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JAK INHIBITION AND PROGRESSIVE KIDNEY DISEASE

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Abstract

Purpose of review—To review the role of JAK-STAT signaling in the progression of chronic kidney diseases.

Recent findings—The JAK-STAT pathway transmits signals from extracellular ligands, including many cytokines and chemokines. While these responses are best characterized in lymphoid cells, they also occur in kidney cells such as podocytes, mesangial cells, and tubular cells. JAK-STAT expression and signaling abnormalities occur in humans and animal models of different chronic kidney diseases. Enhanced expression and augmented activity of JAK1, JAK2 and STAT3 promote diabetic nephropathy and their inhibition appears to reduce disease. Activation of JAK-STAT signaling in autosomal dominant polycystic kidney disease may play an important role in cyst growth. Activation of JAK-STAT signaling promotes HIV-associated nephropathy and may also participate in the tubular responses to chronic obstructive uropathy. Based on data from experimental models, inhibition of JAK-STAT signaling, via increased expression of the suppressors of cytokine signaling proteins or pharmacologic inhibition of JAK and STAT proteins, could play a therapeutic role in multiple chronic kidney diseases.

Summary—Activation of the JAK-STAT pathway appears to play a role in the progression of some chronic kidney diseases. More work is needed to determine the specific role the pathway plays in individual diseases.

Keywords

Janus kinase; chronic kidney disease; suppressors of cytokine signaling

1. Introduction

Many signaling pathways have been shown to be involved in the progression of chronic kidney disease (CKD) in humans and in animal models usually due to persistent activation of these pathways. Perhaps the best well known of such pathways include certain protein kinase pathways, such as protein kinase C (1) and mitogen activated kinase pathways (2)

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which lead to cellular growth and fibrosis, and those such as angiotensin II (3) and TGF-beta/SMAD (4) signaling pathways which enhance fibrosis leading to kidney scarring. In addition, it has become increasingly clear over the last decade that many progressive kidney diseases are also characterized by sustained inflammation which appears to promote and direct much of the chronic injury process (5).

One of the major pathways that responds to and transduces inflammatory signals is the JAK-STAT pathway. The JAK-STAT pathway transmits signals from extracellular ligands, including many cytokines and chemokines as well as growth factors and hormones, directly to the nucleus to induce a variety of cellular responses (6). While many of these responses are present and best characterized in lymphoid cells, they have also been reported in many other cell types including kidney parenchymal cells such as podocytes (7), mesangial cells (8) and tubular cells (7).

Given the role of JAK-STAT activation in response to cytokines and chemokines and the unequivocal role of inflammation in promoting progressive kidney injury it is not surprising that JAK-STAT activation is involved in the pathogenesis of CKD as well as of acute kidney injury. Curiously however, until recently there have been few published reports on JAK-STAT signaling in CKD and only an incomplete and rather general outline of JAK-STAT activation in CKD can be currently sketched.

2. JAK/STAT signaling review

JAK-STAT proteins transduce signals from many different types of non-tyrosine kinase plasma membrane receptors. After binding of their ligands, these membrane receptors dimerize and thereby recruit pairs of JAK proteins to the intracellular receptor domains and activate them by inducing the tyrosine kinase activity of the JAKs via autophosphorylation. The activated JAKs then phosphorylate tyrosine residues on the intracellular domains of the receptors which then serve as docking sites for STAT proteins through the binding of Src Homology 2 (SH2) domains. After phosphorylation by JAK proteins, STAT proteins form hetero- or homo-dimers, which translocate to the nucleus to induce the transcription of target genes (9). Separate from this classical activation process, STAT proteins can be phosphorylated and activated by other tyrosine kinases such as growth factor receptors and non-receptor tyrosine kinases, and can be indirectly activated via G-protein coupled receptors, polycystin 1 and intracellular oxidant species (10–12). In addition, lysine acetylation of STAT proteins can cause STAT activation (13) bypassing or augmenting the effects of JAK-induced phosphorylation (13). The JAK-STAT signaling pathway is negatively regulated by several processes including dephosphorylation, nuclear export, and negative endogenous regulators such as SOCS (suppressors of cytokine signaling) and PIAS (protein inhibitor of activated STAT) (14).

Four members of the JAK family (JAK1, JAK2, JAK3, and TYK2) have been identified in mammals (15, 16). Although JAK proteins are structurally related, their differences in activation and downstream effects allow for a high degree of specificity. JAK1 is activated by the ligands binding to the class II receptors (IFN [interferon] α/β , IFN γ , IL-10) and the γ_c receptor (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21). JAK2 is activated mostly by thrombopoietin

receptor (TPO), IL-3, GM-CSF and IFN γ . While the majority of JAKs are ubiquitously expressed, JAK3 expression appears to be generally restricted to hemopoietic lineages and vascular muscle cells and JAK3 plays a critical role in lymphocyte development and function. Tyk2 mediates mostly signaling induced by IL-12. There are seven STATs in mammalian cells, STAT1-4, 5a, 5b, and 6. The role of individual STATs in the immune system and cancer are discussed below.

a. Role of JAK/STAT signaling in immune cells, autoimmune diseases and cancer

A large body of evidence suggests a critical role for JAKs and STATs in the differentiation and maturation of the immune system. Development of the Th1 response requires IL-12/STAT4 while the Th2 response requires IL-4/STAT6 (17). However, recent data suggest that STAT3 and STAT5A/B are also involved in Th2 differentiation (18, 19). As the mediators of IL-2 signaling, STAT5A and B are also critical for the differentiation of Treg cells (20). STAT3 is required for Th17 differentiation, mediating signals induced by IL-23 and IL-6 (21). Interestingly, IL-2-induced STAT5A/B activation is an important negative regulator of Th17 differentiation (22). STAT3 activation induced by IL-10 and IL-21 is important for CD8 function (23) and STAT5A/B activation induced by IL-7 is important in B lymphocyte survival and development (24). STATs also have numerous functions in innate immunity such as STAT1 in mediating IFN effects. STAT3 induced by IL-6 mediates pro-inflammatory effects while STAT3 activated by IL-10 and IL-22 has anti-inflammatory properties (25). Precisely how STAT3 promotes inflammation in some circumstances and inhibits it in others remains unclear.

