GHetting to know ADPKD proliferative signaling, *STAT*

Ching-Hsien Chen[1] and Robert H. Weiss[1,2,3]

Due to their common pathogenesis and parallel proliferative signaling pathways, the cystic diseases have been recently studied in the context of cancer biology. The present study continues this paradigm by identifying signal transducer and activator of transcription (STAT5) and growth hormone (GH) as potentially modifiable pathways in polycystic kidney disease. GH, which is a potent activator of STAT5, has the additional possibility of being a biomarker, as well as providing a potential mechanism of action of somatostatin analogs in clinical trials.

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The similarity of cystic renal diseases with cancer has become more apparent both from recent investigations and comprehensive reviews of the subject.[1] Concomitant with this relatively new paradigm in polycystic kidney disease (PKD) research, we are witnessing a gradual but inevitable change in the mindset among nephrologists who have finally, and shrewdly, decided to capitalize on the massive corpus of oncology research involving signaling pathways and targeted therapeutics. They are bringing these concepts to their specialty, and such creative thinking revolving around the molecular basis of disease will clearly advance the field of renal therapeutics as it has in cancer. Arguably, the most well-suited renal disease that provides the greatest parallels with cancer is autosomal dominant polycystic kidney disease (ADPKD), because it is now believed to be characterized by a 2-hit model of loss of heterozygosity and consequent proliferation of tubular epithelial cells to form cysts. Those pathways that are arguably most pivotal to oncogenesis—proliferation, (anti-) apoptosis, and metabolic reprogramming—have all now been observed in the setting of experimental cystic disease. In light of these similarities, it has become surprisingly productive to study the cancer signaling pathways as applied to PKD in the hopes of repurposing cancer drugs, even those previously discarded, for PKD. Because all of the currently available targeted therapeutics tested in PKD have not yet shown unqualified success in the clinic, the potential use of cancer therapeutics has considerable untapped promise. An early example of such repurposing came about 10 years ago with a successful demonstration of the use of the cyclin-dependent kinase inhibitor roscovitine in a murine model of PKD.[2]

One of the most fundamental cancer signaling pathways is exemplified by the Janus kinase−signal transducer and activator of transcription (JAK-STAT). The JAK-STATs represent a highly evolutionarily conserved pathway that seems to have evolved to transmit polypeptide signals from the extracellular region directly to the transcriptional machinery,[3] which is obviously a huge advance that promotes survival and reproductive success of the earliest biological systems. Given such a basic system, it makes eminent sense that the JAK-STAT pathway would be involved in such fundamental processes as developmental regulation, homeostasis, and growth control—properties that are clearly relevant to renal physiology. A relatively early finding in this realm was that polycystin-1 affected the cell cycle via the cyclin kinase inhibitor p21,[4] which is also a well-known, cancer-relevant pathway protein that has been subsequently shown to be operative in a variety of PKD models.[5] Further investigation of this pathway showed the critical involvement of one of the JAK-STAT family of transmembrane signal transducers in the observed cyclin-dependent kinase inhibition. Since that initial study, many of the large variety of STATs have been shown to be involved in PKD in some form or another, for example, STAT1 in p21-mediated anti-proliferation,[3] STAT6 in proliferation via the interleukin pathways,[6] and STAT3, which correlates with cyst progression.[7]

The study of Fragiadaki *et al.*[8] (2017) in this issue of the *Kidney International* has significantly furthered this line of investigation by showing the involvement of STAT5 not only in proliferation but in a novel aspect of growth hormone (GH) signaling. Using an RNAi screen, these investigators identified, in a PKD cell line, that several of the STAT transcription factors were responsible for cell proliferation. Based on these data, they used an online analysis tool known as DAVID to identify a cluster of 6 genes that are growth regulatory for further analysis. These included STAT5a, STAT5b, interferon-γ, oncostatin M, and most surprisingly, GH and the GH receptor. In a further set of well-designed experiments, they showed that STAT5 regulated proliferation in PKD cell lines with the expected subcellular localization events, and that the specific STAT5 antagonist, VWR-573108, reversed the effects on proliferation and on the nuclear localization of STAT5 (Figure 1). In light of the background studies described on

[1]*Division of Nephrology, Department of Internal Medicine, University of California, Davis, California;* [2]*Cancer Center, University of California, Davis, California; and* [3]*Medical Service, Sacramento VA Medical Center, Sacramento, California*

Correspondence: *Dr. Robert H. Weiss, Division of Nephrology, Department of Internal Medicine, Genome and Biomedical Sciences Building, Room 6311, 451 Health Sciences Dr., University of California, Davis, CA 95616. E-mail: rhweiss@ucdavis.edu*

