TGF-β in Renal Injury and Disease

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Summary: Chronic progressive kidney diseases typically are characterized by loss of differentiated epithelial cells and activation of mesenchymal cell populations leading to renal fibrosis in response to a broad range of diverse renal injuries. Recent evidence has indicated that epithelial microinjury leads to unbalanced epithelial-mesenchymal communication to initiate the fibrotic response. Transforming growth factors β constitute a large family of cytokines that control key cellular responses in development and tissue repair. Activation of autocrine and paracrine transforming growth factor-β signaling cascades in the context of epithelial microinjuries initiate a variety of cell type–dependent signaling and activity profiles, including epithelial apoptosis and epithelial-to-mesenchymal transition, that trigger fibrogenic foci and initiate progressive fibrogenesis in chronic renal injury.
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The transforming growth factor β (TGF-β) family includes TGF-βs, activins, and bone morphogenetic proteins (BMPs)/growth and differentiation factors that are structurally-related, secreted cytokines.[1] More than 30 family members have been identified (Fig. 1A). TGF-β, the prototypical member of this family and the focus of this review, was discovered more than 25 years ago as a factor produced by transformed cells that induced the anchorage-independent growth of normal rat kidney cells.[2,3] Numerous studies have shown that TGF-β are pleiotropic molecules that regulate cell proliferation, differentiation, apoptosis, migration, and adhesion of many different cell types.[1,4,5] TGF-β–family ligands exert pivotal roles in embryogenesis, tissue repair, and in maintaining tissue homeostasis.[6] In addition, disruption of TGF-β signaling has been linked to various developmental disorders and numerous human diseases including cancer, fibrosis, and autoimmune diseases. Because of their extraordinary multifunctionality, activities of TGF-β family members are tightly controlled at multiple levels. TGF-β are synthesized as inactive precursors and secreted as latent complexes, requiring activation in a highly controlled manner.[7]

TGF-β initiate signaling across the plasma membrane into the cell by inducing heteromeric complexes of type I and type II receptors with serine/threonine kinase activity (reviewed in Derynck and Zhang,[8] Shi and Massague,[9] and ten Dijke and Hill[10]). The family of TGF-β receptors includes 5 type II receptors and 7 type I receptors, also named *activin receptor-like kinases* (ALKs) (Fig. 1B). On ligand-induced heteromeric complex formation, the constitutively active type II receptor kinase phosphorylates the type I receptor on specific serine and threonine residues in the juxtamembrane region, leading to activation of type 1 receptor kinases (Fig. 2).[11]

The ligand-induced activation of TGF-β–receptor complexes leads to the recruitment and activation of major TGF-β signal transducers of the Smad family where activated type I receptor kinases transiently interact with and phosphorylate receptor-regulated Smads (R-Smads) at their extreme C-terminal serine residues (reviewed in Derynck and Zhang,[8] Shi and Massague,[9] and ten Dijke and Hill[10]). Smad2 and Smad3 act downstream of the TGF-β, activin, or nodal type I receptors ALK4, ALK5, and ALK7,

