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STAT Signaling in Polycystic Kidney Disease

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Abstract

The most common form of polycystic kidney disease (PKD) in humans is caused by mutations in the *PKD1* gene coding for polycystin1 (PC1). Among the many identified or proposed functions of PC1 is its ability to regulate the activity of transcription factors of the STAT family. Most STAT proteins that have been investigated were found to be aberrantly activated in kidneys in PKD, and some have been shown to be drivers of disease progression. In this review, we focus on the role of signal transducer and activator of transcription (STAT) signaling pathways in various renal cell types in healthy kidneys as compared to polycystic kidneys, on the mechanisms of STAT regulation by PC1 and other factors, and on the possibility to target STAT signaling for PKD therapy.

Introduction

Mutations in numerous genes can lead to polycystic kidney disease (PKD) in humans and animal models. The most common human form, autosomal-dominant PKD (ADPKD), is caused by mutations in the *PKD1* or *PKD2* genes, and typically leads to slow progression towards end-stage renal failure during adulthood. During disease progression, aberrant proliferation of tubule epithelial cells (TECs) leads to thousands of microscopic and

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DECLARATION OF INTERESTS

TW and JAT are inventors on patent applications by UCSB related to PKD. TW serves on the scientific advisory board of, and receives research funding from, Chinook Therapeutics, Inc. TW, JAT and AS are shareholders of Santa Barbara Nutrients, Inc, and serve in managerial positions and/or on the board of directors. Representing the University Hospital of Cologne, MCL serves as a member of an advisory board for Otsuka Pharmaceuticals.

macroscopic cysts that develop in both kidneys. This causes substantial organ enlargement, fibrosis and destruction of the normal renal parenchyma (Bergmann et al., 2018; Cornec-Le Gall et al., 2019; Müller and Benzing, 2018). Polycystin1 (PC1) and polycystin2 (PC2), the products of the *PKD1* or *PKD2* genes, are the subunits of an apparent cation channel with a poorly understood purpose. It is still controversial, which cations are primarily conducted by this channel, if any (Douguet et al., 2019; Padovano and Caplan, 2018). In addition to their ion channel function, both proteins - either alone or together - also regulate a bewildering number of other signaling functions. This includes the regulation of heterotrimeric G-proteins, mTOR signaling, signal transducer and activator of transcription (STAT) signaling and many more (Bergmann et al., 2018; Ong and Harris, 2015; Torres and Harris, 2019).

The only FDA-approved therapeutic for ADPKD is the vasopressin receptor 2 antagonist tolvaptan which is available to a limited fraction of patients. It's use is further complicated due to significant side effects and potential toxicities (Chebib and Torres, 2018), poor cost-effectiveness (Erickson et al., 2013) and questions about its efficacy (Anderson, 2020). Tolvaptan does not appear to directly affect a mechanism regulated by the polycystins. It is thought to act via inhibition of cAMP signaling in cyst-lining cells but may also act more indirectly, e.g. by increasing water consumption in patients (Gastel and Torres, 2017).

Much effort has been spent on identifying signaling mechanisms that are directly regulated by the polycystins in an effort to devise strategies for pharmacological intervention to slow disease progression in ADPKD (Torres and Harris, 2019; Weimbs et al., 2018). This review will focus on the role of STAT transcription factors that have been found to be regulated by PC1, are frequently found to be activated in various cell types in ADPKD and PKD animal models, and appear to be drivers of disease progression.

STAT transcription factors

STAT proteins are a family of seven (in mammals) sequence-specific transcription factors that most typically act as signal transducers between growth factor receptors on the plasma membrane and specific genes in the nucleus. They reside in the cytoplasm and oscillate between antiparallel and parallel dimer conformation until the parallel dimer conformation is stabilized by tyrosine phosphorylation (Nast et al., 2019). Canonical STAT activation usually occurs through a series of tyrosine phosphorylations by members of the Janus kinase (JAK) family that are non-covalently bound to those specific receptors (O'Shea et al., 2015). Ligand binding brings the JAK proteins in close proximity allowing for transphosphorylation which releases their intrinsic catalytic activity (O'Shea et al., 2013). Following a phosphorylation series of receptor tails, STATs are recruited through the interaction of their Src-homology-2 (SH2) domain with phosphorylation sites (Liongue and Ward, 2013). Phosphorylation of a single tyrosine residue near the C-terminus of the STAT protein results in release from the receptor and homo- or heterodimerization in parallel arrangement (Zhong et al., 2005) allowing the transcription factors to subsequently enter the nucleus. The translocation event is followed by binding of STATs to specific DNA sequences together with transcriptional cofactors to regulate gene expression (Figure 1 and 2) (Rawlings et al., 2004).

Besides JAK-associated receptors, several receptors with intrinsic tyrosine kinase activity, such as the epidermal growth factor receptor (EGFR), the platelet-derived growth factor receptor (PDGFR) and the hepatocyte growth factor receptor (c-Met), are able to activate STATs directly (Leaman et al., 1996; Olayioye et al., 1999; Vignais et al., 1996). Non-receptor tyrosine kinases such as Src (Wang et al., 2000) are also able to phosphorylate and activate STAT proteins (Figure 1 and 2)(Silva, 2004).

The three major classes of negative regulators of the JAK/STAT pathway are members of the SOCS (suppressor of cytokine signaling), PIAS (protein inhibitors of activated stats) and PTP (protein tyrosine phosphatases) protein families. SOCS proteins are part of a negative feedback loop as STATs stimulate SOCS gene transcription which then bind to phosphorylated JAK proteins or phosphorylated tyrosine residues on activated cytokine receptors and suppress their activity (Yoshimura et al., 2007). PIAS proteins bind directly to activated STAT dimers thereby preventing STAT-mediated transcription whereas PTPs antagonize signaling by dephosphorylating activated JAKs, phosphorylated receptors or the STATs themselves (O'Sullivan et al., 2007; Shuai, 2006). Besides tyrosine-phosphorylation, several other post-translational modifications critically affect STAT-driven transcription either promoting or suppressing STAT activity. To date, lysine acetylation of STATs has been identified for five out of seven STAT family members (STAT1, STAT2, STAT3, STAT5, STAT6) (Zhuang, 2013) while STAT1, STAT3, STAT4 and STAT5A/B have all been shown to undergo a second phosphorylation event on serine (Ferreli et al., 2017; Villarino et al., 2017). A conserved arginine residue in STAT1, STAT3 and STAT6 has also been shown to be methylated which prevents PIAS effectors from binding to STATs and thereby increases transcription efficiency (Heppler and Frank, 2017). STAT5-dependent transcription was found to be enhanced by the cooperative action of two methyltransferases (Kleinschmidt et al., 2008). STAT1 was also identified to contain five sumoylation sites while one and two sumoylation sites and were identified for STAT3 and STAT5 respectively (Heppler and Frank, 2017; Van Nguyen et al., 2012).

Another layer of complexity of STAT-driven gene expression is due to unphosphorylated STATs that can mediate gene expression in a manner distinct from STATs activated by tyrosine phosphorylation (Cheon et al., 2011). STAT1 and STAT3 genes are themselves targets of activated STAT1/STAT3 proteins. The STAT-driven gene expression of their own genes results in large amounts of unphosphorylated STAT1/STAT3 in the cytoplasm, which are latent unless they collaborate with other proteins to drive gene expression. Unphosphorylated STAT1 (U-STAT1) together with IRF1 results in expression of low molecular mass peptide (LMP) 2 gene (Cheon and Stark, 2009). U-STAT3 has been found to activate a subset of κB-dependent genes by associating with unphosphorylated NF-κB while U-STAT6 can cooperate with p300 to contribute to cyclooxygenase-2 expression (Cui et al., 2007; Yang and Stark, 2008). Further, through the absence of thrombopoietin, uSTAT5 represses megakaryocytic differentiation by colocalizing with CTCF in the nucleus (Park et al., 2016).

Recently, U-STAT2 has been shown to be involved in a novel mechanism leading to STAT3 activation. By interacting with IRF-9 and the p65 subunit of NF-κB, U-STAT2 can lead to

increased Interleukin (IL)-6 secretion eventually leading to STAT3 activation (Nan et al., 2018).

Members of the STAT protein family display distinctive biological functions and STAT-STAT interactions (Table 1). To date, all STATs except STAT2 have been implicated in PKD and those will be further discussed below.

What is the role of STATs in the healthy kidney and in renal pathologies besides PKD?

STAT signaling appears to be generally turned off in normal, adult kidneys, at least as evidenced by the lack of tyrosine-phosphorylation of STATs. Nevertheless, most STATs are highly expressed in normal kidneys suggesting that STAT signaling pathways are “on standby” and can be rapidly activated in response to various stimuli. Renal STAT activation has been most frequently reported in response to renal injury and other renal pathologies and can occur very rapidly as discussed below for each individual STAT protein.

STAT1.

STAT1 is activated in embryonic kidneys by phosphorylation on Y701 and S727 while healthy adult kidneys lack active STAT1 indicating a certain role in kidney development even if *Stat1* null mice do not display any renal defects in embryogenesis (Durbin et al., 1996; Meraz et al., 1996; Tao et al., 2018; Wang et al., 2010). In contrast, Socs1- deficient mice exhibit delayed renal tubule organization and unilateral polycystic kidneys. However, a concomitant deletion of Interferon γ (IFNγ) is required to prevent early non-renal death making it difficult to define the specific role of STAT1 in renal development (Metcalf et al., 2002). Beside this, STAT1 is well known in mediating inflammation in several renal diseases like diabetic nephropathy (DN) and lupus nephritis (LN) (Dong et al., 2007; Shi et al., 2010; Zhou et al., 2013). Oxidative stress as a major cause of chronic inflammation and tubular hypertrophy in the kidney seems to mediate its effects by JAK2/STAT1/STAT3 signaling in TECs. Using high glucose treatment as oxidative trigger in TEC culture (LLC-PK1) JAK2/STAT1/STAT3 signaling was shown to be highly activated leading to cell hypertrophy and extracellular matrix (ECM) protein accumulation. Treatment with antioxidants like taurin or N-acetylcysteine blocked JAK2/STAT1 activation and reversed these effects pointing to JAK2/STAT1 as a redox sensitive pathway in TECs (Huang et al., 2007). Furthermore, STAT1 activation contributes to chemokine expression of TECs and macrophage regulation (Figure 1). STAT1 depleted TECs revealed significantly decreased expression of CXCl9, IP-10 and MCP-1 upon acute inflammatory conditions in cell culture. An interesting picture emerged when *Stat-1* null mice were subjected to ischemia-reperfusion injury (IRI). During the initial injury phase, STAT1 in TECs appears to be responsible for recruiting macrophages to the injured kidney (Kemmner et al., 2019). Inhibiting STAT1 is therefore beneficial during this phase and lessens the degree of renal damage. However, persistent lack of STAT1 in macrophages leads to their increased M2-polarization and increased fibrosis later after IRI (Kemmner et al., 2019). Therefore, inhibition of STAT1 ultimately leads to worsened progression to chronic kidney disease (CKD). This example highlights the need to be very clear about the cell type that one is studying. Finally, aging human kidneys reveal an

increase in STAT1 activity besides other inflammation-associated transcription factors highlighting its contribution in renal inflammation and injury (Figure 1) (Bai et al., 2018; O'Brown et al., 2015; Shi et al., 2010).

