Therapeutic targets for treating fibrotic kidney diseases

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Renal fibrosis is the hallmark of virtually all progressive kidney diseases and strongly correlates with the deterioration of kidney function. The renin-angiotensin-aldosterone system blockade is central to the current treatment of patients with chronic kidney disease (CKD) for the renoprotective effects aimed to prevent or slow progression to end-stage renal disease (ESRD). However, the incidence of CKD is still increasing, and there is a critical need for new therapeutics. Here, we review novel strategies targeting various components implicated in the fibrogenic pathway to inhibit or retard the loss of kidney function. We focus, in particular, on antifibrotic approaches that target transforming growth factor (TGF)-β1, a key mediator of kidney fibrosis, and exciting new data on the role of autophagy. Bone morphogenetic protein (BMP)-7 and connective tissue growth factor (CTGF) are highlighted as modulators of profibrotic TGF-β activity. BMP-7 has a protective role against TGF-β1 in kidney fibrosis, whereas CTGF enhances TGF-β–mediated fibrosis. We also discuss recent advances in the development of additional strategies for antifibrotic therapy. These include strategies targeting chemokine pathways via CC chemokine receptors 1 and 2 to modulate the inflammatory response, inhibition of phosphodiesterase to restore nitric oxide-cyclic 3′,5′-guanosine monophosphate function, inhibition of nicotinamide adenine dinucleotide phosphate oxidase 1 and 4 to suppress reactive oxygen species production, and inhibition of endothelin 1 or tumor necrosis factor α to ameliorate progressive renal fibrosis. Furthermore, a brief overview of some of the biomarkers of kidney fibrosis is currently being explored that may improve the ability to monitor antifibrotic therapies. It is hoped that evidence based on the preclinical and clinical data discussed in this review leads to novel antifibrotic therapies effective in patients with CKD to prevent or delay progression to ESRD. (Translational Research 2015;165:512–530)

Abbreviations: ACE = angiotensin-converting enzyme; ANG II = Angiotensin II; AP-1 = activator protein-1; ARB = angiotensin II receptor blocker; ASCEND = A Study of Cardiovascular Events in Diabetes; ATF 2 = activating transcription factor 2; ATN = acute tubular necrosis; βig-h3 = TGF-β-inducible gene; BMP = bone morphogenetic protein; BMPR = bone morphogenetic protein receptor; CCL2-CCR2 = CC motif chemokine ligand 2–CC receptor type 2; CCR1 = CC receptor type 1; CKD = chronic kidney disease; CTGF = connective tissue growth factor; ECM = extracellular matrix; eGFR = estimated glomerular filtration rate; EMT = epithelial-to-mesenchymal transition; ET = endothelin; ESRD = end-stage renal disease; ETA = endothelin A receptor; FSGS = focal segmental glomerular sclerosis; HSPG = heparan sulfate proteoglycan; IGF-1 = insulin-like growth factor 1; IκB = inhibitor of kappa B; IPF = idiopathic pulmonary fibrosis; JNK = c-Jun N-terminal kinase; KCP = Kielin/chordin-like protein; LC3 = microtubule-associated

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protein 1 light chain 3; LRP = lipoprotein receptor–related protein; MAPK = mitogen-activated protein kinase; MCP-1 = Monocyte chemoattractant protein-1; MKK = mitogen-activated protein kinase kinase; MKKK = MAPK kinase kinase kinase; NF-κB = nuclear factor kappa B; Nox = nicotinamide adenine dinucleotide phosphate oxidase; PAI-1 = plasminogen activator inhibitor-1; PDE = phosphodiesterase; PPARγ = Peroxisome proliferator–activated receptor γ; RAAS = renin-angiotensin-aldosterone system; ROS = reactive oxygen species; R-Smads = receptor-regulated Smads; siRNA = small interfering RNA; stz = streptozotocin; TAB1 = TAK1-binding protein 1; TAK1 = TGF-β–activated kinase 1; TβRI = TGF-β type I receptor; TβRII = TGF-β type II receptor; TGF-β1 = transforming growth factor β1; TNF-α = tumor necrosis factor α; TrKA = tyrosine receptor kinase A; TSP 1 = thrombospondin type 1; UUO = unilateral ureteral obstruction; USAG-1 = uterine sensitization–associated gene-1; VEGF = vascular endothelial growth factor; vWF = von Willebrand factor