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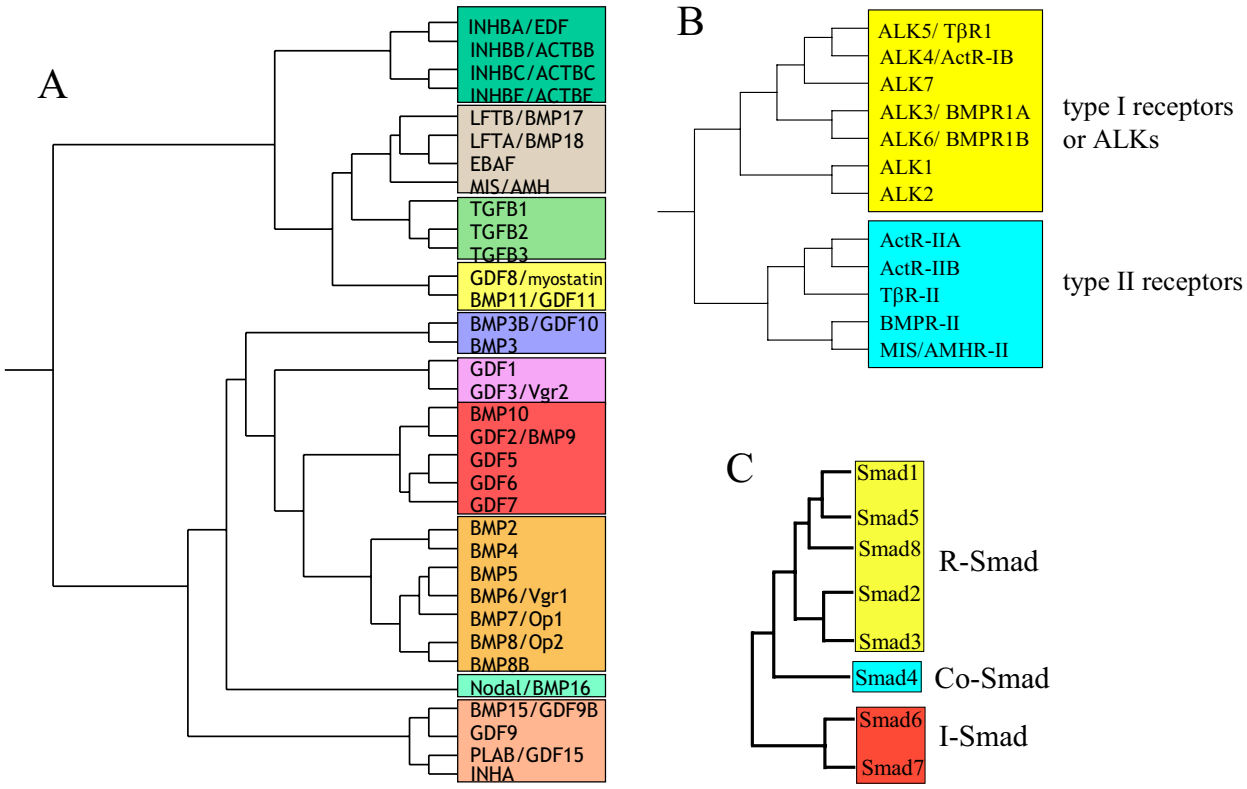

Figure 1. (A) TGF-β family members. Phylogenetic analysis of the TGF-β family. ACT, activin; GDF, growth and differentiation factor; INH, inhibin; MIS/AMH, müllerian inhibiting substance/anti-müllerian hormone; OP, osteogenic protein. (B) TGF-β family type I and type II receptors. Phylogenetic analysis of mammalian type I and type II receptors. ActR, activin receptor; MIS/AMH, MIS/AMH receptor; BMPR, BMP receptor; TβR, TGF-β receptor. (C) Smad family. Phylogenetic analysis of mammalian Smads shows 3 distinct subfamilies: R-Smads, receptor regulated Smads; Co-Smads, common-partner Smads; and I-Smads, inhibitory Smads.

whereas Smad1, Smad5, and Smad8 act downstream of BMP type I receptors ALK2, ALK3, and ALK6 (Fig. 1C). ALK1 is a type I receptor for TGF-β that activates Smad1, Smad5, and Smad8 in neurons and endothelial cells dependent on ALK5 kinase activity.[12] Phosphorylated R-Smads form heteromeric complexes with a common-partner Smad4 and translocate to the nucleus, where these heteromeric complexes can bind to DNA to control transcription of target genes through interaction with co-activators and co-repressors (Fig. 2). Smad6 and Smad7 share a conserved Mad homology 2-, dwarfin type (MH2) domain with R-Smads and Co-Smads and constitute the subgroup of inhibitory Smads. Inhibitory Smads interact with and recruit Smurf (Smad ubiquitination regulatory factor) ubiquitin ligases to ligand receptor complexes, initiating Smurf-induced receptor degradation via proteosomal and lysosomal pathways.[13] In addition to the canonical Smad pathways, TGF-β may signal through mitogen-activated protein kinases, phosphoinositide 3-OH kinases, small guanosine triphosphatases, and other mediators (reviewed in Derynk and Zhang,[8] and Bottinger and Bitzer[14]). However, the molecular mechanisms of Smad-independent TGF-β signaling remain incompletely understood.