STAT3.

STAT3 signaling is known for its important role in inflammation and immunity. For example, STAT3 mediates development, activation and migration of neutrophils, B-lymphocytes, dendritic cells and macrophages throughout different organs upon inflammation (Fielding et al., 2008; Lee et al., 2002; Melillo et al., 2010; Nefedova et al., 2004; Park et al., 2004; Takeda et al., 1999). Overall, STAT3 signaling is thought to be crucial in balancing inflammatory and anti-inflammatory responses (Hillmer et al., 2016). Several kidney diseases including PKD exhibit inflammation and immune cell infiltration (O'Brown et al., 2015; Weimbs et al., 2018). STAT3 activation, for example, was found in macrophages and interstitial fibroblasts facilitating leukocyte infiltration and ECM protein production upon acute kidney injury (AKI) in rats and mice (Bienaimé et al., 2016; Kuratsune et al., 2007; Pang et al., 2010). This indicates that STAT3 signaling in inflammatory and immune cells might likely play a role in development and progression of certain kidney diseases (O'Brown et al., 2015; Weimbs et al., 2018). This section will further focus on the role of STAT3 in renal TECs due to its great importance for PKD.

STAT3 is highly activated in embryonic rat kidneys (phosphorylation on Y705) and in TECs of early postnatal mice (Talbot et al., 2011; Wang et al., 2010) suggesting a certain role in renal development and maturation. *Stat3* null mice have been unhelpful in this regard due to early embryonic lethality (Takeda et al., 1997). With the end of renal proliferation in mice, around day 14, STAT3 activity is strongly down regulated in mature mouse kidneys (Talbot et al., 2011). However, STAT3 expression itself remains high in healthy adult kidneys indicating that it is ready to be activated as shown in the aging human kidney and in several forms of renal insults including tubulointerstitial fibrosis or glomerulosclerosis (Du et al., 2018; Estrada et al., 2018; O'Brown et al., 2015; Talbot et al., 2011). Active STAT3 is localized to a broad spectrum of cells depending on the type of kidney injury. While animal models of DN, focal segmental glomerulosclerosis (FSGS) and rapidly progressive glomerulonephritis (RPGN) reveal STAT3 activation in glomerular cells (Wang et al., 2002), settings of tubulointerstitial fibrosis and AKI exhibit STAT3 activation predominantly in tubular, interstitial and endothelial cells (Bienaimé et al., 2016; Dube et al., 2017; Kuratsune et al., 2007; Pang et al., 2010). Using ureteral obstruction (UUO) as a model of renal fibrosis, STAT3 activation was found between day 1 and day 7 after the onset of obstruction in mice and rats (Kuratsune et al., 2007; Pang et al., 2010). Here, STAT3 activation was localized to both interstitial cells and TECs (Kuratsune et al., 2007). STAT3 inhibition with S3I-201 inhibited renal fibrosis and inflammation in the murine model (Pang et al., 2010). Similarly, 75% nephrectomy, a slower model of CKD, led to STAT3 activation in TECs and interstitial cells after about 6 weeks and coinciding with features of CKD including fibrosis. Remarkably, genetic inactivation of STAT3 specifically in TECs of mice alone was sufficient to prevent the progression to fibrosis and other CKD features after 75% nephrectomy. Based on these *in vivo* studies and additional *in vitro* experiments, these authors concluded that STAT3 activation in TECs leads to expression of a suite of genes including pro-fibrotic,

secreted factors (Figure 1) that then trigger the activation of interstitial myofibroblasts. Consequently, STAT3 is activated in myofibroblasts leading to kidney fibrosis (Bienaimé et al., 2016). This conclusion is consistent with a model showing that necrotic TECs trigger IL-22 secretion in CD45+ phagocytes by releasing TLR4 agonists (Kulkarni et al., 2014). Interestingly, IL-22 receptor expression is exclusively found on TECs while IL-22 is selectively secreted by CD45+ phagocytes in the kidney. However, IL-22 pretreatment in an IRI mouse model increases STAT3 activity in TECs and in contrast ameliorates AKI (Xu et al., 2014). In this model, blocking IL-22 signaling with an IL-22 antibody or by using IL-22 deficient mice led to impaired renal recovery suggesting a protective effect of STAT3 signaling. The same results were achieved by blocking Toll-Like receptor 4 (TLR4) with a TLR4 antibody in the healing phase of this model (Kulkarni et al., 2014). Beside IL-22, pretreatment with IL-6/sIL-6 receptor fusion protein increased STAT3 activity in TECs, too, and strikingly reduced AKI in a mercury-induced AKI mouse model pointing to a similar preventive effect of IL-6/STAT3 trans-signaling (Nechemia-Arbely et al., 2008). Interestingly, endothelial-specific *Stat3* deletion in mice increased kidney injury in an IRI model confirming a beneficial effect of STAT3 (Dube et al., 2017). Furthermore, JAK/STAT3 signaling might be required for survivin-mediated recovery effects in mice upon IRI (Chen et al., 2013a). Pretreatment with the STAT3 inhibitor S3I-201 in this model led to decreased survivin expression and reduced AKI recovery (Chen et al., 2013a). In the past, it has been proposed that STAT3/MAPK/ERK1/2 signaling affects fibrosis and inflammatory responses by mediating the transformation of TECs to myofibroblasts, in a process of epithelial-to-mesenchymal transition (EMT) (Iwano et al., 2002; Jain et al., 1998; Kuratsune et al., 2007; Masaki et al., 2003). The results described above, however, show that EMT does not significantly contribute to the development of myofibroblasts in CKD models and rather suggest that these cells arise from resident fibroblast or pericytes and bone marrow-derived circulating monocytes (Bienaimé et al., 2016; Humphreys et al., 2010; LeBleu et al., 2013). This process seems to involve a crosstalk between interstitial cells with epithelial cells like TECs and glomerular cells that is mediated by STAT3 signaling (Bienaimé et al., 2016).

Therefore, the emerging picture is that several renal insults affect TECs first resulting in STAT3 activation. This triggers the secretion of signaling molecules which attract and regulate fibroblasts - in a process that may also involve STAT3 activation in those cells (Figure 1) (Bienaimé et al., 2016; Kulkarni et al., 2014). Additionally, the interstitial cells can communicate back to TECs by further release of cytokines like IL-22 (Kulkarni et al., 2014). In this way STAT3 signaling appears to mediate early inflammatory-like responses upon kidney injury but also induces recovery mechanisms that are important for later stages but can lead to fibrosis if persistently activated.

STAT5.

STAT5 is described to regulate proliferation, survival and apoptosis in immune and cancer cells (Behbod et al., 2003; Cui et al., 2004; Xiong et al., 2009). STAT5 defines a group of two closely related proteins, STAT5A and STAT5B, encoded by separate genes, that can be activated by several cytokines including GH, EGF and IL −2, −3, −5, −7, −9 and −15 via tyrosine phosphorylation (694/699) by members of the JAK and Src family (Figure 2). Interestingly, Src only mediates STAT5b activation (Kazansky et al., 1999). While *Stat5a*$^{-/-}$

knockout mouse models have not shown any renal alterations, *Stat5b*$^{-/-}$ deficient mice have exhibited renal pathologies in glomerular structure and proteinuria indicating a distinct role of STAT5b in renal development and the function of healthy kidneys (Cui et al., 2004; Udy et al., 1997; Villarino et al., 2016). Furthermore, a CKD rat model revealed a certain impact of GH/STAT5 signaling in renal diseases. Subtotal nephrectomy, as a CKD model, leads to a decrease in JAK2 and STAT5 activity. Additionally, GH receptor (GHR) levels were reduced beside normal GH serum levels suggesting a possible GH resistance. Notably, GH treatment in these CKD rats significantly increased STAT5 phosphorylation without affecting JAK2 activity. Interestingly, CKD rats showed increased levels of IL-6, pSTAT3 as well as SOCS3 which is known to inhibit GH/JAK2 signaling and thus may contribute to a possible GH resistance (Wiezel et al., 2014). On the other hand, it has been shown that STAT5 is activated upon AKI induction in murine kidneys (Huen et al., 2015; Zhang et al., 2017a). Remarkably, using an IRI mouse model, AKI led to tubular secretion of GM-CSF which in turn seems to induce alternative M2 polarization via STAT5 signaling in macrophages (Figure 2). Blocking GM-CSF with an antibody upon IRI partially decreases STAT5 activation leading to decreased M2 polarization and TEC proliferation. This suggests that STAT5 signaling could contribute to renal injury and repair mechanisms by mediating an alternative way of M2 macrophage polarization in renal macrophages (Huen et al., 2015). Moreover, JAK2/STAT5 signaling seems to mediate the cytoprotective effect of erythropoietin (EPO) on TECs. EPO pretreatment of primary murine TECs in the antimycin A-induced ischemic injury model leads to JAK2 phosphorylation and reduces cytotoxicity in these cells. In contrast, this effect is abolished in primary TECs from mice lacking intact STAT5 signaling (EPOR-HM mice) suggesting that JAK2/STAT5 signaling is required for EPO-mediated cytoprotection in TECs (Breggia et al., 2008). Taken together, STAT5 signaling occurs in renal TECs and macrophages possibly affecting renal diseases by mediating cell survival, inflammation and tissue repair mechanisms (Figure 2).