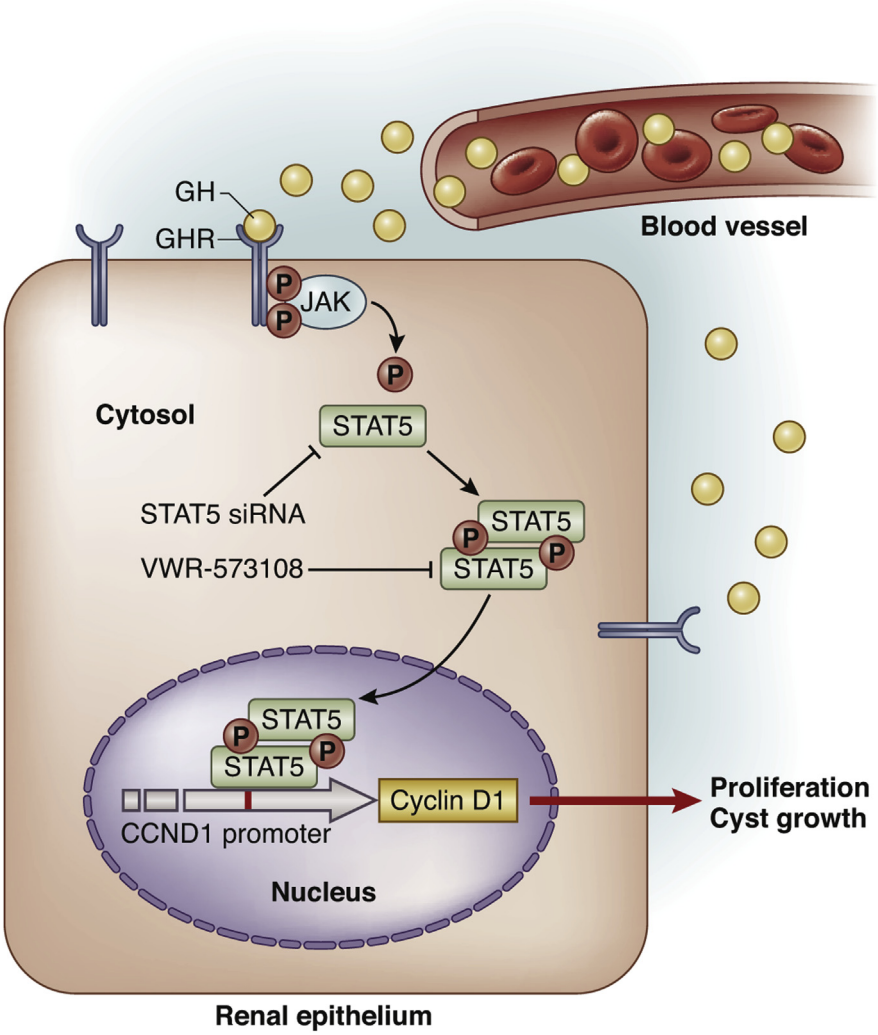

Figure 1 | Growth hormone (GH)-induced activation of the signal transducer and activator of transcription (STAT5)-Cyclin D1 pathway in renal epithelial cells. In response to polycystic kidney disease (PKD1) loss, GH is elevated and interacts with the GH-receptor (GHR). Activated GHR induces tyrosine phosphorylation of Janus kinase (JAK) and STAT5 and results in STAT5 dimerization. After dimerization, STAT5 translocates into the nucleus and binds to the cyclin D1 (CCND1) promoter, leading to an increase in cyclin D1 expression, cell proliferation, and cyst growth. These effects are blocked by STAT5 siRNA and VWR-573108, a STAT5 inhibitor.

the JAK-STAT proteins in PKD, it was not completely surprising that Fragiadaki *et al.* found that STAT5 was similarly involved, but these authors carried the field unexpectedly further when they brought GH into the equation.

The GH story in PKD is quite timely due to the clinical use of the long-acting analog of the GH inhibitor, somatostatin, in clinical trials of PKD.[9] The findings of Fragiadaki *et al.*, that GH mediates proliferation via the STAT5-Cyclin D1 pathway, may well provide a mechanism for the somatostatin paradigm of PKD treatment; in this case, a more surgical strike on this pathway using VWR-573108 (or another STAT5 inhibitor if it becomes available) could increase efficacy in this model and/or minimize adverse effects. Supporting this possibility, Fragiadaki *et al.* further demonstrated that both elevation of serum GH and activation of the GH receptor are noted in a homozygous PKD1(nl/nl) model of ADPKD. If confirmed in other PKD models and human disease, these data would support further investigation of GH antagonism and somastatin analogs in PKD trials. In addition, this study points out that STAT5 inhibition may be an intriguing strategy for targeting GH-driven cyst growth in response to PKD1 loss. A large number of downstream mediators of GH-receptor signaling and various signaling cross-talk pathways would make the specificity of the GH inhibitor treatment difficult, whereas STAT5 is an end effector involved in the GH-induced gene transcription and proliferation. Thus, the superiority of inhibiting the GH-GHR-JAK-STAT5 axis by STAT5 SH2-domain inhibitors for PKD treatment may be more preferable than the use of GH or JAK inhibitors.