TGF-β IS SYNONYMOUS WITH INFLAMMATION AND FIBROSIS

A large body of evidence, accumulated during 2 decades of investigation, establishes TGF-β as a major regulator of inflammation and fibrosis. The fibrogenic activity of TGF-β originally was identified in classic studies showing that TGF-β stimulated granulation tissue when injected subcutaneously into newborn mice and stimu-

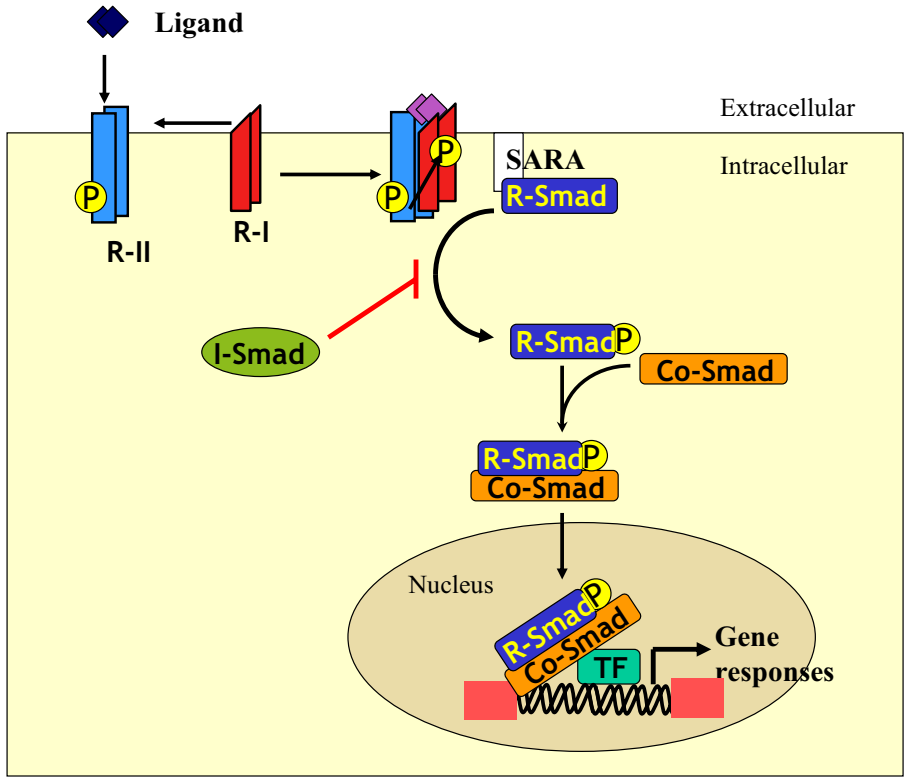

Figure 2. The canonical TGF-β/Smad signaling pathway. On ligand-binding, heteromeric complexes of type I and type II serine/threonine kinase receptors are stabilized. The constitutive type II receptor kinase phosphorylates the type I receptor on specific serine and threonine residues in the juxtamembrane region, enabling the type I receptor to transmit the signal inside the cell through phosphorylation of R-Smads at 2 extreme C-terminal serine residues. Access of R-Smads to the activated type I receptor is controlled through auxiliary proteins, including Smad anchor for receptor activation (SARA), and others. After phosphorylation, activated R-Smads form heteromeric complexes with Smad4. Smad complexes can bind to and regulate promoters of target genes in concert with numerous transcriptional regulators.

