3 phosphorylation and ECM gene expression (81). Additionally, macrophage-derived TGF-β and epithelial cell-fibroblast cross-talk exacerbate ECM accumulation via sustained paracrine loops (82,83). Therapeutic strategies that restore Smad7 expression or employ neutralizing antibodies against TGF-β reduced collagen deposition and improved renal histology in a rodent CKD model (84). Furthermore, inhibiting TGF-β signaling reduced renal fibrosis and enhanced tubular function in preclinical models (85), highlighting its potential as a therapeutic target. Small-molecule inhibitors of TGF-β receptor kinases and modulators of Smad ubiquitination (for example, SMURF2 activators) offer further promise for reversing chronic fibrosis (86).

4. Molecular networks in AKI-CKD transition

AKI is a major risk factor for CKD (87,88), owing to the complex molecular interactions underlying this transition. Multiple biological processes contribute to this progression, including inflammatory responses (89), renal tubular cell injury (90) and maladaptive repair (9,91,92), ECM deposition (93,94), impaired renal microvascular endothelial function (95-97), oxidative stress (95,98,99), mitochondrial dysfunction (100,101) and EMT (102) transition (Fig. 3). Ultimately, the AKI-CKD transition is characterized by persistent renal damage, which likely results from direct tubular cell injury and subsequent fibrotic remodeling due to dysregulated repair mechanisms, resulting in functional

