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Ureteral Obstruction-Induced Renal Fibrosis: An In Vivo Platform for Mechanistic Discovery and Therapeutic Intervention

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Molecular Events Associated with Renal Fibrosis: TGF-β/SMAD Signaling as Transducer of the Fibrotic Phenotype

Interstitial fibrosis, resulting in renal tissue destruction and progressive impairment of organ function, is a hallmark of end-stage kidney disease [1]. The primary sources of matrix synthesis during renal fibrogenesis are activated fibroblasts or myofibroblasts. While their origin remains uncertain, this cell type-predictor of disease progression likely derives largely from resident fibroblasts and epithelial-to-mesenchymal transdifferentiated (EMT) tubular epithelial cells [2]. The transforming growth factor-β (TGF-β)/SMAD system is a potent, perhaps the most well-characterized, inducer of myofibroblast differentiation and EMT. TGF-β drives EMT in renal epithelial cells and promotes fibrosis in animal models by engaging effector pathways and their downstream target genes that impact both the inflammatory and scarring stages of the injury response [3]. SMAD-mediated signaling initiated by TGF-β is pivotal for induction of EMT, fibroblast activation and renal fibrosis [2,3]. SMAD3, in particular, appears critical in several *in vivo* models of renal fibrosis. This was, indeed, confirmed by the finding that SMAD3-deficient mice are significantly protected from disease progression. TGF-β also activates non-SMAD-dependent pathways [4] that impact the expression of pro-fibrotic genes. The continued characterization of such highly-interactive transduction events initiated by TGF-β/TGF-β receptor interactions will likely lead to identification of novel opportunities for anti-fibrotic therapy.

Animal Models for Investigating Obstructive Nephropathies and the Signaling Mechanisms Associated with Renal Fibrosis

Ureteral Unilateral Obstruction (UUO) is an established, relatively short-term, animal model of injury-stimulated renal fibrosis that lends itself to the dissection of critical mechanistic events and evaluation of potential therapeutic targets [5]. Aside from its relative surgical ease, UUO in rodents is pathophysiologically-relevant and recapitulates the biology of human nephropathy associated with congenital urinary tract anomalies (common in pediatric patients), obstructive urolithiasis and age-related lower urinary tract obstruction. The basic pathology of UUO in murine systems is highly reproducible. Within hours after ureteral

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occlusion, the affected kidney is subject to sudden changes in mechanical forces, increased oxidative stress upon generation of free radicals and tissue ischemia resulting in a complex phenotypic response including cellular apoptosis, inflammation (due to infiltrating macrophages and expression of inflammatory cytokines), alterations in gene expression, extracellular matrix (ECM) remodeling and EMT. “Activated” fibroblasts derived from resident interstitial fibroblasts, recruited from extra-renal sources (i.e., the circulation) or arising de novo from EMT of the injured epithelium differentiate into matrix-secreting myofibroblasts and initiate the process of ECM deposition. With persistence of obstruction, overt fibrosis and massive epithelial apoptosis develops with eventual tubular atrophy and loss of renal function. Tubulointerstitial fibrosis in this model appears dependent on upregulation of TGF-β1 expression in the interstitial compartment. Indeed, introduction of 15-mer TGF-β1 antisense phosphorothioate oligodeoxynucleotides by retrograde ureteral injection or administration of TGF-β1 siRNA suppresses tubulointerstitial fibrosis in UUO with reduced expression of the TGF-β1 response genes.

Consistent with the activation of TGF-β1 signaling in UUO, there is a dramatic increase of SMAD2/3 phosphorylation and elevated expression of plasminogen activator inhibitor-1 (SERPINE1, PAI-1) in the obstructed kidney compared to the contralateral controls [2]. PAI-1 is particularly important in the overall context of tissue fibrosis regardless of site and a prominent downstream target of the TGF-β1/SMAD3 [4,5]. A major inhibitor of plasmin generation, PAI-1 inhibits ECM degradation, thereby, contributing to interstitial fibrosis. PAI-1 null mice are, in fact, significantly protected from renal fibrosis and excessive ECM accumulation. Increased PAI-1 expression has been implicated in various animal models of renal diseases and is highly induced by pro-fibrogenic and pro-inflammatory mediators including angiotensin, CTGF, interleukins and TNF-α. PAI-1 null mice subjected UUO, moreover, exhibit a significantly reduced inflammatory response compared to wild-type controls suggesting that this SERPIN may promote infiltration of macrophages and T-cells. PAI-1 also modulates TGF-β1 signaling as PAI-1-null animals (compared to wild-type controls subjected to obstructive nephropathy) have lower TGF-β1 levels. Recombinant PAI-1, in fact, activates the TGF-β1 promoter suggesting that PAI-1 may initiate, and perhaps maintain, a potential pro-fibrogenic “loop” in the context of renal disease. Hence, targeted down-modulation of PAI-1 may provide significant, multiple-level, therapeutic value in inhibiting fibrosis onset and progression as well as in the more difficult clinical challenge of disease reversal.

It is anticipated that cell & developmental biology will be an effective vehicle to communicate these translationally-important findings to the biomedical research community.

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