STAT6.

Renal TECs in adult kidney express STAT6 but exhibit little or no STAT6 activation. However, systemic IL-4 or IL-13 treatment in mice result in rapid (within one hour) and strong STAT6 activation in renal TECs (Olsan et al., 2011, 2018) suggesting that the STAT6 pathway is “on standby” in these cells. Kidney injury by UUO in mice revealed JAK3/STAT6 activation in interstitial cells, too, leading to renal fibrosis with bone marrow derived fibroblast accumulation (Figure 2). Treatment with the JAK3 inhibitor CP690,550 (tofacitinib) in this model led to STAT6 inhibition and reduced these effects. Interestingly, STAT6 deficient mice (*Stat6*$^{-/-}$ by SH2 domain deletion) in the same UUO model revealed reduced M2 macrophage polarization and myofibroblast transformation (Yan et al., 2015). Thus, a model has been suggested where JAK3/STAT6 signaling mediates myofibroblast accumulation and their transformation from circulating monocyte-derived M2 macrophages (Yan et al., 2015; Yang et al., 2013). Additionally, IL-4-receptor deficiency in mice also inhibited STAT6 activation in a folic acid nephropathy model resulting in a decrease of fibroblast activation in the kidney, again supporting the notion that activation of this pathway contributes to renal fibrosis (Liang et al., 2017). Interestingly, aberrant upregulation of IL-13 was found in renal insults like lupus nephritis (Chen et al., 2001). However, some contrasting results suggest a protective role for STAT6 activation in the kidney. Pretreatment

with IL-13 for example reduced tubulointerstitial damage in an IRI model (Sandovici et al., 2008). Moreover, STAT6 null mice (*Stat6*$^{-/-}$ by first exon coding deletion) revealed increased tubule injury and decreased renal function upon IRI and exhibited stronger apoptosis and inflammation compared to wild type mice in a UUO model (Yokota et al., 2003; Yukawa et al., 2005). These conflicting results in *Stat6* null mice might be due to different gene deletion models leading to different phenotypes (Wang et al., 2009). More recent results suggested that EPO treatment in the same UUO model may lead to STAT6 activation protecting mice from AKI by decreasing inflammatory infiltration (Zhang et al., 2018).

In conclusion, JAK3/STAT6 activity was found in TECs and interstitial cells in the kidney primarily in response to IL-4 and IL-13. While IL-4 signaling has been suggested to drive renal fibrosis (Liang et al., 2017) other results showed beneficial effects of IL-13/IL-4 by facilitating tissue repair after renal insults (Sandovici et al., 2008; Zhang et al., 2017a). Again, timing may be crucial in explaining the differences, with STAT6 activation initially playing a beneficial role during injury repair and later playing a detrimental role in fibrosis if the signal is not terminated. Contrasting effects due to STAT6 pathway activation in different renal cell types likely occur and further investigation will be needed to better understand such opposing results (Liang et al., 2017; Zhang et al., 2017a).

The (complicated) mechanisms of STAT regulation by polycystin-1 (PC1)

The loss of functional PC1 leads to ADPKD but “how” is much less clear. PC-1 is a large integral membrane protein with a size exceeding 460 kDa, containing a large extracellular domain consisting of roughly 3,000 amino acids, eleven predicted transmembrane domains and a short cytoplasmic tail of about 200 amino acids (Merrick et al., 2014). It was initially reported that direct association of PC1 with JAK2 leads to STAT1 activation (Bhunia et al., 2002). This mechanism was shown to be dependent on the interaction of PC1 with PC2 and leading to upregulation of $p21^{waf1}$, a potent inhibitor of cyclin-dependent kinase 2 (Cdk2), resulting in growth arrest.

PC1 undergoes cleavage in both the N-and C-terminal domains. The N-terminal cleavage occurs at the G protein-coupled receptor proteolytic site (GPS) (Qian et al., 2002) while the C-terminal domain undergoes at least 3 cleavages. Those cleavage events have been found to release the entire cytoplasmic tail (~30 kDa) (Bertuccio et al., 2009; Chauvet et al., 2004; Low et al., 2006; Talbot et al., 2011), a smaller fragment corresponding to the C-terminal half of the cytoplasmic tail (~15 kDa) (Low et al., 2006; Talbot et al., 2011) and a larger fragment (~100kDa) containing 6 transmembrane domains and the cytoplasmic tail (Woodward et al., 2010). Our group showed that STAT6 activity is inhibited by membrane-anchored PC1 yet cytoplasmic tail fragments can interact with STAT6 and the transcriptional co-activator P100 and co-activate STAT6-dependent gene expression. This on/off regulation of STAT6 activity appeared to be controlled by changes in apical/tubular fluid flow suggesting a mechanism of mechano-transduction (Low et al., 2006) that was proposed to involve the flow-regulated cleavage (Chauvet et al., 2004) of the cytoplasmic tail of PC1. It was further demonstrated that STAT6 is aberrantly activated in cyst-lining epithelial cells in

PKD and that genetic or pharmacological inhibition of STAT6 in a PKD mouse model leads to inhibition of renal cyst growth (Olsan et al., 2011).

PC1 has been ascribed a number of functions relevant to PKD including acting as an adhesion protein (Streets et al., 2009) and regulating microtubule and actin dynamics in response to injury (Castelli et al., 2015). Cleavage of full length PC1 into its C-terminal tail (PC1-CT) appears to be a mechanism of mechanosensation utilizing the STAT3 signaling pathway. Dalagiorgou et al. investigated the PC1-CT/STAT3 axis outside the kidney outlining how PC1-CT/STAT3 contributes to mechanosensation wherein following mechanical stretching of osteoblasts, the JAK2/STAT3 pathway becomes activated to regulate cell differentiation via upregulation of the osteoblastic regulator of differentiation *Runx2* (Dalagiorgou et al., 2017). This activation of JAK/STAT3 via PC1 may be mediated by cleavage of the PC1 C-terminal tail (Dalagiorgou et al., 2017). Our group investigated the possible regulation of STAT3 by PC1 and we reported a dual mechanism (Talbot et al., 2011) as well as a third mechanism (Talbot et al., 2014). JAK2 was found to bind to the membrane-proximal half of the cytoplasmic tail of membrane-anchored PC1 causing direct, JAK2-dependent activation of STAT3 (Talbot et al., 2011). Cleavage of the cytoplasmic tail of PC1 resulted in the loss of its ability to activate STAT3 via JAK2. However, the 30 kDa PC1 tail cleavage product (PC1–p30) was able to translocate to the nucleus and co-activate tyrosine-phosphorylated STAT3 (and also STAT1), which has been activated by cytokine signaling (Talbot et al., 2011). PC1–p30 can also interact with the tyrosine kinase Src and directly activate Src leading to phosphorylation and activation of STAT3 (Talbot et al., 2014). While activation of STAT3 by membrane-bound PC1/JAK2 is inhibited by SOCS3, activation of STAT3 by PC1–p30 is insensitive to SOCS3 inhibition. It was further shown that this signaling pathway is amplified by binding of EGF to its receptor and by increased levels of cAMP. By integrating inputs from EGFR and cAMP signaling, PC1–p30 appears to be able to activate STAT3 in a cytokine/JAK2-independent manner by bypassing inhibition by SOCS3 (Talbot et al., 2014). These observations suggest that STAT3 may be a key integrator transmitting extracellular mechanosensation to changes in gene expression.

Together, these results suggest that PC1 regulates STATs through several distinct pathways. First, the membrane-anchored PC1 can activate STAT1 and STAT3 through JAK2-mediated phosphorylation. Second, PC1 C-terminal fragments can co-activate STAT1, STAT3 and STAT6 depending on whether they had previously been activated by canonical signaling. STAT3, however, can also be directly activated by Src through the interaction with PC1–p30. This complicated situation suggests that PC1 may be an important integrator of several incoming signaling pathways, which can cause various downstream effects depending on the cellular situation (e.g. under flow-vs. no-flow conditions)

STAT1 in PKD

STAT1 was the first STAT family member to be investigated in PKD, leading to the conclusion that PC1 may regulate the cell cycle via JAK2-mediated STAT1 regulation (Bhunia et al., 2002). This regulation was suggested to occur in tubule/cyst epithelial cells but has not been studied further. More recently, STAT1 has been investigated in other tissues and cell types involved in PKD. Cardiovascular complications, including hypertension and

aneurysms are associated with ADPKD caused by mutations in PC1. Kwak et. al recently reported a link between PC1 and STAT1 in endothelial cells in PKD. PC1 is an atypical G-protein-coupled receptor that can undergo cleavage at a conserved GPS motif near the first transmembrane domain. Kwak et. al found that the inhibitory G protein Gαi3 binds the membrane anchored C-terminal tail (CTT) of PC1, and only upon cleavage of PC1 at the GPS motif will Gαi3 dissociate from the PC1-CTT and activate the classical transient receptor potential channel 4 (TRPC4). The activation of TRPC4 causes an influx of calcium which in turn causes the activation of STAT1 to regulate endothelial cell proliferation and apoptosis, which was suggested to relate to cardiovascular abnormalities in PKD (Kwak et al., 2018). This reported mechanism would appear to be quite indirect and very different from the one reported previously in epithelial cells.