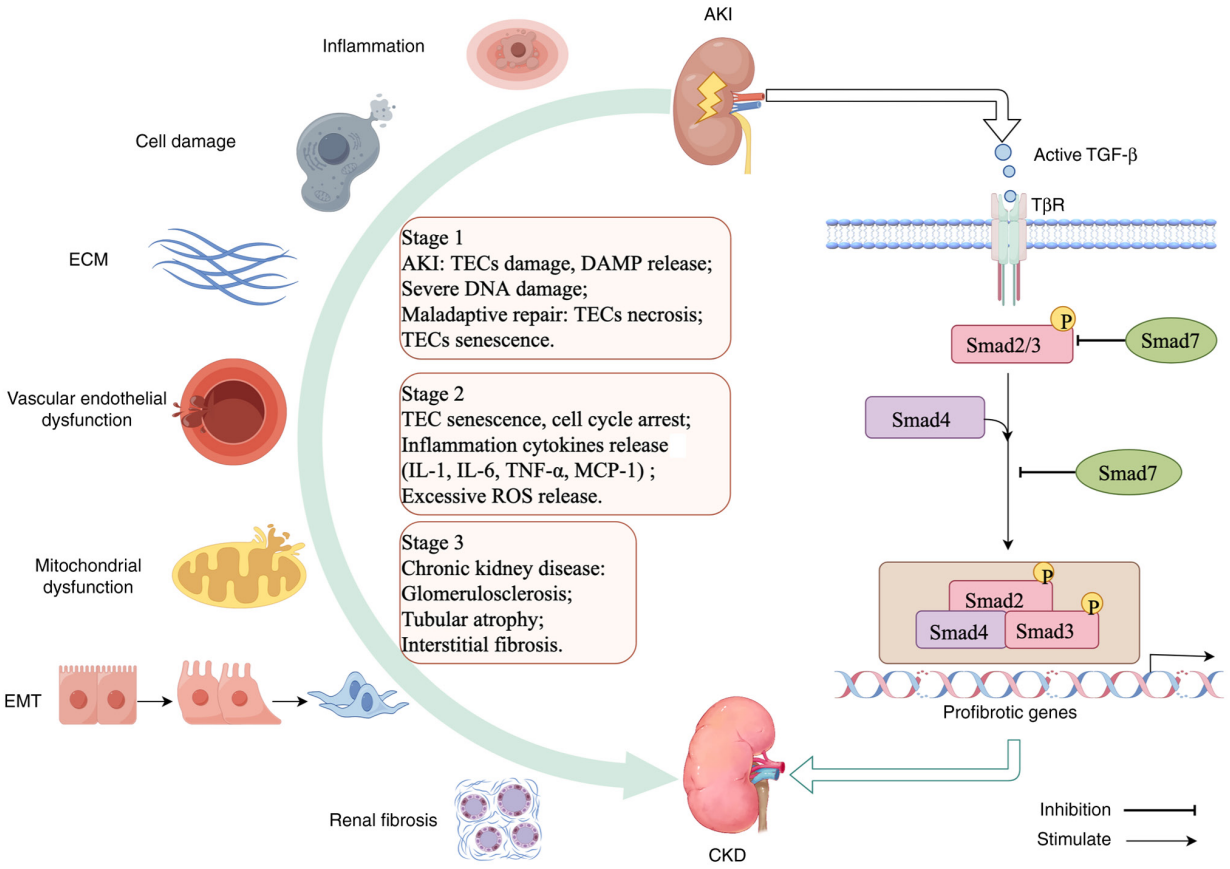

Figure 3. Crosstalk of TGF-β/Smad signaling with other signaling pathways in renal fibrosis. The Figure was created by Figdraw 2.0 (https://www.figdraw.com). AKI, acute kidney injury; ECM, extracellular matrix; CKD, chronic kidney disease; EMT, epithelial-to-mesenchymal transition; TEC, T-cell protein tyrosine kinase; DAMP, damage-associated molecular patterns; MCP-1, monocyte chemoattractant protein-1; ROS, reactive oxygen species; TβR, TGF-β recepter.

loss (103). The TGF-β/Smad signaling pathway is a key contributor to AKI-CKD transition (5). A thorough understanding of these mechanisms is essential for developing targeted therapeutic strategies to prevent CKD progression in AKI individuals.

Gene expression during the AKI-CKD transition. Recent advances in RNA-sequencing (RNA-seq) have expanded our understanding of the molecular dynamics underlying the AKI-CKD transition. Comprehensive transcriptomic analyses using murine ischemia-reperfusion injury (IRI) models [dataset no. GSE98622; Gene Expression Omnibus (GEO); https://www.ncbi.nlm.nih.gov/geo)] (104), spanning multiple time points ranging from hours to 1-year post-injury, have revealed distinct temporal patterns of gene expression closely associated with pathological phases of renal injury progression. In the initial acute phase post-injury, rapid transcriptional activation of inflammatory responses and stress-related genes, such as keratin20 gene (104) and Ankyrin repeat domain-containing protein 1 (Ankrd1) (105), occurs, which is indicative of acute tubular damage and the onset of maladaptive repair mechanisms. Notably, these genes remain elevated beyond the acute phases, correlating with persistent damage and fibrosis development. Similar trends have been observed in human AKI, where urinary biomarkers such as kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin (NGAL) remain elevated months post-injury, further linking early molecular events to chronic disease progression (106).

At the single-cell resolution level, GEO database show that single-nucleus RNA-seq (GSE139107) (107) of mouse IRI models has provided unprecedented insight into the cellular heterogeneity of AKI-CKD transition (108). A distinct subset of proximal tubular cells, termed as 'failed-repair proximal tubular cells' (FR-PTCs), was consistently detected during the recovery phase (108). These FR-PTCs demonstrated a robust pro-inflammatory and pro-fibrotic transcriptional signature, characterized by high expression of inflammatory adhesion molecules (e.g. vascular cell adhesion protein 1), chemokines (e.g. chemokine ligand 2) and fibrotic mediators (e.g. TGF-β2) (108). The cells exhibited persistent G_2/M cell cycle arrest and actively promoted macrophage infiltration and fibrotic remodeling, thus playing a pivotal role in the evolution from AKI progression to chronic fibrosis (108). Moreover, cross-validation analyses in human kidney allograft biopsies confirmed similar maladaptive cellular states, highlighting translational relevance.

Further enhancing these molecular insights, differential RNA-seq analyses comparing mild and severe injury in models (dataset no. GSE179506) (107) revealed pronounced dysregulation of long non-coding RNAs, particularly Neat1_2, which is specifically associated with severe, irreversibly fibrotic outcomes (109). Mechanistically, Neat1_2 mediates tubular epithelial cells apoptosis by competitively sequestering miR-129-5p, thereby increasing the expression of pro-apoptotic genes, including FAS-associated death domain protein, caspase-8 and caspase-3 (109). Zheng *et al* (110) evaluated

the renal NLRP3 expression during the acute and chronic phases of ischemic AKI, using mild and severe IRI-induced AKI mouse models. The results revealed that persistent NLRP3 overexpression was associated with chronic pathological changes following AKI (110). These findings clearly illustrate how severity-specific transcriptional reprogramming influences long-term kidney injury outcomes.

The cisplatin-AKI model has also been used to investigate chronic inflammation following toxicant injury, with findings indicating that sustained activation of STAT1/high mobility group box 1 (HMGB1) activation contributes to chronic tubular damage (111). However, publicly available transcriptomic data from such toxicant- and sepsis-induced models remain relatively limited. To address this, Cui *et al* (112) performed an integrated analysis using datasets from the GEO database (https://www.ncbi.nlm.nih.gov/geo) [dataset nos. GSE207587 (113) and GSE216376 (114)], and further established IRI-, cisplatin- and unilateral ureteral obstruction (UUO)-induced AKI models for RNA-seq analysis (dataset no. GSE183455). Their findings revealed a sustained upregulation of interferon-stimulated gene 15 (ISG15) throughout the course of AKI, which exacerbated AKI and promoted CKD by facilitating ISGylation of TGFβR1 (112).

