A New Pair of SOCS for Diabetic Nephropathy

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Over the years, disorders in a variety of signaling pathways have been implicated in the evolution of diabetic nephropathy. Despite these efforts, there remains no consensus about the signaling abnormalities that are fundamental to renal progression. One example of disordered signaling that has received increasing attention, however, is that of enhanced activation of Janus kinase/signal transducers and activators of transcription (JAK/STAT) proteins in both glomerular and tubulointerstitial cells in humans with diabetic nephropathy and in some animal models.

JAK/STAT members are protein pairs that rapidly and efficiently transduce signaling activated by the binding of cytokines such as IL-6 and G-protein–coupled receptor agonists such as angiotensin II to their cognate receptors. Upon cytokine receptor activation, the associated JAK protein, a tyrosine kinase, phosphorylates residues in SH2 domains on the cytoplasmic domain of the receptor. This initiates recruitment of the STAT partner, which is then phosphorylated by the JAK protein. STAT proteins then homo- or heterodimerize and translocate into the nucleus, where they bind to promoter regions of many target genes to transactivate them. Although there are four members in the mammalian JAK family, the one best studied in renal and vascular tissues is JAK2.

Starting in the early part of the past decade several investigators, led by Marrero’s group, documented that exposure to elevated glucose concentrations results in activation of JAK2/STAT signaling in a variety of cell types as well as in the renal cortex of rodents with early diabetic nephropathy.1–5 Induction of transforming growth factor β (TGF-β) and fibronectin expression from JAK2/STAT signaling is abrogated by JAK2 inhibition.2,5 These studies suggested JAK2 activation associates with the development of diabetic complications. Experiments using a streptozotocin-induced diabetic rat model found that both increased systolic BP6 and albuminuria7 were prevented by treatment with the JAK2 inhibitor AG490, lending further credence to the idea that JAK2 activation plays an important role in diabetic nephropathy.

Until recently, it has been uncertain whether changes in JAK2/STAT activation occur in human diabetic nephropathy. In 2009, Berthier et al.8 documented enhanced expression of a large number of JAK/STAT mRNAs and JAK2 protein in glomeruli and the tubulointerstitium from humans with both early and progressive diabetic nephropathy. JAK2 mRNA levels inversely correlated with estimated GFR in these patients. Moreover, increased JAK2 expression alone enhanced JAK2 activity in cultured glomerular mesangial cells. Interestingly, JAK/STAT expression is not enhanced in glomerular or tubulointerstitial tissues from two of the best current murine models of diabetic nephropathy. Humans with diabetic nephropathy seem to have enhanced JAK/STAT activation both by exposure to high glucose and by enhanced expression of genes encoding JAK/STAT. Thus, the lack of chronically enhanced expression of JAK/STAT genes in mouse models could be one explanation for why rodent models only mimic early human nephropathy and fail to develop progressive disease.

In this issue of JASN, Ortiz-Munoz et al.9 provide a new chapter in the JAK/STAT story by demonstrating that downstream transcriptional targets of this pathway, suppressors of cytokine signaling (SOCS) genes, are activated in rodents with diabetic nephropathy. SOCS proteins bind and interfere with initiating JAK proteins in a negative-feedback manner.10 Some SOCS proteins also bind to receptor phosphotyrosine residues on the cytokine receptors themselves and further inhibit signaling by competing with STAT molecules for recruitment to the receptor/JAK/STAT complex. Thus, SOCS proteins serve to suppress the JAK/STAT signaling that triggers their expression. This presumably protective feedback response could be critical in a chronic disease such as diabetic nephropathy, which is accompanied by enhanced JAK/STAT expression and activation that presumably lasts for years, if not decades.

In the streptozotocin-induced diabetic rat model, Ortiz-Munoz et al.9 demonstrate a robust and seemingly chronic increase in levels of SOCS1 and SOCS3. Both of these SOCS proteins inhibit JAK2 signaling. Increased SOCS1 and SOCS3 expression is also observed in humans with progressive diabetic nephropathy when compared with patients with minimal-change disease.8 It seems the highest expression of SOCS proteins is in proximal tubular cells as well as in some glomerular cells, which is a similar distribution to that of JAK2 in human diabetic nephropathy.8 Ortiz-Munoz et al.9 also ad-
ministered injections of recombinant SOCS1 and SOCS3 adenovirus to rats and examined kidneys after 7 weeks of diabetes. They found evidence of reduced JAK/STAT activation and some amelioration of the very early diabetic changes found in the kidneys of treated animals compared with those that were administered a control adenovirus. Whether such treatment will have salutary effects on more substantial diabetic nephropathy is unclear.

Given the broad expression pattern of SOCS proteins and the critical immunomodulatory role of SOCS1 and SOCS3, systemic therapy might cause unintended adverse effects, which could be problematic for patients with diabetic nephropathy, who would likely require such treatment indefinitely; however, these results do raise the intriguing possibility that patients destined for progressive nephropathy may have a dampened rise in SOCS1 and SOCS3 levels after JAK/STAT activation and therefore are more exposed to JAK/STAT activation than patients with little disease progression. If so, then it is possible that SOCS levels may predict which patients are most susceptible to developing progressive diabetic kidney disease. Further research into inducers of SOCS expression or SOCS1/3 mimetics could ultimately lead to therapies to prevent or retard the progression of diabetic complications.

Inhibition of JAK2 signaling seems a more likely option in the near future. Given the prominent role of JAK2 activation in chronic myeloproliferative disorders, a number of JAK2 inhibitors have been developed and are in clinical trials. Should these inhibitors be safe and effective, they may play a new role in preventing JAK2 activation and progression of diabetic kidney disease and other complications.

DISCLOSURES
None.

REFERENCES


See related article, “Suppressors of Cytokine Signaling Abrogate Diabetic Nephropathy,” on pages 763–772.

Synergistic Interaction between Ciliary Genes Reflects the Importance of Mutational Load in Ciliopathies

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The formation of renal cysts occurs in roughly 10 to 15% of the population, and although simple cysts are largely asymptomatic, the formation of multiple cysts can be extremely detrimental. The two major multicytic syndromes, autosomal recessive polycystic kidney disease (PKD) and autosomal dominant PKD, are primarily linked to disruptions in the pkhd1 and pkd1/pkd2 genes, respectively; however, several additional syndromes are also characterized by kidney cyst develop-