Numerous studies from animal models suggest a role for Type I/II cytokine receptors and the JAK/STAT pathway in autoimmune diseases. These findings have been confirmed in humans by genetic studies (6). Polymorphisms of the genes encoding IL-23, IL6R, JAK2, STAT3 and others have been linked to autoimmune processes such as inflammatory bowel disease (26, 27). These responses are complex and not easily predicted. For example, in contrast to the germline inactivating STAT3 mutations in hyper IgE syndrome, *de novo* activating STAT3 mutations were recently reported as a cause of autoimmune diseases such as type 1 diabetes (28). Multiple genes in the IL-12 pathway including STAT4 are also associated with autoimmune diseases (29). Polymorphisms of STAT6 and IL13 are associated with atopic dermatitis (30).

Activation of some JAK-STAT pathways also plays a major role in cancer and metastasis through regulation of cell proliferation, apoptosis, inflammation, and epithelial-mesenchymal transitions (31–35). Certain JAK2 mutations, especially the V617F mutation, lead to JAK2 activation and development of polycythemia vera, essential thrombocythemia and primary myelofibrosis. Thus, compounds that inhibit JAK2 have been developed for their antineoplastic activities (35). Among the STATs, activated STAT3 appears to be the predominant isoform in promoting cancers and is considered an oncogene (32). Activation of STAT3 has been reported in a variety of human tumor cell lines and primary human tumors. In addition, lysine acetylation and resultant activation of STAT3 is elevated in tumors and acetylated STAT3 induces methylation and inhibition of tumor suppressor genes (36). STAT3 induces not only tumor cell proliferation but also mediates angiogenesis and

metastasis. STAT3 signaling is also a major pathway for cancer inflammation while STAT1 increases anti-tumor immunity. Therefore, STAT3 has emerged as a crucial target for cancer therapy and STAT3 inhibitors are actively being developed (37).

b. Advent of clinically useful JAK inhibitors

Since the JAK-STAT pathways play major activating roles in a variety of disease processes, there has been a robust effort to develop specific inhibitors of this pathway. As it is relatively easy to identify inhibitors of protein kinases, development of JAK inhibitors has received most attention. At present, two JAK inhibitors have received FDA approval for clinical use. Ruxolitinib (INCB018424, Jakafi, Incyte) is a potent inhibitor of both JAK1 and JAK2, and it received FDA approval in November 2011 for the treatment of polycythemia vera and myelofibrosis (38). Tofacitinib (CP690, 550, Xeljanz; Pfizer) was initially designed to be a specific inhibitor of JAK3 kinase and therefore has been used as an immunosuppressant in transplantation and for the treatment of autoimmune diseases (39). More recently, it was found that tofacitinib also inhibits JAK1 (40), which mediates interferon and IL-6-induced pro-inflammatory effects (41). Tofacitinib received FDA approval for the treatment of moderately to severely active rheumatoid arthritis in November 2012. Several other JAK inhibitors have been developed as either immunosuppressive agents or anti-cancer drugs. For example, baricitinib (a JAK1/2 inhibitor) and VX-509 (a specific JAK3 inhibitor) have been shown to be effective in the treatment of arthritis (41). Therefore, it is likely that additional JAK inhibitors will become clinically available in the next few years.

Since STAT3 has a major role in tumorigenesis and inflammation, a number of efforts have been made to develop its inhibitors. There are several natural inhibitors of STAT3 and new synthetic blockers of STAT3 have been also made. However, after a decade of preclinical evaluation, only limited translational studies are currently in progress (42).

3. Role of JAK activation in diabetic kidney disease

The first evidence that JAK-STAT activation could be important in the pathogenesis of CKD came from Marrero, et al. in 1996 when direct activation of JAK-STAT signaling by angiotensin II was found in mesangial cells (11). Subsequent work by Marrero's group found evidence for JAK2 activation in mesangial cells exposed to high glucose concentrations in culture, and in diabetic rodent models, and that some of this activation was due to angiotensin II signaling (43, 44). These studies indicated that activation of TGF- β signaling and fibronectin production was at least partly mediated by JAK2 signaling. These downstream changes were abrogated by JAK2 inhibition (44, 45) confirming that JAK2 activation was responsible for the effects. However, despite these interesting studies, few other investigations of the role of JAK-STAT signaling in diabetic kidney disease were forthcoming until around 5 years ago.

In 2009 we reported that the mRNA expression of JAKs 1,2,3 and STATs 1,3 was substantially increased in subjects with diabetic kidney disease compared to normal subjects (7). Expression was increased in glomeruli from subjects with early nephropathy but was increased in the tubulointerstitial region only in subjects with progressive disease. This

pattern corresponded to the natural pathologic progression of diabetic kidney disease which also initially involves glomeruli and subsequently cortical tubulointerstitium. Indeed, the increased tubulointerstitial expression of all the JAK/STAT genes was tightly and inversely correlated to the decline in estimated GFR in these patients (7). A similar transcriptomic data set was published by other investigators in a study of human subjects with a variety of chronic kidney diseases including diabetes (46). In our analysis of this published dataset we found that increases of JAK1, JAK2, STAT1 and STAT3 gene expression occurred in the subset of 22 subjects with diabetic kidney disease compared to normal control subjects (47). The implication from these 2 sets of studies is that increases in JAK-STAT gene expression result in increases in JAK-STAT activity, though this was not demonstrated *in vivo*.

