GSK3β Plays Dirty in Acute Kidney Injury

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J Am Soc Nephrol 21, 2010
doi: 10.1681/ASN.2009121214

The long-standing notion that the course of acute kidney injury (AKI) is unalterable and portends poor outcomes for patients seems poised to change.1 Several new diagnostic biomarkers undergoing validation for clinical implementation2–5 hold promise for detection of AKI far earlier than afforded by changes in serum creatinine.6 Consequently, one recognized barrier to successful interventional trials for AKI—early patient identification to capture a narrow therapeutic window7,8—may soon fall. These exciting developments resurrect an old question in drug discovery for AKI: Should therapeutic strategies for AKI target one critical step in pathogenesis, or is a shotgun approach aimed at multiple targets preferable?9 Because the latter carries the potential for multiple off-target effects, perhaps the ideal target would be a single factor that stands at the heart of multiple pathogenic steps.

The preclinical study by Wang et al.10 in this issue of JASN provides new insight into such a target. Building on the seminal works by Heidenreich and colleagues,11 Wang et al. show that glycogen synthase kinase 3 beta (GSK3β) promotes apoptosis12 of ATP-depleted renal tubular epithelium in vitro and ischemic renal tubular epithelium in vivo by phosphorylating and activating Bax, a proapoptotic member of the BCL2 family. Preischemic inhibition of GSK3β in the kidneys of rats with a single dose of the small molecule thiadiazolidinone 4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione (TDZD-8)13 significantly limits apoptotic damage to renal tubules, ameliorating but not entirely preventing AKI. These findings identify GSK3β as the latest therapeutic target to suppress the death of renal epithelial cells in AKI, adding to a growing list that already includes several caspases, p53, poly ADP-ribose polymerase, and CDK2.7,14

Although intriguing, Wang’s catchy descriptor for GSK3β as a “molecular switch” governing apoptosis likely understates the collective advantage of therapeutically targeting GSK3β in AKI.13,15 Consider first a few key molecular events that also occur from modulating GSK3β within the renal epithelial compartment. Previous studies showed that renal ischemia activates Wnt signaling, thereby inhibiting GSK3β and stabilizing β-catenin, to promote renal epithelial proliferation and tubular repair.16 Indeed, challenge of embryonic kidney explants with small molecule inhibitors of GSK3β is sufficient alone to induce nephrogenesis,17 a process that partially recapitulates tissue regeneration in AKI. Moreover, whereas the identity of renal epithelial stem cells within specific nephron segments that may contribute to tubular repair in AKI continues to be debated,18 a role for pharmacologic modulation of GSK3β in maintaining such stem cell niches is not.19 Collectively, these additional effects of GSK3β inhibition may significantly contribute to resolution of AKI apart from targeting GSK3β to limit apoptosis.

Outside the renal epithelial compartment, pharmacologic inhibition of GSK3β has been proposed to play an equal if not greater role in ameliorating AKI. Predating the study by Wang et al.,10 extensive preclinical testing of small molecule GSK3β inhibitors, including TDZD-8, by Thiemermann and colleagues20 demonstrated their potency to suppress the inflammatory contribution to AKI in several model systems. From the standpoint of detrimental innate immune responses, this reflects the direct control of NF-κB activation by GSK3β.13,15,20

Perhaps more intriguing is the recent recognition of a central GSK3β axis controlling regulatory adaptive immunity. By fundamentally altering pattern recognition signaling, pharmacologic inhibition of GSK3β induces regulatory responses by dendritic cells, inverting the proinflammatory high IL-12, low IL-10 cytokine secretion ratios.21 The resultant cytokine milieu favors the development of regulatory T lymphocytes (Tregs) and is further reinforced by modulating GSK3β within the T lymphocyte itself; inhibition of GSK3β stabilizes β-catenin to enhance the survival of Tregs while inducing anergy of proinflammatory effector T lymphocytes.22,23 Given that Tregs ameliorate AKI,24 these innate and adaptive immune responses during modulation of GSK3β represent additional potential mechanisms conferring efficacy to GSK3β inhibition.

The studies outlined herein demonstrate that GSK3β plays dirty in AKI, promoting inflammatory responses as well as tubular cell apoptosis, while potentially inhibiting proliferative repair responses. These studies also stand as a reminder that experimental drug development is ripe with detection bias depending on the therapeutic questions being asked and the focused assays used to answer these questions.
Indeed, until that time when type 1 biomarkers to detect modulation of GSK3β directly within its many cellular and signaling contexts in vivo become available, it will be difficult and prone to error to ascribe drug efficacy from targeting GSK3β in AKI to one single molecular outcome. Rather, it may be the ability of GSK3β to play dirty in AKI that will ultimately define this kinase as a highly desirable drug target.

ACKNOWLEDGMENTS

P.J.N. is supported by National Institutes of Health grants DK83375 and DK83912 and is a member of the Kidney Research Institute of the University of Washington School of Medicine. L.C. is supported by National Institutes of Health grants DK83912 and is a member of the Kidney Research Institute of the University of Washington School of Medicine.

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