lated collagen formation in fibroblasts.[15] Other seminal reports established that TGF-β regulates immune function,[16] chemotaxis, and inflammation,[17] and induces its own synthesis.[18] In experimental models of renal and pulmonary fibrogenesis, inhibition of TGF-β with neutralizing anti–TGF-β antisera ameliorates characteristic accumulation of extracellular matrix.[19,20] Together, these studies showed a remarkable multifunctionality of TGF-β and established this growth factor as a putative key regulator in inflammation, tissue repair, and fibrosis.[1,21,22]

REGULATION OF TGF-β IN KIDNEY INJURY AND DISEASE

Since the 1980s, the so-called *intraglomerular hypertension model* has been the classic paradigm for the underlying cause of progression of chronic kidney disease (CKD).[23-25] Glomerular hypertension is induced by intrarenal activation of the renin angiotensin system (RAS).[26,27] A molecular link between intrarenal RAS and TGF-β was established in vitro and in vivo. For example, TGF-β is induced by angiotensin II and is required for induction of hypertrophy in tubular epithelial cells and of matrix synthesis in mesangial cells.[28,29] TGF-β1 also is up-regulated in glomerular diseases[30] and experimental and human diabetic nephropathy.[31,32] Increased expression of TGF-β and TGF-β receptors is a hallmark of virtually all human and experimental CKD (reviewed in Border and Noble,[33] and Bitzer et al[34]). Importantly, inhibitors of the RAS reduce TGF-β expression in renal cells in vitro and in vivo,[35] suggesting that reduction of TGF-β isoform levels may underlie the renoprotective effects of RAS blockade in diabetic and nondiabetic CKD.[36] Independent

of the RAS pathway, TGF-β also is induced directly by a broad range of products of metabolism, including glucose, advanced glycation products, free fatty acids, reactive oxygen species, and others (reviewed in Ziyadeh[37]). In addition, mechanical stretch and shear stress increase TGF-β release and activation in renal and vascular cells.[38-41]

FUNCTIONAL ROLES FOR TGF-β IN KIDNEY INJURY AND DISEASE

Numerous studies have shown that TGF-β inhibition attenuates functional and pathologic abnormalities in experimental renal disease, suggesting a critical role for TGF-β in CKD and renal fibrosis (Table 1).[19,42-48] Transgenic mice overexpressing active TGF-β1 develop progressive glomerulosclerosis and tubulointerstitial fibrosis, indicating that persistently increased TGF-β activity is sufficient to induce progressive renal disease in mice.[49-51] Interestingly, apoptosis of glomerular epithelial cells (podocytes) is induced by TGF-β1 and/or Smad7, and precedes activation of mesangial cells and mesangial matrix deposition in TGF-β1 transgenic mice.[52] Furthermore, knockout of the major signal transducer Smad3 in mice prevents renal defects and fibrosis induced by experimental ureteral obstruction or diabetes mellitus.[53,54] Transgenic overexpression of inhibitory Smad7 ameliorates fibrosis in ureteral obstruction and renal ablation models.[55,56] These and numerous other studies consistently support the paradigm that TGF-β and its signal transducers are central mediators of the progression of CKD.

FIBROGENIC PROGRAMS DOWNSTREAM OF TGF-β

TGF-β broadly controls messenger RNA levels and promoter activities of extracellular matrix genes, including COL1A1, COL1A2, COL3A1, COL5A2, COL6A1, COL6A3, COL7A1, and noncollagenous matrix genes such as fibronectin, proteoglycans, and others (reviewed in Verrecchia and Mauviel,[57] and Schnaper and Kopp[58]). TGF-β controls transcription of several extracellular matrix (ECM) genes through Smad3-dependent mechanisms in which Smad3 interacts with activator protein 1 complexes or Sp1, respectively, on CAGA motif Smad binding elements.[59-62] Smad3 also is required for fibrogenic activation of vascular smooth muscle cells by angiotensin II.[63] In addition, microarray screens in Smad2 and Smad3 knockout fibroblasts indicate a broad role for Smad3, but not Smad2, as a critical mediator of fibrogenic signaling by TGF-β in mesenchymal cells.[64]