A recent review comprehensively summarized current evidence on circulating and urinary biomarkers predictive of AKI-CKD transition. It highlighted the diagnostic and prognostic utilities of biomarkers such as NGAL, liver-type fatty acid-binding protein, HMGB1 and cystatin C, and emphasized the potential of multimarker panels for risk stratification. The authors also called for further validation studies to establish reliable biomarker-guided strategies for early intervention and personalized therapy in AKI-CKD transition (115).

Collectively, these comprehensive RNA-seq datasets from various injury models, including ischemic, toxic and obstructive etiologies, illustrate a common transcriptional theme characterized by sustained activation of inflammatory and fibrotic pathways, failure of metabolic and reparative gene expression normalization, and emergence of maladaptive cell states (116). These persistent transcriptional dysregulations fundamentally drive the progression from AKI to CKD, offering valuable molecular targets for diagnostic biomarkers and therapeutic interventions aimed at halting or reversing renal disease progression.

TGF-β/Smad related biomarkers in the AKI-CKD transition. Due to the pro-fibrotic role of the TGF-β/Smad signaling pathway in the AKI-CKD transition (50), multiple components of pathway undergo characteristic changes in expression during disease progression, making them potential candidate biomarkers. Since 2020, several studies have validated biomarkers such as TGF-β1, Smad3, Smad7, connective tissue growth factor (CTGF), miR-21, ISG15, Ankrd1 and UHRF1. The present study summarized their expression patterns during the AKI-CKD transition, the potential for predicting disease progression or fibrosis severity, validation status in animal models or human specimens, and the sample types and detection methods applicable to each marker.

TGF-β1. TGF-β1 is a well-established pro-fibrotic cytokine. A study by L.S. Gewin (50) reported that injured proximal tubular epithelial cells persistently secrete TGF-β1, thereby promoting the progression of renal fibrosis. TGF-β1 induces epithelial cell dedifferentiation and cell cycle arrest, contributes to capillary rarefaction and tissue hypoxia, stimulates the transdifferentiation of fibroblasts and pericytes into myofibroblasts for excessive ECM production and facilitates macrophage recruitment (50). Collectively, these effects contribute to chronic progressive fibrosis following AKI.

Another study demonstrated that TGF-β1 levels are elevated during both the acute and chronic phases in an IRI-induced CKD model, with the highest serum levels observed in the chronic group (117). These findings suggest that circulating TGF-β1 may help differentiate between acute inflammation and chronic injury and may serve as an indicator of renal fibrotic severity (117). Therefore, TGF-β1 is considered a potential biomarker for predicting fibrotic progression after AKI. It is detectable in both serum and urine, commonly by enzyme-linked immunosorbent assay (ELISA) and its tissue expression can be evaluated by immunohistochemistry (117). Overall, elevated TGF-β1 levels at early stages often predict more severe long-term fibrosis.

Smad3 and Smad7. Smad3 and Smad7 are regulatory factors in the TGF-β/Smad signaling pathway, exerting opposing roles in renal fibrosis post-AKI (118). Smad3 functions as a major downstream transcription factor of TGF-β1 signaling. It is rapidly activated (via phosphorylation) during the early phase of AKI and promotes the expression of multiple pro-fibrotic genes, thereby serving as a critical driver of renal fibrogenesis (13). Deletion of Smad3 mitigates renal dysfunction and chronic scarring following AKI, whereas enhanced Smad3 activity worsens post-AKI fibrosis (119,120).

Conversely, Smad7 acts as an endogenous inhibitor of this pathway by blocking the phosphorylation of receptor-regulated Smads (R-Smads) or promoting their degradation, thereby exerting antifibrotic effects (13). However, during the AKI-CKD transition, sustained TGF-β1 elevation suppresses Smad7 expression, disrupts the Smad3/Smad7 balance and accelerates collagen deposition and fibrotic remodeling. A study in a UUO model demonstrated that Smad7 deficiency exacerbates inflammation and fibrosis, whereas its overexpression attenuates TGF-β/Smad2/3 signaling and reduces the expression of fibrotic markers such as α-SMA and CTGF (13).

Although both Smad3 and Smad7 are intracellular proteins and not easily measured in biofluids, their expression levels can be accessed via immunohistochemistry or molecular analyses of renal biopsy specimens (13). Collectively, a molecular profile characterized by upregulated Smad3 and downregulated Smad7 often reflects overactivation of the TGF-β pathway, more severe renal fibrosis and an increased risk of the AKI-CKD transition.