Around the same time, Lu, et al., reported a transgenic mouse with reduced capacity for STAT3 activation (Stat3SA/– mice) and found that Stat3SA/– animals with STZ diabetes developed less proteinuria, mesangial expansion, cell proliferation, macrophage infiltration, inflammation, and abnormal matrix synthesis at an early stage of diabetic kidney disease (48). As would be expected from generalized increased JAK-STAT activation, downstream transcriptional targets of the JAK-STAT signaling pathway, Suppressors of Cytokine Signaling (SOCS) genes, SOCS1 and SOCS3, have been shown to be activated in diabetic kidney disease in rodents and humans (49). SOCS proteins bind to and interfere with initiating JAK proteins in a negative-feedback manner (50) serving to suppress the JAK-STAT signaling that triggers their expression. It appears that the highest expression of SOCS proteins is in proximal tubule epithelia as well as in glomerular cells, in a similar distribution to what was found for JAK2 in human DKD (7). Rats injected with recombinant SOCS1 and SOCS3 adenovirus showed evidence for reduced JAK/STAT activation and some amelioration of early diabetic changes after 7 weeks of diabetes (49). Additionally, injection of SOCS1 into the tail vein of mice with mild diabetic kidney disease reversed the increases in TGF- β and connective tissue growth factor in this model (51).

During the last 18 months, additional studies have shown evidence for JAK-STAT expression and activation in diabetic nephropathy. A transcriptomic analysis of Pima Indians with early diabetic kidney disease and of 3 good mouse models of nephropathy identified cross-species glomerular transcriptional networks shared between humans and mice that further defined gene networks involved in diabetic kidney disease. When similarities were mapped onto canonical signaling and metabolic pathways, more than one third of the cross-species conserved pathways overlapped between all three human–mouse comparisons. The canonical pathway with the greatest degree of overlap was cytokine induced JAK-STAT signaling (52). Interestingly, this did not necessarily mean that there was increased expression in JAK-STAT proteins themselves in the mouse models but that there was evidence of increased gene expression downstream of STAT signaling. We have also published in preliminary form that podocyte specific overexpression of JAK2 to levels similar to that found in diabetic humans causes increased albuminuria and mesangial expansion and sclerosis, as well as decreased podocyte density (53). Baricitinib, the JAK1/2 inhibitor, is now being tested in a phase 2 randomized clinical trial for efficacy in subjects with diabetic nephropathy (ClinicalTrials.gov Identifier NCT01683409).

A very recent study showed that STAT3 acetylation was increased in both mouse and human diabetic kidneys (54). Acetylation of STAT proteins can affect STAT dimerization which is critical for the translocation of STATs to the nucleus and their ability to modulate gene transcription (13). In human podocytes, advanced glycation end products (AGEs) induced p65 and STAT3 acetylation and overexpression of acetylation deficient mutants of p65 and STAT3 abrogated AGE-induced expression of NF- κ B and STAT3 target genes. Inhibition of AGE formation in diabetic db/db mice by pyridoxamine treatment restored SIRT1 expression, reduced p65 and STAT3 acetylation and attenuated proteinuria and podocyte injury. Moreover, diabetic db/db mice with conditional deletion of SIRT1 in podocytes developed increased acetylation of p65 and STAT3 and enhanced proteinuria and kidney injury when compared to db/db mice without the SIRT1 deletion. Treatment with inhibitors that block acetylation-mediated association of p65 and STAT3 with BET proteins, also attenuated proteinuria and kidney injury in db/db mice. These findings support a significant role for activated STAT3 acetylation in diabetic kidney disease. Perhaps equally importantly, they show that podocyte STAT3 activation via acetylation can result in worsening nephropathy independent of upstream JAK signaling, or at least of changes in upstream JAK signaling. Thus, activation of podocyte JAK2 and podocyte STAT3 (with or without JAK2 activation) is important in the pathogenesis of diabetic kidney disease.

Finally, several papers confirmed the salutary effect of increasing SOCS expression in reducing diabetic kidney disease. Delivery of SOCS vectors systemically or directly into the kidney showed that increased expression of SOCS1 or 3 (55) or of SOCS2 (56) can reduce some of the pathologic features of diabetic nephropathy in rodent models.

Figure 1 summarizes how the JAK-STAT pathway is activated in diabetic kidney disease.

4. Role of JAK/STAT signaling in other kidney diseases

The JAK-STAT pathway has been extensively studied in autosomal dominant polycystic kidney disease (ADPKD) and nicely reviewed in a recent publication (57). Polycystin 1 (PC1) was found to activate multiple JAK-STAT proteins in cyst-lining cells. Membrane-anchored PC1 interacts directly with JAK2 to activate STAT3 (12) while PC1 activates STAT6 through interaction with its C-terminal cytoplasmic tail released from the membrane by proteolytic cleavage (58). Finally, the cleaved cytoplasmic tail of PC1 was recently shown to integrate signaling inputs from several pathways resulting in Src-dependent activation of STAT3 and the proliferative response in tubular cells (59). This cytoplasmic tail cleavage appears to happen in response to injury and is turned on constitutively in ADPKD. STAT3 is strongly activated in cyst-lining cells in human ADPKD kidneys and four different PKD mouse models (12, 57). STAT3 may also mediate the effects of heme oxygenase on renal cyst growth (60). In addition, STAT3 can also mediate macrophage activation and cytokine secretion in PKD (61). Inhibition of STAT3 in PKD mouse models with different inhibitors has given promising results (62, 63). Even though the specificity of these compounds toward STAT3 is not well established, together these studies suggest that STAT3 may be a highly promising therapeutic target for treatment of PKD. STAT6 is also highly activated in cyst-lining cells in two different PKD mouse models (64). Knockout of STAT6 led to a significant improvement in kidney function and decrease in cyst size (64).

STAT6 may mediate cyst formation and growth through regulation of macrophage function (61). Overall, these studies provide strong evidence that the activation of JAK-STAT pathway promotes proliferation of cyst-lining cells. Future studies are required to determine whether JAK-STAT inhibitors could be useful in the treatment of patients with ADPKD.