Smad-independent pathways may have a role in modulation of ECM gene expression by TGF-β. For example, full activation of COL1A1 transcription is dependent on actin cytoskeleton-modulated signals and requires concomitant and interdependent activation of Smad3 and phosphoinositide 3-OH kinase/v-akt murine thymoma viral oncogene homolog 1 (AKT1) signaling, as well as p38 mitogen-acti-

Table 1. Cell Type–Dependent Activities Induced by TGF-β In Vitro

Cell Type	Induced Response
Epithelial cells	
Tubular epithelial cells	Apoptosis, growth inhibition, EMT, hypertrophy
Podocytes	Apoptosis, growth inhibition, basement membrane turnover
Endothelial cells	
Glomerular endothelial cells	Apoptosis, growth inhibition, differentiation
Mesenchymal cells	
Mesangial cells	Myofibroblast activation, ECM turnover, apoptosis
Fibroblasts	Myofibroblast activation, ECM turnover, apoptosis
Inflammatory cells	
Macrophages/monocytes	Chemotaxis
All cells	Autoinduction

vated protein kinase in mesangial cells.[65-67] V-abl Abelson murine leukemia viral oncogene homolog (C-Abl) is required for TGF-β–induced ECM gene expression, myofibroblast transformation, and proliferation independently of any effect on Smad signaling in fibroblasts, and C-Abl inhibition ameliorates pulmonary and renal fibrosis in experimental models.[68,69] Connective tissue growth factor, a secreted cysteine-rich domain protein, is induced by TGF-β in mesenchymal cells, including hepatic stellate cells (HSCs), mesangial cells, and fibroblasts, and may be required for maximal matrix synthesis by TGF-β.[70-74] Although there is increasing evidence for Smad-independent TGF-β signaling mechanisms, Smad3 is considered a key signal transducer for TGF-β–mediated ECM regulation.[75]

CROSS-TALK BETWEEN INFLAMMATORY PATHWAYS AND TGF-β SIGNALING

There is considerable evidence for cross-modulation of TGF-β/Smad signaling by several pathways involved in regulating inflammatory and fibrotic responses. For example, c-Jun N-terminal kinase (JNK) mediates inhibition of Smad-dependent activation of collagen genes by proinflammatory cytokines such as tumor necrosis factor α in dermal fibroblasts.[76] Other mechanisms of transmodulation of TGF-β/Smad-dependent activation of ECM genes by proinflammatory cytokines tumor necrosis factor α or interferon γ involve nuclear factor κ B or signal transducer and transactivator 1–mediated induction of inhibitory Smad7.[77,78] In addition, prostaglandin E2 inhibits TGF-β1–induced collagen synthesis, indicating extensive signaling cross-talk in profibrotic signaling in HSCs.[79] In summary, proinflammatory cytokine pathways negatively regulate ECM synthesis via molecular cross-talk with TGF-β/Smad signaling.

EMERGING ROLE FOR TGF-β IN EPITHELIAL APOPTOSIS AND INITIATION OF FIBROGENIC FOCI

Despite considerable progress in our understanding of fibrogenic signaling mechanisms, it remains unclear how tissue injury that frequently manifests itself initially in epithelial or vascular cell compartments can initiate fibrogenic phenotypes characteristic of mesenchymal cells. In addition, the classic concept of fibrosis as the "dark side of tissue repair"[33] neither involves nor explains the apparent abnormalities of epithelial and/or endothelial cells, such as atrophy and apoptosis of epithelial and/or endothelial cells and loss of tubular epithelial and postglomerular vascular structures, which are hallmarks of progressive CKD.