CTGF. CTGF is a critical pro-fibrotic factor downstream of TGF-β and it is markedly upregulated during renal injury and fibrosis. It promotes fibroblast proliferation and ECM deposition and is considered a mediator of renal fibrogenesis (121). In a contrast-induced AKI mouse model, CTGF gene expression in renal tissue was markedly increased in renal tissue as early as two days post-injury (122). Persistent CTGF upregulation is indicative of maladaptive repair and may indicate the onset of

fibrotic remodeling following AKI (121). Clinically, CTGF has been evaluated as a potential biomarker. As a secreted protein, it can enter the circulation or be excreted in urine. A study in patients with AKI have shown that urinary CTGF levels increase following kidney injury and are correlated directly with CTGF expression in the kidney (122). Although clinical data on CTGF as a prognostic marker remain limited, existing evidence suggests that urinary CTGF levels are associated with the degree of renal interstitial fibrosis, indicating its potential as a non-invasive marker for fibrosis (122). CTGF can be measured in serum or urine using ELISA and its tissue expression can be assessed by immunohistochemistry in renal biopsy specimens. In summary, sustained elevation of CTGF following AKI reflects increased fibroblast activity and excessive ECM deposition, serving as a warning signal for potential progression toward CKD.

miR-21. miR-21 *i*s a non-coding miRNA that plays multifaceted regulatory roles in renal injury and fibrosis and has garnered increasing attention in recent years. TGF-β signaling can induce miR-21 upregulation, which in turn enhances TGF-β/Smad pathway activity by targeting and suppressing anti-fibrotic factors such as Smad7 (123). A study using an AKI-to-CKD model demonstrated that miR-21 expression is persistently elevated during the progression from AKI to renal fibrosis, in both the tubular interstitium and glomeruli (119). Genetic deletion of miR-21 or administration of anti-miR-21 oligonucleotides attenuates interstitial fibrosis following AKI in mice (119), indicating a pro-fibrotic role for miR-21 in this context.

Clinically, miR-21 holds promise as a non-invasive biomarker, as it is stably present in extracellular vesicles within blood and urine. In patients with cardiac surgery-associated AKI, miR-21 levels were elevated post-operatively in both urine and plasma, correlating with the need for renal replacement therapy and in-hospital mortality (124). Another study showed that urinary miR-21 levels increased earlier than proteinuria in a hypertensive nephropathy mouse model and were associated with histopathological changes in the kidney (125).

Currently, miR-21 is primarily quantified using quantitative PCR (qPCR), which is applicable to serum, plasma and urine samples (124). Therefore, miR-21 functions as a downstream effector of TGF-β/Smad signaling and its sustained upregulation throughout the AKI-CKD transition highlights its potential both as a diagnostic biomarker and a therapeutic target.

miR-29c. miR-29 is an antifibrotic microRNA whose expression is typically suppressed by TGF-β signaling, thereby lifting repression of fibrosis-related genes such as those encoding collagens. In patients with CKD, urinary exosomal miR-29c levels have been found to inversely correlate with the degree of tubulointerstitial fibrosis, with lower miR-29c expression associated with more severe tissue fibrosis (126). Accordingly, decreased urinary miR-29c may serve as a non-invasive indicator of renal fibrosis and its quantification is typically performed using qPCR.

In addition, downregulation of miR-29, alongside upregulation of miR-21 and miR-192, has been identified as a hallmark of TGF-β/Smad-mediated miRNA imbalance in chronic conditions such as diabetic nephropathy (127). Although clinical studies on the application of miR-29 application remain limited, its potent antifibrotic properties underscore its potential as a promising biomarker candidate.

Flavin-containing monooxygenase 2 (FMO2). FMO2 is a NADPH-dependent enzyme highly expressed in renal tubular cells but downregulated following IRI (86). Lentiviral overexpression of FMO2 in mice attenuates AKI and subsequent fibrosis by promoting SMURF2 nuclear translocation, which in turn ubiquitinates and degrades phosphorylated SMAD2/3, thereby inhibiting TGF-β1 signaling (86). FMO2 levels can be monitored in kidney tissue and cultured tubular cells using immunohistochemistry, western blotting and reverse transcription (RT)-qPCR (86). Its dynamic expression suggests that FMO2 may serve as a novel regulator of maladaptive repair and a predictive biomarker for AKI-CKD transition.

Fibroblast growth factor-23 (FGF-23). FGF-23 is an endocrine regulator of mineral metabolism. Elevated FGF-23 levels are observed early in patients with AKI and are higher in those who progress to CKD compared to non-progressors (128). In IRI-AKI models, FGF-23 levels increase rapidly following AKI and are associated with the development of renal fibrosis (128). Mechanistically, FGF-23 promotes fibrosis through the activation of the TGF-β/Smad3 and Wnt/β-catenin signaling pathways, contributing to tubular EMT and ECM deposition. The active form, iFGF-23, can be quantified using ELISA. Consequently, FGF-23 not only participates in the molecular mechanisms of the AKI-CKD transition but also demonstrated an early elevation that is closely associated with CKD progression, making it a promising biomarker for the AKI-CKD transition.