Unilateral ureteral obstruction (UUO) is a model of obstructive nephropathy that is commonly used to study renal fibrosis. Pang et al reported that STAT3 activity is involved in the activation and proliferation of interstitial fibroblasts in cultured cells and in the UUO model and treatment of the UUO mice with a STAT3 inhibitor (S3I-201) attenuates fibrosis and inflammation in the UUO kidney (65). Recent studies from the same group demonstrate that inhibition of EGFR attenuates renal fibrosis while STAT3 phosphorylation was also reduced in these mice (66). However, in mice with knockout of SOCS3 (SOCS3^{+/-}), a negative regulator of JAK-STAT3, UUO-induced renal fibrosis was markedly suppressed. In addition, the renal fibrosis was aggravated in the UUO mice pre-treated with a JAK inhibitor-incorporated nanoparticle (pyridine6-PGLA) (67). The authors conclude that JAK/STAT3 signaling may play a role in repair process of renal fibrosis via MMP-2 activation (67). The conflicting data from these studies suggest that JAK/STAT3 may have a dual role in renal fibrosis. It is also possible that activation of JAK/STAT3 pathway in kidney tubular cells and fibroblasts may have different consequences for renal fibrosis. The role of STAT6 in the UUO model is more uncertain because STAT6^{-/-} mice were shown to have enhanced apoptosis and inflammation but less fibrosis in the obstructed kidney (68). Overall, the role of the JAK-STAT pathway in tubulointerstitial fibrosis remains controversial.

HIVAN is characterized by collapsing focal segmental glomerulosclerosis, interstitial nephritis, and tubular microcystic dilatation. A distinctive feature of this disease is the finding of prominent hyperplasia of the glomerular cells leading to the formation of pseudocrescents. We have previously reported that STAT3 phosphorylation is significantly increased in the human kidney of HIVAN (69). STAT3 is highly activated in HIVAN kidney by both viral protein Nef-induced Src and IL6-induced JAK activation. Activation of STAT3 mediates multiple effects in HIVAN including promotion of podocyte proliferation, microcystic formation, and infiltration of inflammatory cells and knockout of STAT3 either globally or specifically in kidney cells leads to a significant improvement of kidney injury in HIV-1 transgenic mice (70, 71). These studies suggest that STAT3 could be a potential target for treatment of HIVAN.

Profiling of the kidney transcriptome in mice with ischemia/reperfusion injury revealed that JAK/STAT pathway is highly enriched in the kidney with AKI (72). Exclusively, STAT3 was rapidly activated in injured renal tubule cells (12). IL6 induced STAT3 activation was observed in mice with HgCl₂-induced AKI (73). Experimental activation of STAT3 prior to HgCl₂ administration protected animals from AKI. This effect was partially due to the induction of heme oxygenase-1 (73). Several studies confirmed that animals with renal ischemia/reperfusion injury had increased expression of un-phosphorylated STAT3 and activation of STAT3 (74, 75). Recent studies suggest that SOCS3 is highly expressed in renal proximal tubules during AKI. Conditional proximal tubular SOCS3 knockout mice maintained better kidney function than their littermates when kidney injury was induced by aristolochic acid or ischemia/reperfusion (76). Thus, this study confirmed a protective role

of STAT3 in AKI. A protective or reparative role of STAT6 was also observed in the kidney following acute injury. Following renal ischemia-reperfusion injury, STAT6^{-/-} mice exhibited more severe tubular injury and worse renal function than did wild-type mice (77). These studies suggest, in contrast to CKD, that the JAK-STAT pathway has a protective role in AKI through activation of STAT3 and STAT6.

In summary, activation of JAK-STAT pathway plays a major role in a variety of non-diabetic kidney diseases. STAT3 and probably STAT6 are most important isoforms involved in the pathogenesis of these kidney diseases. STAT3 is rapidly activated in response to several forms of renal insult and appears to be critical for protection of kidney cells from acute injury. However, prolonged renal STAT3 activation appears to play a role in destructive processes such as persistent inflammation and fibrosis.

5. Conclusion

Enhanced JAK-STAT expression and activation occur in a number of kidney diseases (Table 1). The isoforms that are most frequently regulated in kidney diseases are JAK2 and STAT3. Whereas increased JAK-STAT signaling appears to contribute to the pathogenesis of diabetic kidney disease, ADPKD and HIVAN, it appears to play a protective role in AKI. In both diabetic kidney disease and AKI, expression of SOCS isoforms counteracts the effects of JAK-STAT activation. Enhancement of SOCS expression may help prevent pathologic changes of diabetic kidney disease. Further research to further determine the precise role of JAK-STAT signaling and the effect of its inhibition on the progression of chronic kidney diseases will be critical.

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References and recommended reading

Papers of particular interest, published within the annual period of review, (18 months/2013–2014) have been highlighted as:

- of special interest
 - of outstanding interest
1. Li J, Gobe G. Protein kinase C activation and its role in kidney disease. *Nephrology (Carlton)*. 2006 Oct; 11(5):428–34. eng. [PubMed: 17014557]
 2. Chen J, Chen JK, Harris RC. Angiotensin II induces epithelial-to-mesenchymal transition in renal epithelial cells through reactive oxygen species/Src/caveolin-mediated activation of an epidermal growth factor receptor-extracellular signal-regulated kinase signaling pathway. *Mol Cell Biol*. 2012 Mar; 32(5):981–91. [PubMed: 22215616]
 3. Siragy HM, Carey RM. Role of the intrarenal renin-angiotensin-aldosterone system in chronic kidney disease. *Am J Nephrol*. 2010; 31(6):541–50. [PubMed: 20484892]
 4. Lan HY, Chung AC. TGF-beta/Smad signaling in kidney disease. *Semin Nephrol*. 2012 May; 32(3): 236–43. [PubMed: 22835454]