INTRODUCTION

Development of renal fibrosis is the hallmark of most progressive chronic kidney disease (CKD), irrespective of the cause, and is thought to represent the final common response to injury.[1] Pathogenesis of renal fibrosis is characterized by the relentless accumulation of extracellular matrix (ECM) proteins, such as fibronectin and collagens, accompanied by tubular atrophy and alterations in the renal vasculature.[2] These pathologic changes lead to irreversible loss of tissue and impaired kidney function and, ultimately, end-stage kidney failure. In addition to the development of end-stage renal disease (ESRD) requiring renal replacement therapies, important adverse outcomes of CKD include cardiovascular complications.[3] Furthermore, CKD has increasingly become a major global public health concern and portends high rates of morbidity and mortality.[3] Therefore, treatment strategies for CKD aimed at preventing or slowing its devastating sequelae and progression to ESRD are of utmost importance. Central to the current treatment for patients with CKD is the blockade of the renin-angiotensin-aldosterone system (RAAS) by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) whose renoprotective effects have been impactful in retarding the progression of many CKDs.[4-6] However, the incidence of CKD is still increasing worldwide and the number of patients with CKD who ultimately develop ESRD remains high. Hence, there is a critical need for new therapeutics.

Studies to understand the mechanisms mediating pathogenesis of fibrosis in the kidney have been the focus of intensive research. Development of renal fibrosis underlies virtually all progressive kidney diseases and strongly correlates with deterioration of kidney function.[7] Thus, targeting the various components of the fibrogenic pathways represents attractive therapeutic strategies to inhibit or retard the progressive loss of kidney function in patients with CKD, regardless of the underlying cause of kidney injury. Here, we review recent advances in antifibrotic therapies based on recent preclinical and clinical evidence. We focus, in particular, on potential antifibrotic approaches that target transforming growth factor (TGF)-β1, a key mediator of tissue fibrosis. A growing body of evidence demonstrates that TGF-β1 plays a pivotal role in the pathogenesis of renal fibrosis associated with progressive kidney diseases.[8,9] We highlight several major pathways that either modulate or are modulated by TGF-β1, such as autophagy and bone morphogenetic protein (BMP)-7 having protective roles against TGF-β1 in kidney fibrosis, and connective tissue growth factor (CTGF), which enhances TGF-β–mediated fibrosis. Targeting CC chemokine receptors CCR1 and CCR2 to modulate the inflammatory response and inhibiting phosphodiesterase (PDE) to restore nitric oxide–cyclic 3′,5′-guanosine monophosphate function may also achieve antifibrotic effects. Additional strategies for inhibiting progressive renal fibrosis include inhibiting nicotinamide adenine dinucleotide phosphate oxidase (Nox)1/4 to suppress the production of reactive oxygen species (ROS) and inhibiting endothelin (ET)-1 or tumor necrosis factor α (TNF-α) to ameliorate progressive renal fibrosis. This review focuses on fibrosis of the native kidney. Fibrosis in transplanted kidneys may involve other mechanisms, such as ischemic-reperfusion injury, pre-existing fibrosis in the donated kidney, nephrotoxic effects of immunosuppressant medications, and allogenic immune response.[10,11]

TGF-β1 and signaling. Three mammalian isoforms of TGF-β exist, namely TGF-β1, -β2, and -β3. They belong to the TGF superfamily of cytokines that is composed of more than 30 structurally related polypeptide growth factors including the TGF-βs, activins, inhibins, growth differentiation factors, and BMPs.[12] TGF-β1 represents the predominant isoform that is ubiquitously expressed and is a prototypic multifunctional cytokine regulating a wide variety of cellular functions. TGF-β1 is synthesized as a 390-