Plasminogen activator inhibitor-1 (PAI-1). PAI-1 is a direct transcriptional target of TGF-β and is upregulated in the tubulointerstitial compartment of various kidney diseases (129). It promotes fibrosis primarily by inhibiting fibrinolysis, thereby reducing ECM degradation. Following AKI, damaged kidneys releases PAI-1 into the urine, and studies have confirmed that urinary PAI-1 originates from damaged renal parenchyma (130). Urinary PAI-1 levels are elevated after AKI and correlate with intrarenal PAI-1 expression. Therefore, urinary PAI-1 serves as an indicator of TGF-β activation and fibrotic response triggered by acute injury. Detection is typically performed using ELISA. Further studies are needed to determine the prognostic value of urinary PAI-1 in predicting AKI-CKD transition (130).

Ankrd1. Ankrd1 is a recently identified gene discovered through the analysis of publicly available datasets (GSE139107 and GSE98622) in the GEO database. The protein encoded by Ankrd1 is associated with actin binding (105). In an IRI model of AKI, Ankrd1 was found to be selectively and persistently upregulated in proximal tubular cells, with elevated expression lasting up to 60 days post-injury (105). Mechanistically, TGF-β1 was shown to induces the YAP/TAZ signaling pathway and its downstream target Ankrd1, which is further implicated in TGF-β/Wnt-mediated fibrogenic responses (105). Persistent upregulation of Ankrd1 is associated with increased fibrosis and worsened renal function, suggesting its potential utility as a

biomarker for the transition from AKI to CKD. To date, Ankrd1 has been validated primarily in murine models and *in vitro* systems using RNA-seq, RT-qPCR and immunohistochemistry with detection in renal tissue. However, further studies are required to confirm its clinical significance in human samples.

UHRF1. UHRF1 is a critical epigenetic regulator involved in the AKI-CKD transition via the TGF-β/SMAD signaling pathway. UHRF1 was upregulated in UUO and folic acid-induced fibrosis animal models, and in human fibrotic kidney tissues, where it promoted EMT and ECM deposition by enhancing SMAD2/3 phosphorylation. Genetic knockdown or pharmacological inhibition of UHRF1 effectively attenuated renal fibrosis and suppressed EMT both *in vitro* and *in vivo* (131). Although UHRF1 is not currently measurable in body fluids, its expression in kidney biopsies and functional linkage to TGF-β signaling suggests potential as a tissue-based biomarker for AKI-CKD transition and a therapeutic target for anti-fibrotic intervention.

These biomarkers are closely linked to the TGF-β/Smad signaling pathway, and their dysregulated expression following AKI may indicate the initiation and progression of renal fibrosis. These biomarkers vary in terms of biological source and detection method: Protein markers such as TGF-β1, CTGF and PAI-1 can be measured in serum or urine using ELISA, whereas mRNA or miRNA markers including Smad7, miR-21 and miR-29 can be quantified by qPCR in urinary cells, extracellular vesicles or plasma, and their expression can also be assessed in biopsy tissue using *in situ* hybridization or PCR-based techniques. Although renal biopsy remains the gold standard for diagnosing fibrosis, its invasiveness limits repeated application. Therefore, developing reliable fluid-based alternatives is of great value. Recently, biomarkers associated with the TGF-β/Smad pathway have demonstrated favorable specificity and clinical potential. Notably, their alterations often precede changes in traditional indicators such as Scr or proteinuria, enabling earlier prediction of maladaptive repair outcomes in patients with AKI. Moving forward, combined biomarker panels may enhance the predictive accuracy for AKI-CKD transition (124) and support timely therapeutic interventions targeting the TGF-β/Smad signaling axis.

5. TGF-β/Smad signaling pathway-related drugs inhibit AKI-CKD transition

Inhibition of TGF-β signaling. As a pivotal cytokine in renal fibrosis, TGF-β drives EMT in tubular epithelial cells and activates fibroblasts by promoting ECM deposition (132,133). Due to its central role, therapeutic strategies targeting TGF-β1 have been extensively explored. Emerging approaches include small-molecule inhibitors, neutralizing antibodies and RNA interference. For example, nanoparticle-mediated delivery of TGF-β1 small interfering RNAs (siRNAs) reduces renal inflammation and fibrosis in preclinical models (134). Similarly, WNT1-inducible-signaling pathway protein 1 antibodies inhibit TGF-β signaling and attenuate fibrotic progression (135). MiRNAs such as let-7b, miR-29 and miR-192 also suppress TGF-β1 activity, delaying fibrosis (136-139). Notably, glycogen synthase kinase-3β promotes renal fibrosis by activating TGF-β signaling, and its inhibitor alleviates ischemia-reperfusion-induced progressive fibrosis (140). These findings highlight TGF-β blockade as a critical strategy for managing CKD.