5. Wada J, Makino H. Inflammation and the pathogenesis of diabetic nephropathy. *Clin Sci (Lond)*. 2013 Feb; 124(3):139–52. [PubMed: 23075333]
6. O'Shea JJ, Plenge R. JAK and STAT signaling molecules in immunoregulation and immune-mediated disease. *Immunity*. 2012 Apr 20; 36(4):542–50. Epub 2012/04/24. eng. [PubMed: 22520847]
7. Berthier CC, Zhang H, Schin M, Henger A, Nelson RG, Yee B, et al. Enhanced expression of Janus kinase-signal transducer and activator of transcription pathway members in human diabetic nephropathy. *Diabetes*. 2009 Feb; 58(2):469–77. eng. [PubMed: 19017763]
8. Choudhury GG, Ghosh-Choudhury N, Abboud HE. Association and direct activation of signal transducer and activator of transcription1alpha by platelet-derived growth factor receptor. *J Clin Invest*. 1998 Jun 15; 101(12):2751–60. [PubMed: 9637709]
9. Levy DE, Darnell JE Jr. Stats: transcriptional control and biological impact. *Nat Rev Mol Cell Biol*. 2002 Sep; 3(9):651–62. Epub 2002/09/05. eng. [PubMed: 12209125]
10. Simon AR, Rai U, Fanburg BL, Cochran BH. Activation of the JAK-STAT pathway by reactive oxygen species. *Am J Physiol*. 1998 Dec; 275(6 Pt 1):C1640–52. [PubMed: 9843726]
11. Marrero MB, Schieffer B, Paxton WG, Heerdt L, Berk BC, Delafontaine P, et al. Direct stimulation of Jak/STAT pathway by the angiotensin II AT1 receptor. *Nature*. 1995 May 18; 375(6528):247–50. Epub 1995/05/18. eng. [PubMed: 7746328]
12. Talbot JJ, Shillingford JM, Vasanth S, Doerr N, Mukherjee S, Kinter MT, et al. Polycystin-1 regulates STAT activity by a dual mechanism. *Proc Natl Acad Sci U S A*. 2011 May 10; 108(19):7985–90. Epub 2011/04/27. eng. [PubMed: 21518865]
13. Zhuang S. Regulation of STAT signaling by acetylation. *Cell Signal*. 2013 Sep; 25(9):1924–31. [PubMed: 23707527]
14. Schindler C, Levy DE, Decker T. JAK-STAT signaling: from interferons to cytokines. *J Biol Chem*. 2007 Jul 13; 282(28):20059–63. Epub 2007/05/16. eng. [PubMed: 17502367]
15. Darnell JE Jr. STATs and gene regulation. *Science*. 1997 Sep 12; 277(5332):1630–5. Epub 1997/09/12. eng. [PubMed: 9287210]
16. Stark GR, Darnell JE Jr. The JAK-STAT pathway at twenty. *Immunity*. 2012 Apr 20; 36(4):503–14. Epub 2012/04/24. eng. [PubMed: 22520844]
17. Murphy TL, Geissal ED, Farrar JD, Murphy KM. Role of the Stat4 N domain in receptor proximal tyrosine phosphorylation. *Mol Cell Biol*. 2000 Oct; 20(19):7121–31. Epub 2000/09/13. eng. [PubMed: 10982828]
18. Liao W, Schones DE, Oh J, Cui Y, Cui K, Roh TY, et al. Priming for T helper type 2 differentiation by interleukin 2-mediated induction of interleukin 4 receptor alpha-chain expression. *Nat Immunol*. 2008 Nov; 9(11):1288–96. Epub 2008/09/30. eng. [PubMed: 18820682]
19. Stritesky GL, Muthukrishnan R, Sehra S, Goswami R, Pham D, Travers J, et al. The transcription factor STAT3 is required for T helper 2 cell development. *Immunity*. 2011 Jan 28; 34(1):39–49. Epub 2011/01/11. eng. [PubMed: 21215659]
20. Burchill MA, Yang J, Vogtenhuber C, Blazar BR, Farrar MA. IL-2 receptor beta-dependent STAT5 activation is required for the development of Foxp3+ regulatory T cells. *J Immunol*. 2007 Jan 1; 178(1):280–90. Epub 2006/12/22. eng. [PubMed: 17182565]
21. Chen Z, Laurence A, O'Shea JJ. Signal transduction pathways and transcriptional regulation in the control of Th17 differentiation. *Semin Immunol*. 2007 Dec; 19(6):400–8. Epub 2008/01/02. eng. [PubMed: 18166487]
22. Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity*. 2007 Mar; 26(3):371–81. Epub 2007/03/17. eng. [PubMed: 17363300]
23. Cui W, Liu Y, Weinstein JS, Craft J, Kaech SM. An interleukin-21-interleukin-10-STAT3 pathway is critical for functional maturation of memory CD8+ T cells. *Immunity*. 2011 Nov 23; 35(5):792–805. Epub 2011/11/29. eng. [PubMed: 22118527]
24. Malin S, McManus S, Cobaleda C, Novatchkova M, Delogu A, Bouillet P, et al. Role of STAT5 in controlling cell survival and immunoglobulin gene recombination during pro-B cell development. *Nat Immunol*. 2010 Feb; 11(2):171–9. Epub 2009/12/01. eng. [PubMed: 19946273]

