Beyond EMT: Epithelial STAT3 as a Central Regulator of Fibrogenesis

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Studies from early human diabetic kidney disease (DKD) in Pima Indians have suggested that gene targets downstream of signal transduction and activator of transcription 3 (STAT3) are hyperactivated in early disease (initially in the glomerulus and subsequently, in the tubular and interstitial anatomic compartments) and may be contributing to DKD progression. Moreover, a recent phase 2 clinical trial using a Janus Kinase 1/2 (JAK1/2) inhibitor Baricitinib, which blocks activation of STATs including STAT3, has shown promise in reducing proteinuria in patients with DKD after 6 months of treatment (https://www.sciencedaily.com/releases/2015/06/150610111129.htm). Although there is no genetic association of kidney disease with STAT3 or its upstream receptors and ligands, STAT3 polymorphisms have been associated with inflammatory diseases, such as Crohn colitis, Bechet disease, and autoimmune thyroiditis, implicating the signaling pathway as an important regulator of inflammatory signaling in humans. CKDs are increasingly recognized to be characterized dominantly by activation of the innate immune response. Innate immune signaling pathways were described initially in leukocytes, but current thinking suggests that activation of innate immune signals in parenchymal and resident cells of the kidney may dominate, pointing to innate immune signaling as an important contributor to disease progression.

STAT3 is a transcription factor and a transducer of multiple cell surface receptors, including the gp130-associated receptors, such as IL-6R, OSMR, CNTFR, LIFR, and IL-11R (Figure 1). In addition, STAT3 transduces signals from IFN receptors IFNAR1 and IFNRA2, although these receptors have been reported to signal dominantly through similar transducers STAT1 and STAT2. Increasingly, the recognition that persistent activation of IFN receptors (an IFN signature) potentially triggered by IFNα and IFNβ may also be playing a role in disease progression further points to a potential role for STAT3 as an important intermediate in IFN signaling. The gp130-associated receptors have been implicated in a number of diseases, including rheumatoid arthritis, and IL-6 as well as Oncostatin-M are very highly expressed in certain kidney diseases, where they may contribute to disease progression. In addition, STAT3 is activated in response to signaling from tyrosine kinase receptors, including PDGFRs, FGFRs, and VEGFRs, although the importance of STAT3 target genes from these receptors is not well elucidated (Figure 1). Finally, STAT3 has been reported to transduce signals from anti-inflammatory receptor IL-10, suggesting that it may be an important regulator of anti-inflammatory signaling responses. Overall, STAT3, like other potential nodes that coordinate cell signaling, such as MyD88, NF-κB, c-Jun N-terminal kinase, API, or P38, seems to be a potentially interesting target for therapeutic small molecule inhibition. STAT3 is activated by phosphorylation of residues by JAKs, on which it dimerizes and translocates to the nucleus to activate target genes. Additional phosphorylation of the complex may occur under the regulation of MAPK signaling.

Over the last 5 years, the paradigm that the epithelial to mesenchymal transition (EMT) drives many aspects of kidney disease progression and fibrogenesis has been reconsidered. The most comprehensive animal model studies suggest a much smaller role for this canonical developmental pathway regulated by ZEB, SNAI1, and SLUG transcription factors in adult disease. Comprehensive cell fate mapping indicates that fibroblasts do not arise from epithelium undergoing EMT and that human CKD genomic and transcriptional analysis also provide little role for the EMT as a dominant process in the chronically injured epithelium. This has been underscored by recent failures of large clinical trials in kidney diseases that attempted to block the TGFβ-dependent signaling pathways, which have been most closely associated with the EMT. Instead, human tissues reveal DNA damage, senescence, mitochondrial dysfunction, activation of cell stress pathways, such as the unfolded protein response, and activation of innate immune signaling, including JAK/STAT–dependent immune signaling, as major dysregulated cell processes in the epithelium. In addition, recent in-depth studies of the kidney fibroblast point to a hostile interstitium encasing the epithelium with fibroblasts generating a myriad of cytokines that can activate gp130-dependent receptors and IFN receptors, including IL-6, IL-11, OSM, CRLF, and IFNα/β.2–4,14 (Figure 1).

In the current issue of the Journal of the American Society of Nephrology, Bienaimé et al. from Institut National de la Santé et de la Recherche Médicale in France have directly addressed the role of STAT3 in the epithelium and its role in directing profibrotic signaling to the interstitium. Using the model of 5/6 nephrectomy, nuclear (active) STAT3 was found in injured epithelium as well as neighboring interstitial cells. Specific deletion of STAT3 in the epithelial compartment using CreER/loxP genetic recombination under the control of systemic tamoxifen injections resulted in high levels of recombination in the epithelium and consequently, deletion of STAT3 production. This resulted in significant protection of the epithelium and a reduction in interstitial fibrosis. Bienaimé et al. identified epithelial factors, including PDGF-BB, TIMP1, and Lipocalin2, that are secreted in a STAT3-dependent manner in response to Oncostatin-M, by epithelial cells (Figure 1). Such factors are well recognized to promote fibroblast survival,
proliferation, and activation. Bienaimé et al. observed significant reduction of these STAT3 target genes in the whole kidney that lacked STAT3 in the epithelium. These findings support the human data that already exist showing a potentially important role for STAT3 in driving chronic disease and suggest a model of bidirectional signaling, whereby a positive feedback loop between fibroblasts and epithelium may be important in mediating disease persistence (Figure 1).

These new studies shed additional light on the critical interdependence of pathologic fibroblasts with distressed epithelial cells in the kidney via inflammatory signals predominantly through the gp130–coupled receptor family, provide additional evidence for STAT3 as a target for intervention, and suggest that such a hostile interaction may maintain the epithelial cell in a pathologic state. Although these findings support further strategies for advancing therapies that can safely inhibit JAK/STAT signaling in patients with progressive kidney disease, several important questions remain unanswered. (1) What is the relative importance of STAT3 over STAT1/2? (2) What is the relative role of JAK/STAT signaling in the myofibroblast compared with the epithelium? (3) Does OSMR signaling dominate over IL-6R signaling? (4) Can IL-6R and OSMR be more safely targeted by antibodies blocking ligand-receptor interactions to achieve similar effects on cell function as JAK/STAT blockade? Because antibodies that block IL-6 and OSM are now available, a concerted effort to interrogate the pathway in human CKD is merited.

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References


Preserving Residual Kidney Function in Hemodialysis Patients—Back in the Spotlight

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The importance of residual kidney function (RKF) is well established in peritoneal dialysis (PD). RKF has been shown to contribute to better solute clearance, uremic toxin removal, and improved quality of life in patients on PD.

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