Inhibition of Smad. To avoid compromising the anti-inflammatory effects of TGF-β, researchers are increasingly prioritizing downstream targets such as Smad2/3/4, Smad7 and Smad-dependent miRNAs (141). The Smad3-specific inhibitor (SIS3) reduces excessive ECM production in TGF-β1-stimulated fibroblasts and suppresses Btg2-mediated podocyte EMT, suggesting its therapeutic potential against glomerulosclerosis (78,142). Overexpression of Smad7 inhibits renal inflammation and fibrosis in CKD models (16,143). Additionally, BMP-7, an endogenous TGF-β antagonist, counteracts fibrotic signaling in CKD (144,145). Small molecules such as BT173 (a HIPK2 analog) inhibit Smad3 phosphorylation and ECM deposition in UUO and Tg26 mice (146). Niclosamide phosphate suppresses Smad3/NF-κB activation by blocking Smad3-HIPK2 promoter interaction, offering promise for fibrosis treatment (147). Combinatorial therapies, such as telmisartan/pitavastatin synergistically inhibit TGF-β1-Smad/NF-κB signaling (148). Additionally, FTY720 (a sphingosine analog) mitigates collagen deposition and tubulointerstitial fibrosis (149). Melatonin combined with poricoic acid A disrupts Smad3-β-catenin interaction, attenuating AKI-to-CKD progression (55,80).

Natural products modulating TGF-β/Smad3 signaling. Several natural compounds demonstrate antifibrotic activity by modulating TGF-β/Smad3 signaling. Poricoic acids (ZG, ZH) from *Poria cocos (syn. Wolfiporia extensa)* attenuates renal fibrosis and podocyte injury by blocking Smad anchor for receptor activation-TGFβRI-Smad3 interaction (70). Curcumin reduces fibroblast proliferation and ECM accumulation via PPAR-γ and Smad-dependent pathways (150). Sinomenine alleviates UUO-induced fibrosis by activating Nrf2 to counteract oxidative stress (151). Oxymatrine suppresses myofibroblast activation and inflammation via Smad3 inhibition (152,153). Tanshinone IIA (154) and leonurine (155) dual-target Smad3/NF-κB pathways to mitigate fibrosis. (±)-Sinensilactam A, a rare metabolite, inhibits Smad3 phosphorylation in TGF-β1-stimulated renal tubular cells (156). Epigallocatechin-3-gallate activates Nrf2 to suppress Smad2/3 phosphorylation and EMT (157). Astragaloside IV (AS-IV), the primary bioactive component of *Astragalus membranaceus*, is recognized as a nephroprotective agent. It attenuates TGF-β1-induced EMT in peritoneal mesothelial cells by promoting Smad7 expression to inhibit Smad2/3 activation (158). Subsequently, an *in vitro* and *in vivo* study confirmed that AS-IV upregulates Smad7, thereby blocking the upregulation of TGF-β1, α-SMA and CTGF, as well as the activation of phosphorylated Smad2/3, which contributes to its renoprotective effects against fibrosis (159). Chrysophanol, an anthraquinone from *Rheum palmatum*, disrupts Smad3-TGFβRI binding, reducing phosphorylated-Smad3 and interstitial fibrosis (160). These findings highlight the promise of natural products in slowing the AKI-CKD transition.

Table I summarizes additional drug interventions (84,92,153,158,161-178), both targeting and non-targeting TGF-β/Smad3 signaling in AKI-CKD transition, to provide a reference for future studies on the AKI-CKD transition.

Table I. Summary of studies on inhibiting the AKI-CKD transition.