An extended hypothesis/concept for fibrosis has been advanced recently in which epithelial or vascular microinjury initiates epithelial or vascular degeneration through epithelial or endothelial apoptosis (or possibly epithelial-to-mesenchymal transition [EMT]), which initiates myofibroblast-like cell phenotypes and fibrogenic foci with progressive ECM accumulation.[14,80,81] Epithelial cell injury and apoptosis are initial responses to various forms of renal injury[52,82-85] (Fig. 3). TGF-β provides a plausible link between epithelial/endothelial injury and mesenchymal cell activation. For example, the engulfment and phagocytosis of apoptotic bodies by myofibroblasts, mesangial cells, HSCs, Kupffer cells, or macrophages directly stimulates increased synthesis and secretion of TGF-β1 by the phagocytosing cells,[86-89] suggesting that cells that phagocytose apoptotic bodies generate and secrete TGF-β1 (Fig. 3). TGF-β itself may act on epithelial cells to induce apoptosis in renal tubular epithelial cells and glomerular podocytes and thereby may promote further epithelial injury, resulting in increased phagocytic activity and alteration in epithelial-mesenchymal cell communication.[84,90]

Proof-of-concept studies show that prevention of epithelial apoptosis ameliorates tissue fibrosis in hepatic and pulmonary experimental models and that engineered persistent epithelial/parenchymal cell apoptosis is sufficient to induce progressive fibrotic responses. For example, prevention of TGF-β–induced apoptosis of alveolar epithelial cells in mice deficient for the proapoptotic Bcl2 family protein Bid protects these mice against bleomycin-induced pulmonary apoptosis and fibrosis, but not inflammation.[91] In addition, pharmacologic or transgenic inhibition of apoptosis is associated with attenuation of experimental pulmonary fi-