In summary, the present study advances the field of PKD research in several areas and will lead to new avenues of exploration for discovery of new targeted therapies in a disease with pitifully few available treatments. Furthermore, the study provides a blueprint for the design of other investigations of renal disease signaling in the continuing quest for targeted therapeutics in a field where few currently exist.

DISCLOSURE
All the authors declared no competing interests.

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M1 macrophage triggered by Mincle leads to a deterioration of acute kidney injury

Tsuyoshi Inoue[1]

In the early stage of acute kidney injury, M1 macrophages are proinflammatory and destructive. In this study, Lv *et al.* reveal that Mincle (macrophage-inducible C-type lectin, Clec4e) is expressed on M1 macrophages in acute kidney injury, and the kidney is protected in a murine model of cisplatin-induced renal injury by inhibiting Mincle expression on macrophages. Mincle expression is regulated by Toll-like receptor 4/nuclear factor κB signaling, and Mincle maintains the inflammatory phenotype through spleen tyrosine kinase signaling, leading to acute kidney injury.

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Acute kidney injury (AKI) contributes to an increased risk of mortality, and incomplete recovery from AKI may lead to chronic kidney disease and end-stage renal disease. Unfortunately, interventional clinical trials in AKI have been unsuccessful so far, and there are no treatment options that enhance kidney repair or few that attenuate progressive kidney disease. Therefore, a better understanding of the pathogenesis of AKI is needed to develop novel therapeutic targets to prevent or treat AKI. The cumulative evidence indicates that infiltration of immune cells in the kidney, particularly macrophages, plays an important role in the initiation and propagation of the kidney injury. However, the roles of infiltrating macrophages in the pathogenesis of acute or chronic renal injury are still incompletely understood.[1] Recently, the anti-inflammatory and reparative roles of macrophages have attracted attention. Macrophages with the M2 phenotype were reported to be predominant in the repair process of kidney disease models including ischemia-reperfusion injury, unilateral ureteral obstruction (UUO) nephropathy, and diphtheria toxin–mediated kidney injury.[1] M2 macrophages suppress inflammation and enhance wound healing. In contrast, M1 macrophages infiltrate kidneys early after ischemia-reperfusion injury and exhibit proinflammatory and destructive properties. Both experimental models in rodents and humans showed that glomerular and interstitial macrophage infiltration were detected in many types of AKI and progressive chronic renal diseases. In human studies, the extent of macrophage infiltration has been shown to correlate with the severity of kidney injury in patients with glomerulonephritis. These data imply that infiltrated macrophages have a pathogenic role in a variety of kidney diseases. The causal role of these proinflammatory macrophages in tissue destruction was demonstrated through studies either depleting macrophages or studies transferring macrophages. Depletion of macrophages by liposomal clodronate at an early stage after injury significantly attenuates kidney injury and preserves kidney function in acute ischemia-reperfusion injury[2] and UUO models. In addition, high expression of inducible nitric oxide synthase (a marker of M1 macrophage), instead of arginase-1 (a marker of M2 macrophage), was detected in F4/80+ macrophages 24 hours after the acute injury. This suggests that proinflammatory M1 macrophages predominate in the early stage of kidney injury.[3]

In this issue of *Kidney International*, Lv and colleagues (2017) uncovered a new and previously unrecognized role of macrophage-inducible C-type lectin (Mincle) expressed on macrophages in the pathogenesis of AKI.[4] Mincle is a transmembrane pattern recognition receptor involving the innate immunity. Mincle is expressed mainly in macrophages (monocytes, neutrophils, and dendritic cells, and some subsets of B cells also express Mincle) and is induced after exposure to various stimuli and stresses. Mincle recognizes necrotic cells via spliceosome-associated protein130 (SAP-130, an endogenous ligand of Mincle receptor).

[1]*Division of Nephrology and Center for Immunity, Inflammation, and Regenerative Medicine, University of Virginia, Charlottesville, Virginia, USA*

Correspondence: *Tsuyoshi Inoue, Division of Nephrology and Center for Immunity, Inflammation, and Regenerative Medicine, University of Virginia, Charlottesville, Virginia 22908-0746 USA. E-mail: Ti5s@virginia.edu*