Drug	Model	Mice type	Cell type	Outcome	Mechanism	(Refs.)
Integrin β8	STZ-induced DKD	Integrin β8 knock-in mice	Pericyte	Prevent pericyte-myofibroblast transition	Inhibiting the TGF-β1/TGFβR1/Smad3 pathway	(160)
SIS3	STZ-induced DKD	B6.Cg-Tg (Tek-cre) 12F1v/J mice, B6.Cg-Tg (ACTB-Bgeo/GFP) 21Lbe/J mice, C57BL/6J mice, α-SMA/EYFP mice	MMEC	Inhibit EMT	Inhibiting Smad3 activation	(161)
TG2	-	-	EC; Human dermal foreskin fibroblasts	Prevent EMT	Fine-tune of TGFβ1 signaling	(159)
Fasudil	High glucose-induced EMT	-	HK-2 cells	Inhibit EMT	Reducing activation of RhoA/ROCK signaling, and decreased expression of TGF-β1 and CTGF	(158)
Oxymatrine	High glucose-induced EMT	-	NRK52Es	Inhibit EMT	Upregulating SnoN expression and inhibiting TGF-β1/Smad signaling pathway activation	(137)
AS-IV	TGF-β1-induced EMT	-	HMrSV5	Inhibit EMT	Inhibiting the activation of Smad2/3	(142)
Sodium molybdate	Cisplatin-induced CKD	Wistar rats	-	Inhibit EMT	Inhibiting TGF-β/Smad signaling pathway and up-regulation of Smad7 expression, decreasing ROS NF-κB and TNF-α levels and extracellular collagen accumulation	(72)
Clodronate liposomes	IRI-induced AKI-CKD	C57BL/6J mice	-	Attenuate renal fibrosis and prevent AKI-CKD transition	Depleting of macrophages, reduce IL-10 and TGF-β	(157)
PKM2	uIRI-induced AKI-CKD UUO	C57BL/6J mice, tdTomato mice	Renal pericytes	Reducing import of PKM2 can inhibit renal pericyte-to-myofibroblast transdifferentiation	Modulating downstream LDHA and GLUT1 transcription as well as a decrease in lactate production	(156)

Table I. Continued.

Drug	Model	Mice type	Cell type	Outcome	Mechanism	(Refs.)
Endothelin-A antagonist	Prolonged ischemia-induced AKI	C57BL/6J mice	-	Prevent AKI-CKD transition	Reduced circulating and renal inflammation, improved macrovascular and microvascular function	(155)
RP81-MNP	Cisplatin-induced CKD	C57BL/6J mice	-	Protect against cisplatin-induced CKD	RP81-MNP specifically delivered to the renal proximal tubules, decreasing cell death and improving the viability of the renal proximal tubule, suppressing inflammatory macrophages and myofibroblasts	(154)
FG4592 (Roxadustat)	UIRI-induced AKI-CKD model	C57BL/6J mice	-	Retard the AKI-CKD transition	Activating the HIF-1α/VEGFA/VEGFR1 signaling pathway and driving the expression of the endogenous antioxidant SOD2	(79)
FIH-1	IRI-induced AKI-CKD	C57BL/6 mice	-	Prevent AKI-CKD transition	Overexpression of FIH-1 inhibited HIF-1α C-TAD	(153)
Spironolactone	IRI-induced AKI-CKD	Wistar rats	-	Prevent AKI-CKD transition	Reduction of inflammation and increased endothelin-B-receptor expression and endothelial nitric oxide synthase activation in the first 10 days after IR	(152)
Gal-8	Folic acid-induced AKI	Female C57BL/6NTac mice	-	Prevent the transition from AKI to renal fibrosis	Reducing cell death, promote epithelial cell redifferentiation, and inhibiting fibroblast activation, decreasing expression of fibrotic genes	(151)
TMNPs	IRI	Self-assembling into TAT-MKK3b nanoparticles	-	Ameliorate AKI-CKD transition	Inhibited ferroptosis via its SLC7A11/GPX4 axis-inducing capacity and synergistic potent antioxidant property	(150)
Diosgenin	IRI-induced AKI-CKD	C57BL/6 mice	HK-2 cells	Mitigate the development from AKI to CKD	Modifying the NOX4/p65 signaling pathways, reducing renal expression of inflammatory, fibrotic and EMT markers	(80)

Table I. Continued.

Drug	Model	Mice type	Cell type	Outcome	Mechanism	(Refs.)
PBMC	bIRI-induced AKI-CKD	CD-1 mice	-	Prevent tissue fibrosis after AKI	Modulating the pattern of monocyte/macrophage survival in tissue, reducing NLRP3, IL-1β, Caspase 1, cell death and increasing GPX4	(149)
NGAL release from PBMC	bIRI-induced AKI-CKD	C57BL/6J and B6 129P2-Lcn2tm1Aade/AkiJ (NGAL KO) mice	NRK52e	Against AKI and prevent AKI induced fibrosis	Induced epithelial proliferation and activation of PI3K/Akt pathway	(148)
Liposomal-packaged miR-486-5p	IRI-induced AKI-CKD	Male rats	-	Against CKD development and systemic endothelial dysfunction.	Inhibition of endothelial ICAM-1 and occur despite reduction in eNOS	(147)
Remimazolam	Folic acid-induced AKI	Male C57BL/6 mice	-	Inhibit the transformation of macrophages to myofibroblasts in FA nephropathy	Related to the peripheral benzodiazepine receptor pathway	(146)
miR-204	uIRI-induced AKI-CKD	C57BL/6J male mice	HK2 cells	Inhibit EMT	Suppressing SP1/EMT signaling pathway by directly targeting SP1	(145)