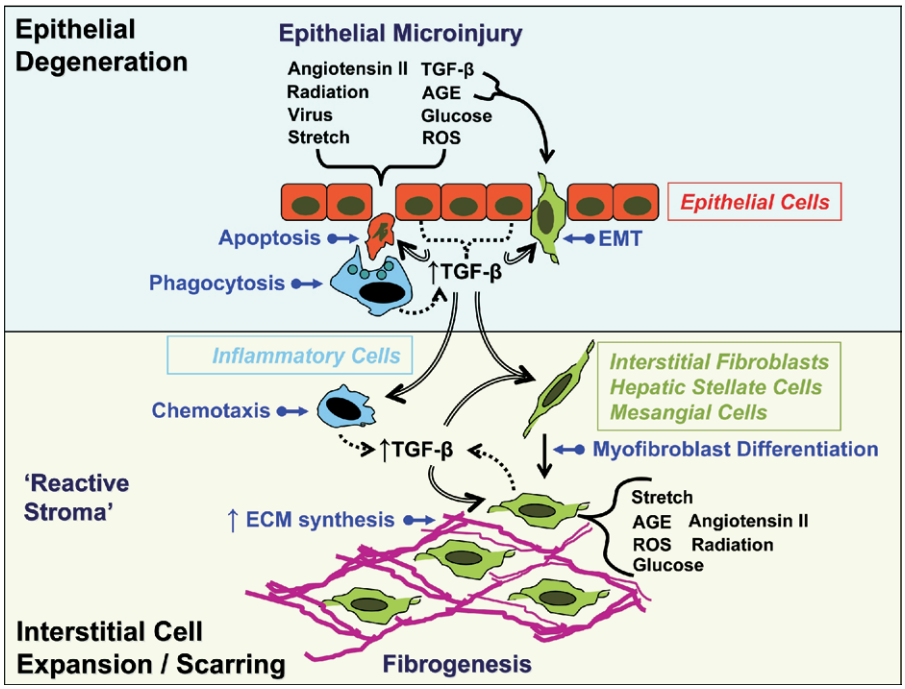

Figure 3. Integrated model of TGF-β as a key signal linking epithelial microinjury and fibrogenesis. Epithelial microinjury may manifest as apoptosis or EMT, depending on the signaling context and cell state, and can be induced by a diverse spectrum of stimuli including angiotensin II, radiation, viral infection, stretch/pressure, TGF-β, advanced glycation end products, high ambient glucose, reactive oxygen species, and others. Epithelial microinjury induces release and activation of TGF-β by apoptosing and neighboring epithelial cells. TGF-β also is released by cells recruited to phagocytose apoptotic epithelial cell bodies. Locally increased TGF-β itself can induce epithelial apoptosis and/or EMTs, depending on the signaling context. The TGF-β–dependent epithelial microinjury promotes disintegration of differentiated/loss of epithelial cell layers, contributing to the epithelial degeneration characteristic of fibrotic conditions. In addition, locally increased TGF-β recruits inflammatory cells (macrophages/monocytes) through chemotaxis and stimulates proliferation and myofibroblast differentiation of local mesenchymal cells such as interstitial fibroblasts, hepatic stellate cells, or glomerular mesangial cells. External stimuli such as advanced glycation products, reactive oxygen species, glucose, stretch, or angiotensin II also can act directly on mesenchymal cells and myofibroblasts to release TGF-β. Infiltrating inflammatory cells release TGF-β and additional cytokines, contributing further to increased local TGF-β levels and mesenchymal cell proliferation and myofibroblast differentiation. Increased local TGF-β activates fibrogenesis through synthesis of ECM and inhibits ECM degradation characteristic of myofibroblast-like mesenchymal cells. Mesenchymal cell expansion and fibrogenesis result in ECM accumulation and organization, leading to scar formation. TGF-β autoinduction contributes to persistently increased TGF-β activity, which promotes the progression of epithelial degeneration and interstitial cell expansion/scarring, leading to gradual organ destruction and loss of function characteristic of chronic fibrotic conditions.

brosis.[92-94] Mice with cre/lox-mediated hepatocyte-specific deletion of the anti-apoptotic BcL-xL gene manifest spontaneous, prolonged hepatocyte apoptosis associated with increased expression of TGF-β1 in adjacent hepatocytes and macrophages. In these animals, prolonged hepatocyte apoptosis leads to progressive hepatic fibrosis.[95]

Whether prevention of epithelial apoptosis in experimental renal disease would ameliorate kidney injury and fibrosis similarly, however, remains to be established. Early evidence suggests that disturbance of the epithelial-mesenchymal cell balance causes progressive glomerulosclerosis and/or interstitial fibrosis. For example, titratable ablation of podocytes in rat and mouse models is sufficient to initiate progressive focal segmental glomerulosclerosis and renal failure.[96,97] Type 1 diabetes, induced by streptozotocin in Renin2 transgenic rats, is associated with increased TGF-β1 expression and apoptosis in renal tubular epithelial cells dependent on angiotensin II.[98] Unilateral ureteral obstruction is associated with increased tubular

epithelial apoptosis in mice deficient for decorin, a natural inhibitor of TGF-β1, compared with control wild-type mice.[99] In murine models of progressive glomerulosclerosis, including TGF-β1 transgenic mice[52] and CD2-associated protein knockout mice, a striking increase of apoptosis of podocytes is one of the first detectable cellular lesions.[84] Interestingly, TGF-β1 expression is increased in podocytes at the time of apoptosis.[84]

These findings support a model to link initial epithelial microinjury and apoptosis with local generation of TGF-β1 and activation of mesenchymal cells as a trigger mechanism of fibrogenesis (Fig. 3). Fibrosis may occur at sites of sustained epithelial injury associated with apoptosis and TGF-β activation as a paracrine mediator of mesenchymal cell activation and phagocyte recruitment and/or gain of fibroblasts.[14,80,81] Thus, aberrant autocrine and paracrine TGF-β signaling may have a central role in epithelial-fibroblast miscommunication, triggering fibrogenesis.