The importance of the dysregulation of immune system components, specifically inflammation, in ADPKD has gained increasing attention. Inflammatory cells such as macrophages are known to accumulate in polycystic kidneys where they differentiate into the M2 phenotype (Swenson-Fields et al., 2013). Furthermore, it has been reported that the alternative complement pathway is aberrantly activated in PKD and that its inhibition ameliorates the disease severity through decreased macrophage infiltration and complement factor B (CFB) expression (Su et al., 2014; Zhou et al., 2012). CFB is over expressed in ADPKD patient kidneys and Cy/+ Han:SPRD rat kidneys and was found to be correlated with an increase in JAK2/STAT1 activation and expression of the 30 kDa PC1-CTT in these cystic kidneys (Wu et al., 2016). The JAK2/STAT1 pathway is known to promote tumor growth primarily through its pro-inflammatory properties (Graziani et al., 2010). Henceforth, it was found that over expression of STAT1 in UCL93 renal epithelial cells causes increased CFB expression and inhibition of STAT1 leads to decreased CFB expression. Illuminating where the PC1-CTT fits into this pathway, over expression of PC1-CTT in renal epithelial cells leads to increased JAK2/STAT1 activation and CFB up regulation (Wu et al., 2016). Macrophage differentiation into the M2 phenotype once in the cystic kidneys was hypothesized to be caused by a soluble factor secreted by renal epithelial cells. Strikingly, CFB promotes macrophage conversion to the M2 phenotype and this conversion is inhibited by inhibition of STAT1 (Wu et al., 2016). These results begin to paint a picture that the PC1-CTT increases CFB through STAT1 activation, which may in turn cause M2 macrophage phenotype conversion. This pathway may play a major role in the inflammatory phenotype seen in ADPKD cystic kidneys. Furthermore, these findings suggest that STAT1 inhibition may be a promising new target in inhibiting M2 macrophage conversion and the subsequent inflammation in ADPKD kidneys.

STAT3 in PKD

STAT3 dysregulation has been studied intensively within the cancer research field with a number of parallels between STAT3 activity in cancer and PKD. Activation of STAT3 signaling is frequently implicated in tumor angiogenesis, tumor survival, immunomodulation, extracellular matrix remodeling and EMT of precancerous cells (Avalle et al., 2017). Similarly, polycystic kidneys are characterized by increased expression of extracellular matrix proteins (Bello-Reuss et al., 2001; Liu et al., 2012), EMT phenotypes (Togawa et al., 2010), altered cellular growth, apoptosis and changes to immune cell

function. The effects of STAT3 in cancer are believed to be contextual as STAT3 may play both pro-oncogenic and tumor suppressor roles dependent on other gene mutations within the cell (Avalle et al., 2017). A contextual role for STAT3 may also be at play in PKD. Our lab has previously reported that polycystic kidneys in multiple rodent models of PKD exhibit increased phospho-tyrosine-STAT3 (pY-STAT3) within cyst lining epithelia (Talbot et al., 2011) with others having reported pY-STAT3 in immune cells within polycystic kidneys (Peda et al., 2016). STAT3 as a driver of disease progression is suggested by the use of putative STAT3 inhibitors in PKD rodent models resulting in decreased cystic disease (Leonhard et al., 2011; Patera et al., 2019; Takakura et al., 2011) with the caveat that these inhibitors have limited specificity and affect more than just cystic epithelial cells. Recently, the role of STAT3 as a driver of cyst progression was tested by cell specific deletion of *Stat3* within mouse proximal tubule cells. Cell-specific *Stat3* deletion led to modestly diminished cystic kidneys but paradoxically decreased kidney function. The loss of *Stat3* was found to induce a strong inflammatory response, recruiting infiltrating macrophages. It was suggested that STAT3 expression in proximal tubules regulates the immune response in PKD by suppression of the pro-inflammatory chemokines CCL5 and CXCL10 (Viau et al., 2019). These findings imply that the role of STAT3 in PKD is more complex than promoting cystogenesis and it is the signaling between the kidney and the immune system that is critical for how kidney function declines. The benefit of STAT3 pharmacological inhibition on cystic disease progression may therefore be due to inactivation of STAT3 in kidney immune cells such as CD8+ T-cells or interstitial macrophages. Both of which have been shown to affect PKD progression (Cassini et al., 2018; Kleczko et al., 2018; Peda et al., 2016; Swenson-Fields et al., 2013; Yang et al., 2018). Under normal conditions, AKI induces recruitment of bone marrow-derived monocytes and proliferation of resident kidney macrophages (Peda et al., 2016), after which these cells undergo a shift to an M2-like phenotype to promote tissue repair. IL-10 is released following kidney injury to promote the stimulation of macrophages to begin the repair process via activation of JAK1, Tyk2, and subsequently STAT3 (Mosser and Zhang, 2008). This repair process in ADPKD may be dysfunctional leading to enhanced cyst growth, cyst expansion and fibrosis (Swenson-Fields et al., 2013). Human ADPKD tissue samples display increased IL-10 expression, enrichment of IL-10 within cyst fluid along with increased STAT3 expression. Stimulation *in vitro* with ADPKD cell culture media induced the activation of kidney macrophages and blocking IL-10 with an IL-10 function blocking antibody prevented STAT3 activation in these macrophages. Besides the release of IL-10 from cystic epithelia to activate STAT3, multiple factors may play a role in the reprogramming of macrophages, including prostaglandins, cAMP, lipid resolvins and adenosine (Peda et al., 2016). Recently, the transcription factor Interferon Regulatory Factor 5 (IRF5) was found to promote cystogenesis following unilateral nephrectomy in *Pkd1*-null mice via activation of resident kidney macrophages. IRF5 is known to be expressed in macrophages and regulate the expression of inflammatory cytokines IL-6 and TNF-α. Treatment with an antisense oligonucleotide (ASO) against Irf5 prevented accelerated cyst expansion but not cyst number. Using flow cytometry, the authors concluded that Irf5 ASO affected primarily resident kidney macrophages preventing their release of IL-6 and the subsequent activation of STAT3 in tubule epithelial cells (Zimmerman et al., 2020).

Recently, our lab discovered a role for STAT3 in response to AKI and how this response contributes to cystic disease progression. Torres et. al found that kidneys challenged with calcium oxalate (CaOx) microcrystals led to the activation of PKD-associated pathways in TECs including STAT3, mTOR, and Src. Wild-type rats challenged with CaOx crystals displayed temporary tubule dilation along the entire length of the nephron to allow for the passage of precipitated crystals and coincided with the activation of pY-STAT3 (Torres et al., 2019). Challenging both the Han:SPRD and the PCK rat models of PKD with dietary induced renal crystals led to increased numbers of cysts and worsened disease progression, implicating crystals as triggers for cystogenesis (Torres et al., 2019). In summary, this study suggests that STAT3 activation is required for crystal-induced tubule dilation as a reno-protective mechanism and that this process is inappropriately activated in PKD leading to cystogenesis.

In addition to the activators discussed above, STAT3 activity has also been shown to be modulated by the Renin-Angiotensin-Aldosterone-System (RAAS). RAAS has been well characterized and its involvement in ADPKD extensively studied in the HALT clinical trials testing the efficacy of angiotensin converting enzyme (ACE) inhibitors alone or in combination with angiotensin receptor blockers (ARB) (Schrier et al., 2014; Torres et al., 2012a, 2014). These studies found no beneficial effect for patients with ADPKD. Despite having no beneficial effect in humans, subsequent studies in rodent models have shown that RAAS inhibition can slow PKD progression (Fitzgibbon et al., 2018; Ravichandran et al., 2015; Saigusa et al., 2016). This beneficial effect may be mediated via STAT3 signaling as STAT3 has been shown to be activated by angiotensin II (Ang II) and mediated by TLR4 (Xu et al., 2019). In support of the role of Ang II activation of STAT3, following TLR4 knockdown in rat TECs (NRK-52E), JAK2 and STAT3 activation is diminished with a subsequent reduction of TGF-ß and collagen production (Xu et al., 2019). The lack of efficacy in slowing disease progression in human ADPKD with ACE and ARB inhibitors may indicate that Ang II activity plays a role early in the disease and therefore inhibition at later stages provides no benefit.

Taken together, these data present a compelling case for the importance of STAT3 signaling in the pathogenesis of PKD.

Src *in PKD*

Multiple publications have linked activation of the tyrosine kinase Src to pathophysiology of PKD and STAT3 activation. Src-mediated activation of STAT3-dependent transcription was initially identified in models of Src-mediated tumorigenesis. Src induces phosphorylation of Y705 of STAT3 thus promoting its dimerization and nuclear translocation (Silva, 2004). A link between Src and PKD proteins was initially suggested when PC1 was found to form a complex with focal adhesion proteins and that Src could induce tyrosine phosphorylation of the cytoplasmic tail of PC1 (Li et al., 1999; Wilson et al., 1999). Importantly, Src activity correlates with disease severity in both orthologous and non-orthologous mouse models of ARPKD although the mechanisms underlying Src activation remain incompletely understood (Elliott et al., 2011; Sweeney et al., 2008). Pharmacological inhibition of Src attenuates the phenotype in various PKD models (Sweeney et al., 2008). Tesevatinib, a

multi-tyrosine kinase inhibitor that affects EGFR and Src activity, has been shown to ameliorate progression of PKD in rodent models and is currently in first clinical trials for both ARPKD and ADPKD (Sweeney et al., 2017)(ClinicalTrials.gov identifiers NCT03096080 and NCT03203642). The efficacy and safety of Bosutinib, an oral dual Src/Bcr-Abl tyrosine kinase inhibitor, was recently evaluated in a phase 2 trial in ADPKD patients in early stages. The annual rate of kidney enlargement was reduced in bosutinib-treated patients but no beneficial effect on kidney function was detected, and adverse effects were common leading to high rate of discontinuation (Tesar et al., 2017).

As already described above, PC1 regulates STAT3 activity via several distinct mechanisms including one pathway involving Src. Our lab has reported that the cleaved, soluble cytoplasmic tail of PC1 induces Src-dependent activation of STAT3 (Talbot et al., 2011, 2014). The same tail fragment of PC1 also increased the activating effect of EGFR on the Src-STAT3 axis (Talbot et al., 2014). Importantly, hyperactivation and apical mislocalization of EGFR have been described in various PKD models (Orellana et al., 1995; Richards et al., 1998). Patients with severe ARPKD courses and increased expression of EGFR have been described (Arbeiter et al., 2008). Conversely, mutations in *Egfr* that result in reduced tyrosine kinase activity can attenuate the PKD phenotype in a rodent model of PKD (Richards et al., 1998). Pharmacological inhibition of the EGFR tyrosine kinase results in a less pronounced phenotype in a murine PKD model (Sweeney et al., 2003). Taken together, the data suggests that EGF/EGFR signaling seems to contribute to the development and severity of a PKD phenotype.