STZ, Streptozotocin; SIS3, specific inhibitor of Smad3; TG2, Transglutaminase 2; EC, endothelial cell; DKD, Diabetic kidney disease; MMEC, mouse pancreatic microvascular endothelial cell line; EMT, epithelial-mesenchymal transition; HMrSV5, human peritoneal mesothelial cells; AS-IV, Astragaloside IV; uIRI, unilateral renal ischaemia-reperfusion injury; UUO, Unilateral ureteral obstruction; bIRI, bilateral ischemia-reperfusion injury; VEGFA/VEGFR1, vascular endothelial growth factor A/VEGF receptor 1; SOD2, superoxide dismutase 2; RP81-MNP, mesoscale nanoparticles-encapsulated RP81; UIR, unilateral kidney ischemia-reperfusion; Gal-8, Galectin-8; TMNPs, TAT-mitogen-activated protein kinase kinase 3b nanoparticles; SLC7A11/GPX4, solute carrier family 7 member 11/glutathione peroxidase 4; PBMC, peripheral blood mononuclear cell; AKI, acute kidney injury; NRK52es, rat renal tubular epithelial cells; PKM2, pericyte pyruvate kinase M2; HK-2 cells, human kidney proximal tubule epithelial cell line; a-SMA, a-Smooth muscle actin; --, No report.

Current therapeutic challenges. Despite substantial advances in researching and targeting the TGF-β/Smad signaling pathway, several major challenges limit the clinical effectiveness of these therapies in preventing or reversing the transition from AKI-CKD transition.

First, current clinical agents targeting the TGF-β/Smad pathway exhibit distinct limitations. The TGF-β family comprises multiple isoforms (TGF-β1, TGF-β2, TGF-β3), each playing roles beyond fibrosis, including immune modulation and cellular homeostasis. Current inhibitors such as Fresolimumab, a pan-TGF-β monoclonal antibody, broadly neutralize all isoforms. This non-specific blockade can inadvertently disrupt beneficial physiological processes, potentially resulting in undesirable systemic effects (179). Pirfenidone, an FDA-approved antifibrotic agent, has demonstrated only modest efficacy in clinical practice, typically slowing rather than reversing fibrosis, with common gastrointestinal side effects often reducing patient compliance (41). SIS3, while promising in preclinical models, has yet to demonstrate efficacy and safety in human studies, with concerns remaining about unintended impacts on normal cellular functions and tissue homeostasis (180).

Second, the chronic inhibition of TGF-β signaling carries a risk of serious side effects. Although blocking this pathway can effectively reduce renal fibrosis, TGF-β also serves essential anti-inflammatory and tumor-suppressive functions in tissues. Consequently, prolonged suppression of TGF-β activity may impair immune responses, increase susceptibility to infections, or trigger autoimmune-like conditions (181,182). Galunisertib, a TGF-β receptor kinase inhibitor, sustained inhibition may impair tissue regeneration and repair, potentially increasing long-term malignancy risks, as indicated by an early clinical trial involving Galunisertib and related kinase inhibitors (183). Moreover, extensive crosstalk between TGF-β signaling and other pathways, such as Akt, Wnt and MAPK, further complicates therapeutic precision (67). Selective targeting of specific isoforms or downstream effectors remains to be elucidated.

Third, translating promising preclinical findings into effective clinical treatments remains challenging. Animal models used in preclinical studies often fail to replicate the complexity of human CKD progression, limiting predictive accuracy for clinical outcomes. Drug delivery poses another barrier, as therapeutic agents, particularly siRNAs or microRNA-based therapeutics (such as anti-miR-21), often suffer from poor renal targeting and low bioavailability (184). Furthermore, the slow and heterogeneous progression of CKD complicates the definition of reliable clinical endpoints, posing challenges for clinical trial design and outcome assessment (185,186).

Overall, overcoming these therapeutic challenges requires a multi-faceted approach involving improved drug specificity, enhanced delivery systems, identification of novel therapeutic targets within the TGF-β/Smad pathway, and the development of clinically relevant biomarkers to accurately assess therapeutic efficacy and safety.

6. Conclusion

In conclusion, the TGF-β/Smad signaling pathway plays a pivotal role in the AKI-CKD transition and holds significant promise for guiding future research and clinical practice. A deeper understanding of this pathway and its interactions may facilitate the development of more effective strategies for preventing and treating CKD, which will ultimately improve.

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Authors' contributions

LW and JLa conceived and revised the review. YZ and JD wrote the original draft preparation. YZ, JLi, GL and ML reviewed and edited the manuscript. JLa, RL and JD mainly helped to draw figures and generate tables included in the article and revise the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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