25. Sonnenberg GF, Fouser LA, Artis D. Border patrol: regulation of immunity, inflammation and tissue homeostasis at barrier surfaces by IL-22. *Nat Immunol.* 2011 May; 12(5):383–90. Epub 2011/04/20. eng. [PubMed: 21502992]
26. Momozawa Y, Mni M, Nakamura K, Coppieters W, Almer S, Amininejad L, et al. Resequencing of positional candidates identifies low frequency IL23R coding variants protecting against inflammatory bowel disease. *Nat Genet.* 2011 Jan; 43(1):43–7. Epub 2010/12/15. eng. [PubMed: 21151126]
27. Stahl EA, Raychaudhuri S, Remmers EF, Xie G, Eyre S, Thomson BP, et al. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nat Genet.* 2010 Jun; 42(6):508–14. Epub 2010/05/11. eng. [PubMed: 20453842]
28. Flanagan SE, Haapaniemi E, Russell MA, Caswell R, Lango Allen H, De Franco E, et al. Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. *Nat Genet.* 2014 Aug; 46(8):812–4. Epub 2014/07/21. eng. [PubMed: 25038750]
29. Zhernakova A, Stahl EA, Trynka G, Raychaudhuri S, Festen EA, Franke L, et al. Meta-analysis of genome-wide association studies in celiac disease and rheumatoid arthritis identifies fourteen non-HLA shared loci. *PLoS Genet.* 2011 Feb; 7(2):e1002004. Epub 2011/03/09. eng. [PubMed: 21383967]
30. Paternoster L, Standl M, Chen CM, Ramasamy A, Bonnelykke K, Duijts L, et al. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. *Nat Genet.* 2012 Feb; 44(2):187–92. Epub 2011/12/27. eng. [PubMed: 22197932]
31. Yu H, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer.* 2009 Nov; 9(11):798–809. Epub 2009/10/24. eng. [PubMed: 19851315]
32. Siveen KS, Sikka S, Surana R, Dai X, Zhang J, Kumar AP, et al. Targeting the STAT3 signaling pathway in cancer: role of synthetic and natural inhibitors. *Biochim Biophys Acta.* 2014 Apr; 1845(2):136–54. Epub 2014/01/07. eng. [PubMed: 24388873]
33. Wendt MK, Balanis N, Carlin CR, Schiemann WP. STAT3 and epithelial-mesenchymal transitions in carcinomas. *JAKSTAT.* 2014 Jan 1.3(1):e28975. Epub 2014/05/21. eng. [PubMed: 24843831]
34. Teng Y, Ross JL, Cowell JK. The involvement of JAK-STAT3 in cell motility, invasion, and metastasis. *JAKSTAT.* 2014 Jan 1.3(1):e28086. Epub 2014/04/30. eng. [PubMed: 24778926]
35. Gotlib J. JAK inhibition in the myeloproliferative neoplasms: lessons learned from the bench and bedside. *Hematology/the Education Program of the American Society of Hematology American Society of Hematology Education Program.* 2013; 2013:529–37. [PubMed: 24319228]
36. Lee H, Zhang P, Herrmann A, Yang C, Xin H, Wang Z, et al. Acetylated STAT3 is crucial for methylation of tumor-suppressor gene promoters and inhibition by resveratrol results in demethylation. *Proc Natl Acad Sci U S A.* 2012 May 15; 109(20):7765–9. Epub 2012/05/02. eng. [PubMed: 22547799]
37. Sellier H, Rebillard A, Guette C, Barre B, Coqueret O. How should we define STAT3 as an oncogene and as a potential target for therapy? *JAKSTAT.* 2013 Jul 1.2(3):e24716. Epub 2013/09/27. eng. [PubMed: 24069560]
38. Verstovsek S, Kantarjian H, Mesa RA, Pardanani AD, Cortes-Franco J, Thomas DA, et al. Safety and Efficacy of INCB018424, a JAK1 and JAK2 Inhibitor, in Myelofibrosis. *N Engl J Med.* 2010 Sep 16; 363(12):1117–27. Epub 2010/09/17. eng. [PubMed: 20843246]
39. Borie DC, Si MS, Morris RE, Reitz BA, Changelian PS. JAK3 inhibition as a new concept for immune suppression. *Curr Opin Investig Drugs.* 2003 Nov; 4(11):1297–303. Epub 2004/02/05. eng.
40. Karaman MW, Herrgard S, Treiber DK, Gallant P, Atteridge CE, Campbell BT, et al. A quantitative analysis of kinase inhibitor selectivity. *Nat Biotechnol.* 2008 Jan; 26(1):127–32. Epub 2008/01/10. eng. [PubMed: 18183025]
41. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus kinase inhibitors in autoimmune diseases. *Ann Rheum Dis.* 2013 Apr; 72(Suppl 2):ii111–5. Epub 2013/04/03. eng. [PubMed: 23532440]
42. Debnath B, Xu S, Neamati N. Small molecule inhibitors of signal transducer and activator of transcription 3 (Stat3) protein. *J Med Chem.* 2012 Aug 9; 55(15):6645–68. Epub 2012/06/02. eng. [PubMed: 22650325]