In addition to EGFR, increased intracellular cAMP has been shown to further enhance the activating effect of the cleaved PC1 tail on the Src-STAT3 axis (Talbot et al., 2014). This effect could be inhibited by the protein kinase A (PKA) inhibitor H89 suggesting that PKA is involved in this process (Talbot et al., 2014). PKA activation has been associated with both hepatic and renal phenotypes including Src activation in an orthologous PKD animal model (Banales et al., 2008; Ye et al., 2017). Intracellular cAMP levels can be increased by activation of the vasopressin V2 receptor (V2R), which has been described in PKD and is thought to drive cystic progression (Gattone et al., 2003; Wang et al., 2008). These landmark experimental studies paved the way for translation of basic research into the clinic and led to the approval of the V2R antagonist Tolvaptan as the first drug therapy for ADPKD in adult patients in certain disease stages (Gastel and Torres, 2017; Torres et al., 2012b, 2017). A clinical trial for safety and tolerability of Tolvaptan in children with ADPKD is ongoing (Schaefer et al., 2019).

In summary, there is ample evidence for activation of Src and Src-associated signaling in PKD. However, it is not completely clear whether STAT3 is the most critical downstream effector of Src, EGFR and cAMP signaling that drives cystic progression or whether other pathways are more important.

STAT5 in PKD

The research group of Albert Ong reported that STAT5 signaling may play an important role in aberrant cell proliferation in ADPKD. Inhibition of STAT5 by siRNA or a small molecule

inhibitor (VWR 573108) reduced cell proliferation and mitosis as well as cyst growth in PKD cell lines. Furthermore, STAT5 activation was found to be significantly increased in cyst lining cells of two murine ADPKD models (*Pkd1*$^{nl/nl}$ mice, *Pkd1*$^{fl/fl}$, Ksp-CreERT2 mice) peaking at 4 weeks of age and decreasing after week 10 (Fragiadaki et al., 2017). However, it remains unknown whether STAT5 is excessively activated in human ADPKD kidneys, too.

This altered STAT5 activation might be mediated by increased growth hormone/receptor (GH-GHR) signaling since GHR signals via STAT5 and since *Pkd1*$^{nl/nl}$ mice exhibit aberrantly elevated GH serum levels. Moreover, using a GH overexpressing mouse model, GH seems to induce STAT5 activation independently of *Pkd1* expression status (Fragiadaki et al., 2017). Interestingly, this mouse model was previously shown to display renal tubular dilatations (Friedbichler et al., 2012). STAT5 was found to be activated and localized in these dilated tubules beside increased expression of Cyclin D1. Additionally, GH stimulation of human *PKD1* wild type TECs (UCL93) revealed increased binding of STAT5 to the CyclinD1 promoter suggesting that GH-induced STAT5 activation promotes proliferation mediated by CyclinD1 (Fragiadaki et al., 2017). However, it remains to be elucidated whether GH levels are also elevated in human ADPKD.

Taken together, this is the first evidence that the GH-STAT5 axis could affect the pathogenesis of ADPKD. However, additional upstream activators may be considered as an alternative driving force such as EGF/EGFR known to be elevated in PKD kidneys and to mediate STAT5 signaling (Groner et al., 2000; Sweeney and Avner, 2006). Furthermore, analyzing the specific STAT5 isoform as well as the involvement of activating kinases could lead to more insights into its role in ADPKD.

STAT6 in PKD

Our group first investigated the role of STAT6 in PKD. The initial study suggested that PC1 suppresses STAT6 activity under normal conditions but that cessation of apical fluid flow triggers cleavage of the cytoplasmic tail of PC1 allowing nuclear translocation of the PC1 tail and STAT6 in complex with the co-activator P100 (Low et al., 2006). Building on these initial findings, we then reported STAT6 over expression in cysts in ADPKD human kidneys and high levels of activated STAT6 in the cyst-lining cells of two different PKD mouse models (Olsan et al., 2011). Genetic removal or pharmacologic inhibition of STAT6 in the bpk mouse model led to a significant decrease in cyst size and improvement in kidney function. Furthermore, the cytokine and potent activator of STAT6, IL-13, was found to be significantly over expressed by cyst lining cells and accumulates in cyst fluid, while the IL-13 receptor is also over expressed in cyst lining cells (Olsan et al., 2011). These results suggested that a positive feedback loop between IL-13, its receptor and STAT6 leads to persistent activation of this pathway in cystic epithelial cells.

STAT6 activation in TECs may play a role in the pathology of PKD via activation of fibrosis pathways and dysregulation of immune system components. Fibrosis is a major factor in the severity of ADPKD, and it has been shown that IL-13 can activate fibrosis pathways in the lung and liver (Kaviratne et al., 2004; Wynn, 2004). We reported that IL-13 and STAT6

activity mediate the expression and upregulation of periostin, galectin-3 and IL-24 in various forms of PKD (Olsan et al., 2018). Periostin has previously been shown to be highly overexpressed in renal tissue of human ADPKD and ARPKD patients, and in multiple mouse models of PKD, where it appears to be secreted by cyst lining cells, accelerate cyst growth and promote fibrosis (Raman et al., 2018; Wallace, 2019; Wallace et al., 2008, 2014; Watanabe et al., 2019). Periostin expression increases after IL-13 treatment in kidney epithelial cells, and *Stat6* gene ablation in bpk mice leads to a substantial reduction of periostin expression down to the level in wild-type kidneys (Olsan et al., 2018). Periostin may contribute to renal cyst growth in an auto/paracrine fashion in response to STAT6 signaling via IL-13 activation in cyst lining cells. Galectin-3 is a β-galactoside-binding lectin that is expressed during kidney development, has been shown to be upregulated and promote fibrosis after kidney injury, is known to play a role in CKD, chronic heart failure, and may contribute to inflammatory processes in Systemic Lupus Erythematosus Nephritis (Chen and Kuo, 2016). Furthermore, pharmacological inhibition of galectin-3 has been shown to reduce renal fibrosis in renal damage associated with obesity and aortic stenosis (Martinez-Martinez et al., 2016). Galectin-3 has also been found to localize to cystic epithelial cells in both the cpk mouse model and in human ARPKD, suggesting galectin-3 contributes to the fibrosis seen in PKD (Chiu et al., 2006; Winyard). Galectin-3 expression increases after IL-13 treatment in kidney epithelial cells and after injecting IL-13 *in vivo* (Olsan et al., 2018). This suggests that in cystic epithelial cells, IL-13 activation of STAT6 may cause activation of galectin-3, which in turn promotes the fibrosis seen in PKD kidneys. IL-24 has been shown to play a role in tissue integrity, wound healing, the response of epithelial cells to infections (Ouyang et al., 2011), tissue remodeling in the kidney in response to UOO in newborn mice (Castelli et al., 2015), and plays a role in the pathophysiology of irritable bowel syndrome and Crohn's Disease in humans (Fonseca-Camarillo et al., 2014). IL-24 expression is upregulated by both IL-13 treatment and PC1–p30 overexpression in mouse and human kidney cells (Olsan et al., 2018) suggesting that it may play a role in epithelial cell dysregulation that leads to cyst formation.

The IL-13/STAT6 pathway is known to orchestrate a complex set of cellular responses and to play a role in multiple human diseases including allergic asthma (Antczak et al., 2016). When IL-13/STAT6 signaling is constitutively activated, this pathway appears to promote renal cyst growth and disease progression in PKD. While their exact roles remain largely unclear, a commonality in the possible functions of periostin, galectin-3 and IL-24 are their roles in regulating innate immune responses. Macrophages are a crucial component of the innate immune system, have recently been strongly implicated in the pathogenesis of PKD (Cassini et al., 2018; Karihaloo et al., 2011; Song et al., 2017; Swenson-Fields et al., 2013; Viau et al., 2018; Weimbs, 2018; Yang et al., 2018; Zimmerman et al., 2019, 2020) and may be involved in STAT6-mediated effects. Interestingly, M2 macrophages are IL-4 and IL-13 secreting (and responding) cells (Van Dyken and Locksley, 2013). In orthologous mouse models of both PKD1 and PKD2, a significant abundance of M2 macrophages was found in the interstitial space surrounding cysts and contribute to disease progression (Cassini et al., 2018; Karihaloo et al., 2011). In addition, it has been shown that galectin-3 expression and secretion by macrophages is critical in the activation of renal fibroblasts that leads to the promotion of renal fibrosis (Henderson et al., 2008). Moreover, it was found that following

AKI there is an increase in periostin expression from TECs that drive macrophage proliferation and expression of regenerative factors (Kormann et al., 2019). Together, these findings may begin to paint a picture in which macrophages and tubule/cyst cells stimulate each other via IL-13 secretion and STAT6 activation leading to increased cyst proliferation and fibrosis. Furthermore, macrophage secretion of galectin-3 is critical in activation of renal fibroblasts (Henderson et al., 2008) and may play a role in the fibrosis seen in PKD. Altogether, these findings suggest that the IL-13/STAT6 pathway and its downstream targets, including periostin, galectin-3 and IL-24, may be promising therapeutic targets for PKD therapy.

JAK inhibitors

Janus kinases (JAKs) as the essential signaling mediators downstream of pro-inflammatory cytokines and many other growth factors have been pharmacologically targeted for the treatment of inflammatory diseases and cancers (Winthrop, 2017). JAK inhibitors (also called jakinibs) have been associated with numerous undesired effects such as an increased risk for infection as well as anemia and leukopenia due to signals from hematopoietic growth factors including erythropoietin transduced by JAK2 being inhibited (Schwartz et al., 2017).

To date, several JAK inhibitors have been FDA approved (See Table 2 for a comprehensive list of JAK inhibitors). Among the early JAK inhibitors are Tofacitinib (November 2012), which potently inhibits JAK1 and JAK3 and to a lesser degree also inhibits JAK2 (Kontzias et al., 2012, Danese et al., 2015) and Ruxolitinib, a selective inhibitor of JAK1/2 (Mesa et al., 2012). Second generation Janus kinase inhibitors such as Baricitinib (June 2018), Fedratinib (August 2019) and Upadacitinib (August 2019) have emerged more recently as more specific compounds. Most of the JAK inhibitors are approved for the treatment of myelofibrosis, rheumatoid arthritis (RA) or as immunosuppressants with none of them approved for treatment of renal diseases. Since different STAT pathways are aberrantly activated in ADPKD, targeting JAK proteins may be promising, although long-term side effects of these relatively broad-acting drugs will likely be a significant concern for this slowly-progressive disease requiring long-term therapy (Weimbs et al., 2018).