TGF-β AND EMT

EMT is an extreme manifestation of epithelial plasticity in which polarized epithelial cells embedded in organized cell layers convert into motile fibroblastic cells (reviewed by Thiery[100]). In nonmalignant epithelial cells of renal, pulmonary, or hepatic origins, EMT manifestations may be triggered rather easily by diverse modes of stress and injury in vitro (reviewed in Kalluri and Neilson,[101] Yang and Liu,[102] and Zavadil and Bottinger[103]). TGF-β is sufficient to induce EMT in nonmalignant and malignant epithelial cells in vitro and is considered a major factor promoting EMT in invasive and metastatic cancers in vivo (reviewed in Zavadil and Bottinger[103]).

In contrast, proof of concept for EMT in nonmalignant renal fibrosis, or hepatic and pulmonary fibrosis, has proven difficult. By using complex genetic engineering in mice, Iwano et al[104] showed in vivo evidence for EMT in a model of tubulointerstitial fibrosis induced by unilateral ureteral obstruction. However, with few exceptions, in vivo evidence for EMT in fibrotic tissues is derived largely from the experimental model of unilateral ureteral obstruction.[101,102] Increased TGF-β expression is a prominent feature in this model.[105,106] Biopsy specimens of diseased human kidney show few isolated epithelial cells in tubular structures which manifest molecular evidence for EMT by co-expression of epithelial and mesenchymal markers.[107-109] In addition, to date there is very little evidence documenting EMT in experimental liver fibrosis and pulmonary fibrosis models in vivo.[110] Thus, the extent to which transitioning epithelial cells contribute to tubular epithelial degeneration and/or initiation of mesenchymal expansion by generating fibroblastic cells that initiate fibrogenesis still remains unclear (Fig. 3).

EMERGING ANTIFIBROTIC THERAPIES TARGET TGF-B SIGNALING

Large-molecule TGF-β antagonists and small-molecule inhibitors of the TGF-β–receptor type 1 kinase are under development for primary indications in fibrotic diseases, diabetic nephropathy, and possibly metastatic cancers (reviewed in Yingling et al[111] and Laping[112]). Intriguing recent reports have shown that long-term inhibition of TGF-β in rodent models by transgenic overexpression of soluble TGF-β receptor type 2 Fc chimera or the use of pan-neutralizing antibody 1D11 appear to be well tolerated without evidence for increased carcinogenesis or autoimmunity in these models.[113,114]

In addition, several antifibrotic compounds may exert their antifibrotic activities through down-modulation of TGF-β activity and signaling. The low-molecular-weight plant alkaloid halofuginone inhibits extracellular matrix accumulation in several animal models of fibrotic disorders,[115] associated with inhibition of Smad2/Smad3 phosphorylation and up-regulation of inhibitory Smad7.[116] Pentoxifylline, a nonselective phosphodiesterase inhibitor, attenuates tubulointerstitial fibrosis by dual mechanisms, including inhibition of Smad3-/4-activated transcription, and blockade of profibrogenic effects of connective tissue growth factor.[117] Pirfenidone is an antifibrotic agent that reduces ECM deposition in numerous fibrosis models, possibly through reduction of TGF-β1 synthesis.[118] Finally, hepatocyte growth

factor and BMP7 are thought to attenuate EMT and fibrosis in the unilateral ureteral obstruction renal injury model by antagonizing TGF-β signaling.[119-121]

Chronic administration of antagonists of TGF-β signaling in suitable patients with non–immune-mediated CKD will need to be guided by biomarkers as surrogate readouts for efficacy.[48,111] In addition to classic fibrosis markers, markers for epithelial and/or endothelial microinjury characteristic of early and potentially reversible stages of CKD need to be developed. The concept of using antagonists of TGF-β to prevent progression of CKD and stabilize life-sustaining functions of the kidney is promising if the extraordinary challenge of navigating their safe administration over long periods of time can be met.

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