43. Banes AK, Shaw S, Jenkins J, Redd H, Amiri F, Pollock DM, et al. Angiotensin II blockade prevents hyperglycemia-induced activation of JAK and STAT proteins in diabetic rat kidney glomeruli. *American journal of physiology*. 2004 Apr; 286(4):F653–9. Epub 2003/12/18. eng. [PubMed: 14678947]
44. Wang X, Shaw S, Amiri F, Eaton DC, Marrero MB. Inhibition of the Jak/STAT signaling pathway prevents the high glucose-induced increase in tgf-beta and fibronectin synthesis in mesangial cells. *Diabetes*. 2002 Dec; 51(12):3505–9. [PubMed: 12453907]
45. Marrero MB, Banes-Berceli AK, Stern DM, Eaton DC. Role of the JAK/STAT signaling pathway in diabetic nephropathy. *American journal of physiology*. 2006 Apr; 290(4):F762–8. Epub 2006/03/11. eng. [PubMed: 16527921]
46. Woroniecka KI, Park AS, Mohtat D, Thomas DB, Pullman JM, Susztak K. Transcriptome analysis of human diabetic kidney disease. *Diabetes*. 2011 Sep; 60(9):2354–69. Epub 2011/07/15. eng. [PubMed: 21752957]
47. Brosius FC 3rd, Alpers CE. New targets for treatment of diabetic nephropathy: what we have learned from animal models. *Curr Opin Nephrol Hypertens*. 2013 Jan; 22(1):17–25. Epub 2012/12/05. eng. [PubMed: 23207723]
48. Lu TC, Wang ZH, Feng X, Chuang PY, Fang W, Shen Y, et al. Knockdown of Stat3 activity in vivo prevents diabetic glomerulopathy. *Kidney international*. 2009 Jul; 76(1):63–71. Epub 2009/04/10. eng. [PubMed: 19357722]
49. Ortiz-Munoz G, Lopez-Parra V, Lopez-Franco O, Fernandez-Vizarra P, Mallavia B, Flores C, et al. Suppressors of cytokine signaling abrogate diabetic nephropathy. *J Am Soc Nephrol*. 2010 May; 21(5):763–72. Epub 2010/02/27. eng. [PubMed: 20185635]
50. Croker BA, Kiu H, Nicholson SE. SOCS regulation of the JAK/STAT signalling pathway. *Semin Cell Dev Biol*. 2008 Aug; 19(4):414–22. Epub 2008/08/19. eng. [PubMed: 18708154]
51. Shi Y, Du C, Zhang Y, Ren Y, Hao J, Zhao S, et al. Suppressor of cytokine signaling-1 ameliorates expression of MCP-1 in diabetic nephropathy. *Am J Nephrol*. 2010; 31(5):380–8. Epub 2010/03/20. eng. [PubMed: 20299783]
52. Hodgin JB, Nair V, Zhang H, Randolph A, Harris RC, Nelson RG, et al. Identification of cross-species shared transcriptional networks of diabetic nephropathy in human and mouse glomeruli. *Diabetes*. 2013 Jan; 62(1):299–308. Epub 2012/11/10. eng. This transcriptomic study showed increased evidence for enhanced expression and activation of JAK-STAT pathways in early diabetic glomerulopathy in both humans and 3 of the better mouse models of diabetic kidney disease. [PubMed: 23139354]
53. Zhang H, Saha J, Atkins K, Brosius F III. Podocyte JAK2 Augments Glomerular Injury Induced by Diabetes and Angiotensin II. *J Am Soc Nephrol*. 2012; 23:478A.
54. Liu R, Zhong Y, Li X, Chen H, Jim B, Zhou MM, et al. Role of transcription factor acetylation in diabetic kidney disease. *Diabetes*. 2014 Jul; 63(7):2440–53. This set of studies documented for the first time that STAT3 activation occurred via lysine acetylation that was enhanced by reduced SIRT1 activity in diabetic kidney disease. This presented a new paradigm, independent of enhanced JAK activation, by which diabetes leads to STAT3 activation and increased kidney pathology. [PubMed: 24608443]
55. Liu Q, Xing L, Wang L, Yao F, Liu S, Hao J, et al. Therapeutic effects of suppressors of cytokine signaling in diabetic nephropathy. *J Histochem Cytochem*. 2014 Feb; 62(2):119–28. Epub 2013/11/13. eng. [PubMed: 24217922]
56. Zhou Y, Lv C, Wu C, Chen F, Shao Y, Wang Q. Suppressor of cytokine signaling (SOCS) 2 attenuates renal lesions in rats with diabetic nephropathy. *Acta Histochem*. 2014 Jun; 116(5): 981–8. Epub 2014/05/08. eng. Injection of SOCS2 adenovirus prevented development of some early aspects of diabetic nephropathy in a rodent model. [PubMed: 24802166]
57. Weimbs T, Olsan EE, Talbot JJ. Regulation of STATs by polycystin-1 and their role in polycystic kidney disease. *JAKSTAT*. 2013 Apr 1.2(2):e23650. Epub 2013/09/24. eng. [PubMed: 24058808]
58. Low SH, Vasanth S, Larson CH, Mukherjee S, Sharma N, Kinter MT, et al. Polycystin-1, STAT6, and PI00 function in a pathway that transduces ciliary mechanosensation and is activated in polycystic kidney disease. *Dev Cell*. 2006 Jan; 10(1):57–69. Epub 2006/01/10. eng. [PubMed: 16399078]

59. Talbot JJ, Song X, Wang X, Rinschen MM, Doerr N, LaRiviere WB, et al. The cleaved cytoplasmic tail of polycystin-1 regulates Src-dependent STAT3 activation. *J Am Soc Nephrol*. 2014 Aug; 25(8):1737–48. In this study the cleaved cytoplasmic tail of polycystin 1 which occurs constitutively in ADPKD was found to activate STAT3 via a Src-dependent process. This places STAT3 in the center of the abnormal signaling from polycystin to cyst growth in ADPKD. [PubMed: 24578126]
60. Zhou J, Ouyang X, Schoeb TR, Bolisetty S, Cui X, Mrug S, et al. Kidney injury accelerates cystogenesis via pathways modulated by heme oxygenase and complement. *J Am Soc Nephrol*. 2012 Jul; 23(7):1161–71. Epub 2012/04/21. eng. [PubMed: 22518005]
61. Karihaloo A, Koraishy F, Huen SC, Lee Y, Merrick D, Caplan MJ, et al. Macrophages promote cyst growth in polycystic kidney disease. *J Am Soc Nephrol*. 2011 Oct; 22(10):1809–14. Epub 2011/09/17. eng. [PubMed: 21921140]
62. Leonhard WN, van der Wal A, Novalic Z, Kunnen SJ, Gansevoort RT, Breuning MH, et al. Curcumin inhibits cystogenesis by simultaneous interference of multiple signaling pathways: in vivo evidence from a Pkd1-deletion model. *Am J Physiol Renal Physiol*. 2011 May; 300(5):F1193–202. Epub 2011/02/25. eng. [PubMed: 21345977]
63. Takakura A, Nelson EA, Haque N, Humphreys BD, Zandi-Nejad K, Frank DA, et al. Pyrimethamine inhibits adult polycystic kidney disease by modulating STAT signaling pathways. *Hum Mol Genet*. 2011 Nov 1; 20(21):4143–54. Epub 2011/08/09. eng. [PubMed: 21821671]
64. Olsan EE, Mukherjee S, Wulkersdorfer B, Shillingford JM, Giovannone AJ, Todorov G, et al. Signal transducer and activator of transcription-6 (STAT6) inhibition suppresses renal cyst growth in polycystic kidney disease. *Proc Natl Acad Sci U S A*. 2011 Nov 1; 108(44):18067–72. Epub 2011/10/26. eng. [PubMed: 22025716]
65. Pang M, Ma L, Gong R, Tolbert E, Mao H, Ponnusamy M, et al. A novel STAT3 inhibitor, S3I-201, attenuates renal interstitial fibroblast activation and interstitial fibrosis in obstructive nephropathy. *Kidney international*. 2010 Aug; 78(3):257–68. Epub 2010/06/04. eng. [PubMed: 20520592]
66. Liu N, He S, Ma L, Ponnusamy M, Tang J, Tolbert E, et al. Blocking the class I histone deacetylase ameliorates renal fibrosis and inhibits renal fibroblast activation via modulating TGF-beta and EGFR signaling. *PLoS One*. 2013; 8(1):e54001. Epub 2013/01/24. eng. [PubMed: 23342059]
67. Koike K, Ueda S, Yamagishi S, Yasukawa H, Kaida Y, Yokoro M, et al. Protective role of JAK/STAT signaling against renal fibrosis in mice with unilateral ureteral obstruction. *Clin Immunol*. 2014 Jan; 150(1):78–87. Epub 2013/12/18. eng. [PubMed: 24333535]
68. Yukawa K, Kishino M, Goda M, Liang XM, Kimura A, Tanaka T, et al. STAT6 deficiency inhibits tubulointerstitial fibrosis in obstructive nephropathy. *Int J Mol Med*. 2005 Feb; 15(2):225–30. Epub 2005/01/14. eng. [PubMed: 15647835]
69. He JC, Husain M, Sunamoto M, D'Agati VD, Klotman ME, Iyengar R, et al. Nef stimulates proliferation of glomerular podocytes through activation of Src-dependent Stat3 and MAPK1,2 pathways. *J Clin Invest*. 2004 Sep; 114(5):643–51. Epub 2004/09/03. eng. [PubMed: 15343382]
70. He JC, Lu TC, Fleet M, Sunamoto M, Husain M, Fang W, et al. Retinoic acid inhibits HIV-1-induced podocyte proliferation through the cAMP pathway. *J Am Soc Nephrol*. 2007 Jan; 18(1):93–102. Epub 2006/12/22. eng. [PubMed: 17182884]
71. Gu L, Dai Y, Xu J, Mallipattu S, Kaufman L, Klotman PE, et al. Deletion of podocyte STAT3 mitigates the entire spectrum of HIV-1-associated nephropathy. *AIDS*. 2013 Apr 24; 27(7):1091–8. Epub 2013/01/25. eng. [PubMed: 23343908]
72. Correa-Costa M, Azevedo H, Amano MT, Goncalves GM, Hyane MI, Cenedeze MA, et al. Transcriptome analysis of renal ischemia/reperfusion injury and its modulation by ischemic preconditioning or hemin treatment. *PLoS One*. 2012; 7(11):e49569. Epub 2012/11/21. eng. [PubMed: 23166714]
73. Nechemia-Arbely Y, Barkan D, Pizov G, Shriki A, Rose-John S, Galun E, et al. IL-6/IL-6R axis plays a critical role in acute kidney injury. *J Am Soc Nephrol*. 2008 Jun; 19(6):1106–15. Epub 2008/03/14. eng. [PubMed: 18337485]
74. Arany I, Reed DK, Grifoni SC, Chandrashekar K, Booz GW, Juncos LA. A novel U-STAT3-dependent mechanism mediates the deleterious effects of chronic nicotine exposure on renal