Ruxolitinib is a JAK1/2 inhibitor and is approved for treatment of polycythemia vera and myelofibrosis (Verstovsek et al., 2012). Renal dysfunction is common in patients with primary myelofibrosis (PMF). A recent study showed that Ruxolitinib significantly improved renal function in patients with PMF (Strati et al., 2019) and discontinuation of the drug treatment resulted in worsening of renal function in PMF patients (Tefferi Pardanani, 2011). It is unknown how Ruxolitinib may affect renal function in PMF and, to date, there have been no studies to investigate Ruxolitinib as a treatment for renal disease.

The spice compound cinnamaldehyde, has also been shown to inhibit JAK/STAT3 activation following advanced glycation end-product (AGE) stimulation of the AGE specific receptor (RAGE) in HK2 cells. Following AGE stimulation for 48 hours with co-treatment of cinnamaldehyde, decreased pY-STAT3 and increased expression of SOCS3 levels were

observed, and after 5 days of co-treatment a decrease in collagen 4 expression (Huang et al., 2015).

Recently, Patera et al. treated human and murine derived PKD cell lines *in vitro* with the JAK inhibitor Tofacitinib and reported inhibition of STAT3 tyrosine phosphorylation that they attributed to JAK2 inhibition (Patera et al., 2019). These authors also reported high JAK2 expression levels in cystic kidneys in the $Pkd1^{nl/nl}$ mouse model. However, the level of activation of JAK2 was not investigated in that study and no *in vivo* experiments were conducted with Tofacitinib. These authors' hypothesis that STAT3 activation in PKD cysts may be due to JAK2 activity contradicts previous results by our group showing that the level of tyrosine-phosphorylation of JAK2 is not increased in two different PKD mouse models, and that STAT3 activation in PKD is independent of JAKs and mediated by Src instead (Talbot et al., 2014). Altogether, it is currently unclear whether JAK inhibitors may be beneficial in PKD.

STAT3 Inhibitors

STAT3 inhibition has been intensely studied as a therapeutic approach because of STAT3's immune modulating effects, and in the cancer field because of its involvement in cancer cell transformation, apoptosis and proliferation (Beebe et al., 2018). Similarly, these effects of STAT3 are beginning to be tested in PKD and the inhibitors used to do so are growing in number. STAT3 can be targeted in a number of ways and each method attempted has both pros and cons in execution. Many of the compounds developed to target STAT3 act upstream of its activation targeting either cytokine or growth factors/receptors (e.g. GP130, IL-6R, IL-10R, EGFR, PDGF, FGFR) or GPCR type receptors. Blockade of activating cytokines (e.g. HGF, EGF, IL-5, IL-6, IL-10, interferons, Bone Morphogenic Proteins (BMP), Leukemia Inducing Factor (LIF)) inhibits their respective receptor activity. Alternatively, inhibition of the non-receptor tyrosine kinases Src and Abl, and receptor tyrosine kinases (e.g. c-Met, EGFR, FGFR, etc.) may also prevent STAT3 activation. As would be expected, inhibition of many of these kinases may have profound effects outside of STAT3 inhibition as each has numerous downstream effectors. Some of the compounds that inhibit these tyrosine kinases and subsequently STAT3 include the JAK and Src inhibitors (discussed above), triptolide (Jing et al., 2018), imatinib (Gleevac) (Zaki et al., 2018), and the Met inhibitor crizotinib (Mesarosova et al., 2017) (See Table 2 for a more comprehensive list of STAT3 inhibitors). Because STAT3 has pleiotropic effects, targeting specificity becomes paramount to avoid potentially life-threatening complications. Direct inhibition of STAT3 can be achieved by blocking its dimerization, activation by kinases, translocation via the SH2 domain, or by blocking DNA binding via the DNA binding domain (DBD). Compounds that target STAT3 dimerization such as S3I-201 (Takakura et al., 2011) have been tested in PKD. Outside of PKD, the natural product cryptotanshinone (Chen et al., 2013b, 2017) has been tested with some success. An alternative to STAT3 inhibition may be targeting translational and transcriptional regulation of STAT3. The use of antisense oligonucleotides and oligodeoxynucleotide decoys have also been tested in the cancer field (Miklossy et al., 2013). There may be other compounds that can be used for the inhibition of STAT3 as demonstrated by the repurposing of compounds for use as STAT3 inhibitors such as the antibiotic nifuroxazide which was found to inhibit STAT3 in diabetic rats, reducing

macrophage infiltration, fibrosis and decreased mRNA and protein levels of TNF-α and IL-18 (Said et al., 2018).

Natural products are an exciting area of research for the treatment of PKD and specifically those that affect STAT3 signaling. The Indian spice turmeric, and its active component, curcumin (Leonhard et al., 2011), have already begun to be tested in clinical trials for the treatment of ADPKD (ClinicalTrials.gov Identifier: NCT02494141). Recently, other natural products have begun to show promise as STAT3 inhibitors. Stevioside, a component of the sugar substitute stevia was tested in the *Pkd1*$^{flox/+}$*:Pkhd1-Cre* mouse model and shown to inhibit cyst growth (Yuajit et al., 2014) and has been shown to inhibit STAT3 following cisplatin induced kidney injury, preventing both Erk and STAT3 phosphorylation (Potočnjak et al., 2017). The observed effect on cyst growth by stevioside may also involve activation of AMPK followed by inhibition of mTOR, and degradation of CFTR channels (Yuajit et al., 2014). With the increased need for specific STAT3 inhibitors, the list of available compounds for this purpose will undoubtedly continue to expand.

STAT5 inhibitors

Inhibition of STAT5 may be a promising approach in ADPKD but, so far, specific STAT5 inhibitors have been primarily developed for hematopoietic cancer therapy but mostly have not reached the clinic yet (See table 2 for a comprehensive list of STAT5 inhibitors) (Wingelhofer et al., 2018).

Pimozide is, so far, the only STAT5 inhibitor that is approved by the FDA for neuroleptic treatment. It showed a suppression of STAT5 activity in chronic myeloid leukemia (CML) cells of which the mechanism has not been fully clarified yet (Nelson et al., 2011).

Stafib-2, a small molecule inhibitor, and AC-3–19, a SH2 domain inhibitor, showed more specific STAT5 inhibition. Stafib-2 for example has been shown to selectively inhibit STAT5b activation in human leukemia cells without affecting STAT5a activity (Cumaraswamy et al., 2014; Elumalai et al., 2017). However, their effect was not sufficient to justify clinical trials (Wingelhofer et al., 2018). More recently, AC-4–130 another SH2 domain inhibitor of STAT5 inhibited proliferation of primary human acute myeloid leukemia cells and, furthermore, suppressed growth of an *in vivo* tumor xenograft in mice indicating a better chance for transfer into clinical studies (Wingelhofer et al., 2018).

Beside small molecule inhibitors, STAT5 activation is additionally approached by activation of peroxisome proliferator-activated receptor γ (PPARγ). The PPARγ activator and antidiabetic drug pioglitazone, for example, seems to be capable of decreasing STAT5 phosphorylation in CML cells (Prost et al., 2015).

Finally, histone deacetylase 6 (HDAC6) has been proposed as another target that may reduce STAT5 transcription and could therefore reduce cyst growth in PKD models (Cebotaru et al., 2016; Pinz et al., 2015).

STAT6/IL-13 inhibitors

Targeting IL-13/STAT6 for PKD therapy is a potentially very promising approach because it may be possible to repurpose several drugs that have already been developed for other indications (See Table 2 for a comprehensive list of STAT6 inhibitors).

The immunosuppressant teriflunomide, the active metabolite of leflunomide, is a broad range tyrosine kinase inhibitor that is approved for treatment of multiple sclerosis (Bar-Or et al., 2014). Our lab has previously shown that teriflunomide inhibits STAT6 activation and ameliorates disease progression in bpk mice (Olsan et al., 2011). Teriflunomide itself may not be viable for PKD therapy because of its many unwanted effects due to inhibition of additional molecular targets. Another small molecule drug reported to inhibit the STAT6 pathway is niflumic acid. Niflumic acid is a chloride channel inhibitor classified as a non-steroidal anti-inflammatory (NSAID) used for treatment of RA. It is thought to suppress IL-13 induced asthma phenotypes *in vivo* via inhibition of the calcium activated chloride channel, mCLCA3 which subsequently may inhibit JAK/STAT6 activation (Nakano et al., 2006).

Additional small molecule inhibitors of STAT6 have been developed (Miklossy et al., 2013). Of note are three that have been developed for asthma therapy and have shown promising preclinical results, AS1517499, YM-341619, and PM-43I. AS1517499 and YM-341619 both inhibit phosphorylation of STAT6 and PM-43I targets the STAT5/STAT6 Src Homology 2 (SH2) domain (Knight et al., 2018). AS1517499 ameliorates antigen-induced bronchial hypercontractility in mice (Chiba et al., 2009) and blocks IL-13 induced STAT6 phosphorylation in human esophageal fibroblasts and esophageal epithelial cells with minimal cellular toxicity (Cheng et al., 2016). YM-341619 inhibits IL-4 induced STAT6 dependent gene expression and has been shown to inhibit allergen induced Th2 responses *in vitro* and airway hyperresponsiveness *in vivo* (Ohga et al., 2008). The most recently developed inhibitor is PM-43I, which was shown to inhibit STAT5 and STAT6 dependent allergic airway disease and reversed preexisting allergic airway disease in mice with no long-term toxicity (Knight et al., 2018).

Another strategy for inhibition of STAT6 is targeting its upstream activator, the IL-4/−13 receptor or the cytokines IL-4 or IL-13. Several anti-IL-13 monoclonal antibodies have been developed and undergone human studies including lebrikizumab and tralokinumab. Lebrikizumab was initially developed to treat asthma and has undergone 11 clinical trials with over 4,000 patients, but after two phase III trials that had conflicting results is being repurposed as a potential novel treatment for atopic dermatitis (AD); (Corren et al., 2011; Hanania et al., 2015; Noonan et al., 2013; Scheerens et al., 2014). Lebrikizumab recently underwent a randomized, placebo-controlled, phase II study in adults with moderate to severe AD and yielded promising results. This study led to significant improvement in symptoms and was well tolerated in these patients (Simpson et al., 2018). Tralokinumab has had a similar path as lebrikizumab. Tralokinumab, an IL-13 neutralizing antibody, was tested in phase 3 studies for asthma but gave disappointing results (Wollenberg et al., 2019; Panettieri et al., 2018) and is also being re-purposed for treating AD. In phase 2b studies for treatment of AD, Tralokinumab treatment was associated with sustained and early

improvements in AD symptoms while giving a promising safety and tolerability profile (Wollenberg et al., 2019). Tralokinumab is currently undergoing phase 3 studies for AD (ClinicalTrials.gov Identifiers: NCT03587805, NCT0376157, NCT03556592).

Both of these antibodies are of the IgG isotype and our lab has shown that IgG antibodies do not effectively reach the lumen of renal cysts (Olsan et al., 2015) and would therefore not be expected to be effective for PKD therapy since IL-13 appears to signal mainly *via* the luminal surface of cyst cells (Olsan et al., 2011). However, our lab has discovered that antibodies in dimeric IgA format are targeted to renal cyst lumens *via* transcytosis by the polymeric immunoglobulin receptor (pIgR) that is highly expressed on cysts (Olsan et al., 2015). This mechanism can potentially be exploited to target inhibitory antibodies - against IL-13 or other luminal targets - specifically to cysts in PKD which may make effective, long-term therapy possible while avoiding extra-renal effects (Weimbs et al., 2018).

Conclusion

Overall, STAT signaling features a large number of different STAT proteins which are activated by an even larger number of upstream regulators leading to a very broad spectrum of possible downstream effects that, on top of everything else, are also often highly cell-type specific.

Research revealed direct connections between PC1 and STAT signaling, which underlines the significance of STAT signaling in PKD. The general theme is that STAT signaling is generally inactive in healthy adult kidneys but that all components of STAT signaling are generally well expressed. This suggests that the various STAT signaling pathways are generally on standby in the kidney and are meant to quickly respond to changes in circumstances. The main factors that seems to lead to STAT activation are different forms of renal insults leading to injury and necessitating fast immune responses followed by slower injury repair responses. Different renal cell types, especially TECs and immune cells, appear to closely communicate with each other - generally via growth factors and cytokines - to orchestrate activation or downregulation of the various STAT pathways between them. In PKD, many of these processes seem to be disrupted leading to permanent activation of STAT signaling in epithelial and immune cells as well as myofibroblasts. This then appears to lead to a persistent state of a futile repair program that is characterized by epithelial proliferation, fibrosis and a persistent involvement of the immune system. Pharmacological approaches to attempt to disrupt individual STAT signaling pathways may lead to breaking the cycles of cross-activation between renal cells and may be promising for PKD therapy. Since numerous drugs affecting STAT signaling have been, or are being, developed - primarily for cancer therapy - repurposing these drugs for PKD therapy is a timely proposition.

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Highlights

- Most STAT signaling pathways are activated in kidneys in PKD
- STAT signaling is regulated by polycystin-1, the protein affected by mutations in ADPKD
- STAT signaling pathways can be activated in different renal cell types leading to different effects
- Inhibitors of STAT signaling may be promising for PKD therapy

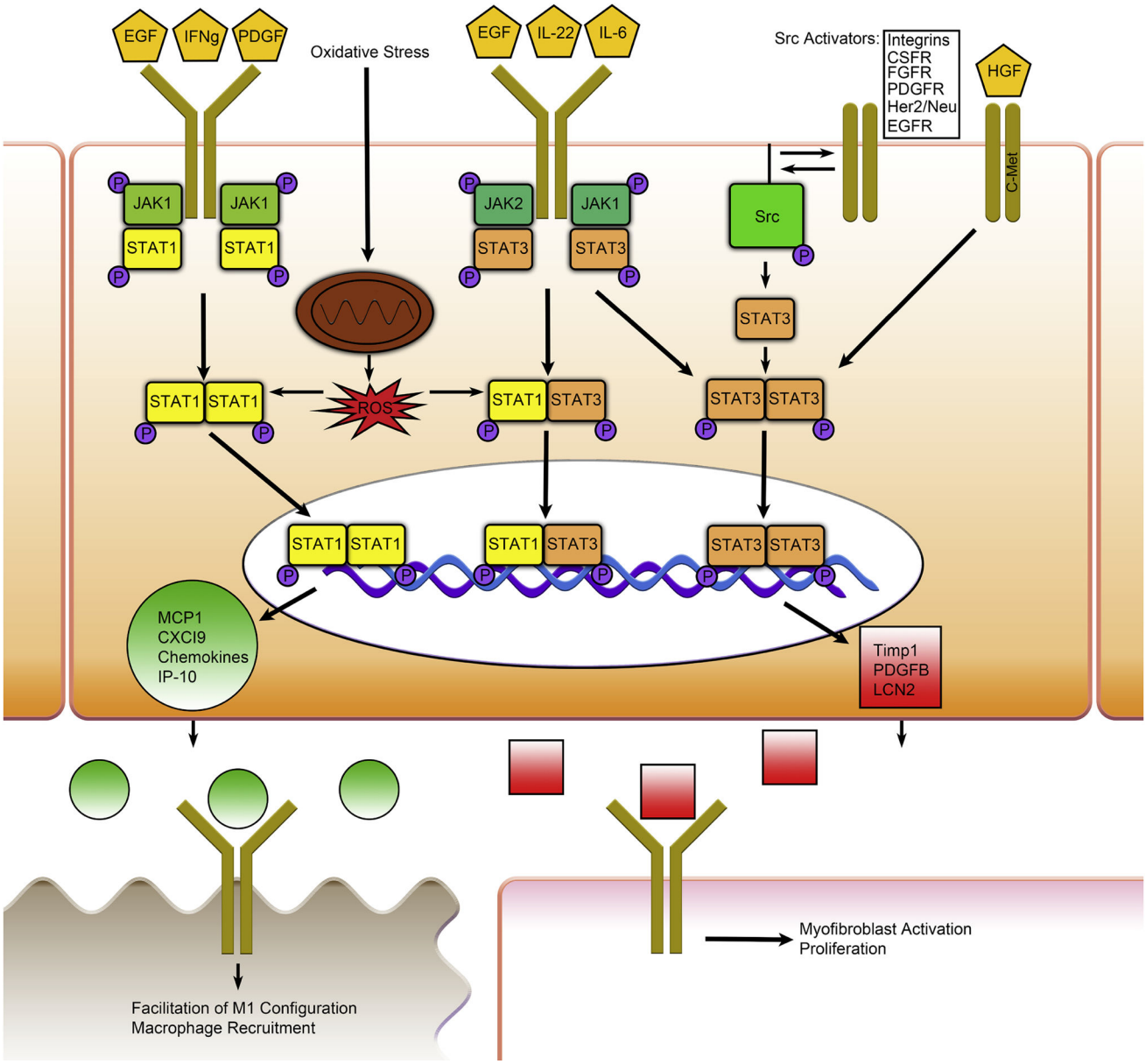

Figure 1. Model of STAT1 and STAT3 signaling in the healthy kidney.

Binding of certain cytokines and growth factors to their receptors leads to activation of JAKs which in turn phosphorylate intracellular receptor tyrosine residues. STAT1 and STAT3 molecules bind to these residues, which leads to their phosphorylation by JAKs. After dissociation from the receptor, phosphorylated STATs dimerize and translocate to the nucleus resulting in modified target gene expression. Beside JAK, the tyrosine kinase receptor c-Met and the non-receptor associated kinase Src are also capable of STAT3 phosphorylation. STAT1 signaling in the kidney was shown to occur in TECs regulating the macrophage phenotype and, thus, inflammation and fibrosis in the kidney. STAT3 signaling exists in renal TECs and myofibroblasts and seems to mediate a cross talk between these cell types, which regulates myofibroblast attraction and activation.