injury. *Am J Physiol Renal Physiol*. 2012 Mar 15; 302(6):F722–9. Epub 2011/12/16. eng. [PubMed: 22169004]

75. Ogata K, Shimamura Y, Hamada K, Hisa M, Bun M, Okada N, et al. Upregulation of HNF-1beta during experimental acute kidney injury plays a crucial role in renal tubule regeneration. *Am J Physiol Renal Physiol*. 2012 Sep; 303(5):F689–99. Epub 2012/07/05. eng. [PubMed: 22759397]
76. Susnik N, Sorensen-Zender I, Rong S, von Vietinghoff S, Lu X, Rubera I, et al. Ablation of proximal tubular suppressor of cytokine signaling 3 enhances tubular cell cycling and modifies macrophage phenotype during acute kidney injury. *Kidney Int*. 2014 Jun; 85(6):1357–68. Epub 2014/01/10. eng. In this study proximal tubular SOCS3 knockout mice maintained better kidney function when kidney injury was induced by aristolochic acid or ischemia/reperfusion confirming a protective role of STAT3 in AKI. [PubMed: 24402091]
77. Yokota N, Burne-Taney M, Racusen L, Rabb H. Contrasting roles for STAT4 and STAT6 signal transduction pathways in murine renal ischemia-reperfusion injury. *Am J Physiol Renal Physiol*. 2003 Aug; 285(2):F319–25. Epub 2003/04/24. eng. [PubMed: 12709397]

Key Points

- Enhanced JAK-STAT expression and signaling contributes to the pathogenesis of several chronic progressive kidney diseases including diabetic nephropathy, ADPKD and HIVAN.
- JAK2 and STAT3 are the JAK and STAT isoforms, respectively, that have been most clearly identified in progressive chronic kidney diseases.
- In contrast, JAK-STAT signaling may help protect the kidney from damage during acute kidney injury.
- Enhancement of SOCS expression inhibits JAK-STAT signaling and may help prevent pathologic changes of diabetic nephropathy.
- JAK inhibitors are now being tested in patients with diabetic kidney disease.

Fig. 1. Schema of JAK-STAT3 activation in diabetic nephropathy

In diabetes, high glucose levels induce advanced glycation end-product (AGE) formation. Both high glucose and AGE stimulate growth factors and cytokine production in kidney cells. After binding to their receptors, cytokines activates JAKs which in turn lead to tyrosine phosphorylation of STAT3. Growth factors can activate tyrosine receptor kinases and Src family kinases which also induce tyrosine phosphorylation of STAT3. STAT3 is also phosphorylated at its serine site by MAPK to enhance its transcriptional activity. MAPK is activated in diabetes by either activation of the AGE receptor (RAGE) or by growth factors (EGF and TGF- β). Phosphorylated STAT3 then dimerizes and enters the nucleus to activate gene transcription. Recent data suggest that acetylation of STAT3 is also required for its activation. Acetylation of STAT3 is induced by ROS-mediated PCAF

activation and is inhibited by SIRT1, a deacetylase. STAT3 mediates transcription activation of SOCS which in turn inhibits STAT3 activation, forming a negative feedback loop.

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Table 1

Increases in expression and/or activation of JAK-STAT pathway molecules in various kidney diseases

Disease	JAK	STAT	SOCS
Diabetic nephropathy	JAK1, 2	STAT1, 3	SOCS1, 3
ADPKD	JAK2	STAT3, 6	No data
Obstructive uropathy	*	STAT3	No data
HIVAN	No data	STAT3	No data
Acute kidney injury	No data	STAT3, 6	SOCS3

ADPKD-autosomal dominant polycystic kidney disease; HIVAN-HIV associated nephropathy,

* Possible role of unidentified JAK isoform based on inhibitor study.