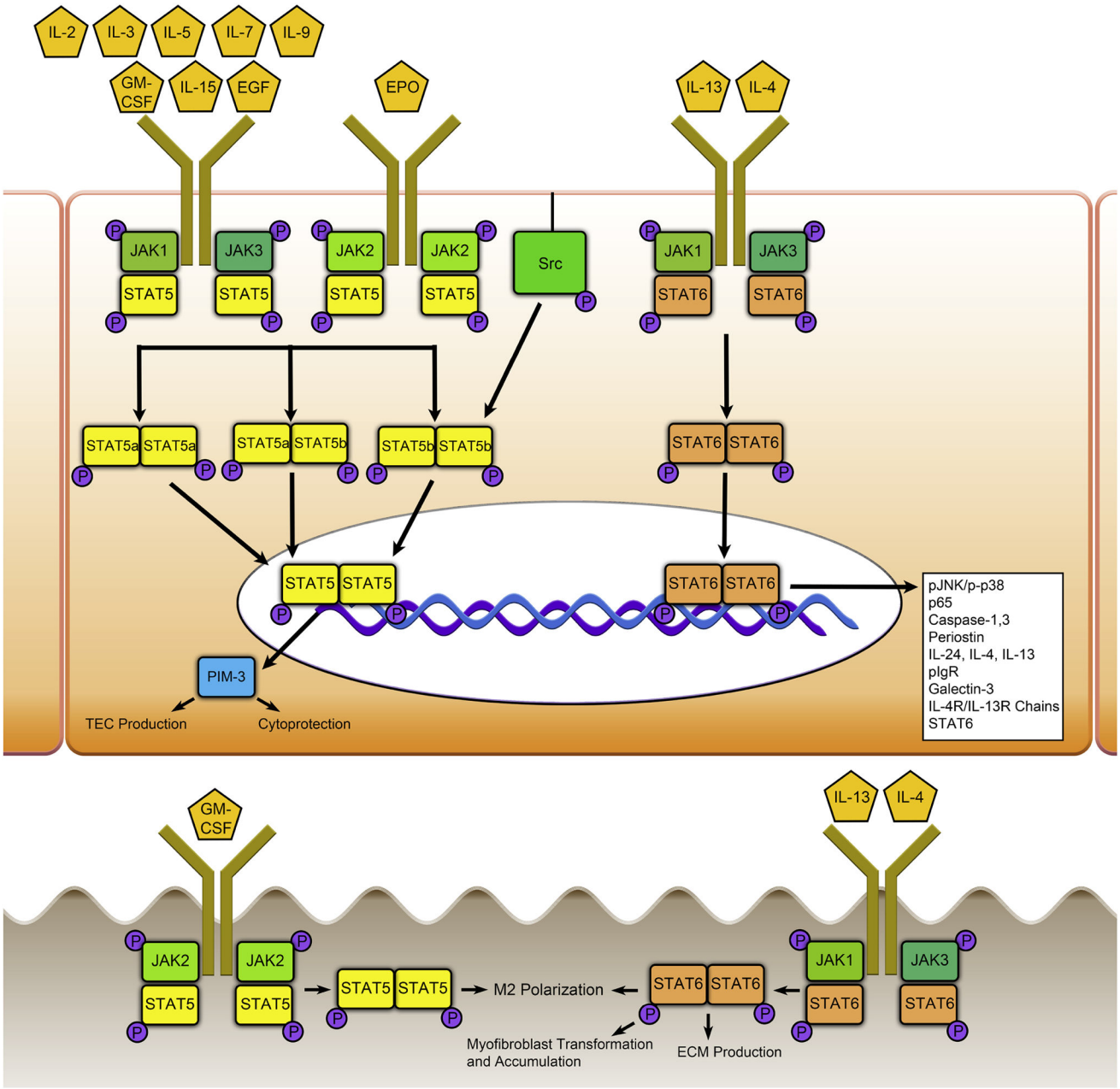

Figure 2. Model of STAT5 and STAT6 signaling in the healthy kidney

Cytokine and growth factor mediated JAK kinase activation can also lead to STAT5 and STAT6 phosphorylation in renal TECs and macrophages. STAT5 and STAT6 dimers translocate to the nucleus and regulate target gene expression. Additionally, the non-receptor associated Src kinase was shown to activate STAT5b. STAT5 signaling seems to mediate inflammation and tissue repair mechanisms and is involved in alternative M2 macrophage polarization upon GM-CSF secretion of damaged renal TECs. STAT6 signaling in the kidney might also be involved in fibrosis and tissue repair mechanisms. Upon IL-4 and IL-13 activation STAT6 signaling was described to primarily drive M2 polarization of

macrophages, myofibroblast transformation and accumulation and contributes to fibrosis by regulating the production of ECM proteins.

Table 1:

STAT functions, activators and interactions

STAT family member	Biological function	Selection of activators	Heterodimerization partners	References
STAT1	Growth arrest and apoptosis, immune response	Type I IFN Type II IFN IL-6,−10,−27,−35 EGF/PDGF/HGF/CSF-1/ angiotensin/growth hormone	STAT2 STAT3 STAT4	(Zhang et al., 2017b) (Ihle, 1996)
STAT2	Antiviral protection	IFNα/IFNβ	STAT1 STAT6	(Perry et al., 2011)
STAT3	Often oncogenic; protects from apoptosis	IL-2,−5,−6,−10,−23,−27 MCSF GCSF	STAT1 STAT5	(Yu et al., 2009)
STAT4	T_H1 differentiation	IL-12,−23,−35	STAT1 STAT3	(Wurster et al., 2000)
STAT5A	Lymphocyte development Mammary cell differentiation	IL-2,−7,−15	STAT3 STAT5b	(Creamer et al., 2010) (Haricharan and Li, 2014)
STAT5B	Regulation of sexual dimorphism in liver	IL-2,−7,−15	STAT3 STAT5a	(Udy et al., 1997)
STAT6	Lymphocyte development; $CD4^+$ T-cell polarization into T_h2 cells; macrophage M2 polarization IgE class switching	Type I IFN IL-3,−4,−13	STAT2	(Wurster et al., 2000) (Takeda et al., 1996) (Shimoda et al., 1996)

Table 2:

Pharmacological approaches to STAT inhibition

Molecule	Effect	Target(s)	Indication (Clinical Trial Phase)	Ref
JAK				
Ruxolitinib	Direct inhibition of JAKs	JAK1, JAK2	Approved for treatment of polycythemiavera and myelofibrosis (MF)	(Verstovsek et al., 2010)
Tofacitinib	Direct inhibition of JAKs	JAK1, JAK3	Treatment of Rheumatoid Arthritis (RA) and ulcerative colitis	(Kremer et al., 2009)
Baricitinib	Direct inhibition of JAKs	JAK1, JAK2	Treatment of RA	(Taylor et al., 2017)
VX-509	Direct inhibition of JAK3	JAK3	Treatment of RA	(Genovese et al., 2016)
Fedratinib	Direct inhibition of JAK2	JAK2	Treatment of MF	(Harrison et al., 2017)
Upadacitinib	Direct inhibition of JAK1	JAK1	Treatment of RA	(Genovese et al., 2018)
STAT3				
Triptolide	Inhibits phosphorylation of JAK2/ STAT3	JAK/STAT3 pathway	Phase 3 trial for HIV, Uncontrolled trial in PKD	(Jing et al., 2018)
AZ505	Inhibits STAT3 phosphorylation	SMYD2	Not Applicable	(Ferguson et al., 2011)
Anti-IL10	Inhibition of macrophages	Macrophages	Not Applicable	(Peda et al., 2016)
Pyrimethamine	STAT3 dimerization	STAT3	Treatment for Toxoplasmosis,	(Takakura et al., 2011)
Curcumin	Decreased STAT3 phosphorylation	Wnt, TNF-a, MAPK, HIF1, notch-1 and mTOR and STAT3	Phase 3 trial planned for CKD Phase 2 Trial for AKI Phase 4 trial planned for PKD	(Leonhard et al., 2011)
Nifuroxazide	Reduced renal macrophage infiltration, TNF-a, IL-18, Decreased STAT3 phosphorylation	Jak2/ STAT3, Tyk2	Treatment of colitis and diarrhea	(Said et al., 2018)
Imatinib	Inhibits STAT3 phosphorylation	Tyr-Kinases	Treatment of Chronic myeologenous leukemia (CML), gastrointestinal stromal tumors (GISTs)	(Zaki et al., 2018)
Crizotinib	Inhibits STAT3 phosphorylation	c-Met	Treatment of non-small cell lung cancers, Phase 2 trials for renal cancers	(Mesarosova et al., 2017)
Stevia/Stevioside	Inhibits STAT3 phosphorylation, Inhibits ERK1/2 phosphorylation	Not known	Several trials for diabetes mellitus (DM) and obesity	(Potočnjak et al., 2017)
Cryptotanshinone	Inhibits STAT3 phosphorylation	SH2 Domain of STAT3	Trial planned for polycystic ovary syndrom	(Chen et al., 2017)
Cinnamaldehyde	Inhibits STAT3 phosphorylation	JAKs	Trials planned for DM and obesity	(Huang et al., 2015)
Paclitaxel	Inhibits nuclear translocation	Tubulin	Treatment of breast, ovarian and lung cancer	(Zhang et al., 2015)
Resveratrol	Inhibits pY-STAT3 and acetyl-STAT3	Sirtuin 1	Several trials for CKD and diabetic nephropathy	(Ni et al., 2014b)

Molecule	Effect	Target(s)	Indication (Clinical Trial Phase)	Ref
MS-275	Inhibits STAT3 and Akt phosphorylation	HDAC1	Phase 1 trial for CML, acute myeloid leukemia (AML), and breast cancer Phase 2 trial for renal cancer	(Tang et al., 2014)
Oligodeoxynucleotidedecoys	Decreased STAT3 translation	STAT3 mRNA	Not Applicable	(Miklossy et al., 2013)
Antisense oligonucleotide	Decreased STAT3 translation	STAT3 mRNA	Not Applicable	(Miklossy et al., 2013)
STAT5				
Pimozide	Decreased STAT5 phosphorylation	Not known	Approved for treatment of Tourette Syndrome	(Nelson et al., 2011)
E804 (Indirubin derivatives)	Decreased STAT5 phosphorylation and DNA binding activity	Most likely Tyr kinases	Not Applicable	(Nam et al., 2012)
Chromone based nicotinyl hydrazine	Weakly inhibit STAT5 phosphorylation	STAT5	Not Applicable	(Müller et al., 2008)
Stafib-2	STAT5b SH2 domain inhibitor	STAT5	Not Applicable	(Elumalai et al., 2017)
AC-3-19	STAT5 SH2 domain inhibitor	STAT5	Not Applicable	(Cumaraswamy et al., 2014)
AC-4-130	STAT5 SH2 domain inhibitor	STAT5	Not Applicable	(Wingelhofer et al., 2018)
STAT6				
Teriflunomide	Inhibits Phosphorylation of STAT6	Various Protein Kinases	Approved for treatment of Multiple Sclerosis	(Bar-Or et al., 2014; Olsan et al., 2011)
AS1517499	Inhibits Phosphorylation of STAT6	STAT6	Not Applicable	(Chiba et al., 2009)
Niflumic acid	Inhibits Phosphorylation of STAT6	JAK2/ STAT6	Commonly used for treatment of Rheumatoid Arthritis	(Nakano et al., 2006)
YM-341619	Inhibits Phosphorylation of STAT6	STAT6	Not Applicable	(Ohga et al., 2008)
PM-43I	STAT5/STAT5 SH2 Domains	STAT5/STAT6	Not Applicable	(Knight et al., 2018)
Tralokinumab	IL-13 neutralizing monoclonal antibody	IL-13	Positive phase 2b study for AD, currently in phase 3 study for AD	Wollenberg et al., 2019
Lebrikizumab	IL-13 neutralizing monoclonal antibody	IL-13	Positive phase 2b results for Atopic Dermatitis	(Corren et al., 2011; Hanania et al., 2015; Noonan et al., 2013; Scheerens et al., 2014; Simpson et al., 2018)