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EDITORIAL COMMENT

The Kidney, Bone Marrow, and Heart Connection in Acute Kidney Injury

Role of Galecin-3*

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In this issue of *JACC: Basic to Translational Science*, Prud'homme et al. (1) report that experimental acute kidney injury (AKI) in mice induces remote cardiac injury through the upregulation of a novel mediator galectin-3 (Gal-3). The major findings are that acute (up to 72 h) ischemia/reperfusion-induced AKI in mice stimulated an increase in Gal-3 expression in tubular inflammatory cells in the kidney and in cardiac tissues, with an increase in circulating levels of Gal-3. Along this line, ischemia/reperfusion also stimulated macrophage infiltration ($CD68^+$ cells) and an increase in plasma proinflammatory cytokines. With Gal-3 disruption (Gal-3 knockout [KO]), ischemia/reperfusion in KO mice abrogated the inflammatory response supported by decreases in cardiac $CD68^+$ cells and cytokines levels. Long-term (1-month) ischemia/reperfusion upregulated Gal-3 expression and induced cardiac injury and dysfunction with myocardial inflammation, fibrosis, decrease of fractional shortening, and an increase of left ventricular diastolic diameter. Gal-3 blockade with Gal-3 KO or pharmaceutical inhibition by modified citrus pectin significantly attenuated these abnormal myocardial events. The modified citrus pectin effect was confirmed in a second long-term (up to 2 months) model of kidney injury induced by unilateral ureteral obstruction, in which the obstruction increased Gal-3, inflammation, and fibrosis, and reduced fractional shortening. This second model was a rigorous test of the hypothesis of Prudhomme et al. (1) that the kidney communicates with the heart via Gal-3.

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From a mechanistic perspective, an intriguing observation made by the investigators using the ischemia/reperfusion model together with Gal-3 KO mice bone marrow transplant revealed that Gal-3 originated from bone marrow mediated the pathophysiologic responses such as inflammation and fibrosis in the 1-month study. Additionally, in a highly translational study, the investigators performed a Gal-3 biomarker study in human AKI. Plasma Gal-3 at discharge from the hospital in a cohort of 645 critically ill patients with AKI showed a stepwise elevation, with severity of AKI from AKI-free, subclinical, stage 1, stage 2, and stage 3, supporting its role as an AKI biomarker.

AKI is characterized by an abrupt decline of renal function, with a decrease of glomerular filtration rate or urine output. It has a high prevalence rate especially in critically ill patients and is also a powerful risk factor for heart failure incidence. AKI remains a challenging clinical problem, and to date no therapies have been approved by the Food and Drug Administration for AKI patients. Thus, innovative AKI therapeutics represent an unmet clinical need. Here in this elegantly designed study, Prud'homme et al. (1) demonstrated that Gal-3 can serve as both a drug target for AKI-induced cardiac dysfunction and a biomarker for AKI.

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There is no doubt that understanding the pathophysiology of AKI, discovering effective therapeutic targets, and identifying novel sensitive biomarkers will provide tremendous benefits for AKI therapeutics, thus improving the outcomes of patients with AKI. Indeed, recently published preclinical studies in large-animal AKI models have reported the potential of multiple promising innovative drugs, which includes targeting the particulate guanylyl cyclase A receptor pathway (2), adenosine A2 receptor signaling (3), and vascular endothelial growth factor (4), as well as suppressing CD47 (5). Furthermore, according to the Clinical Trials Register, investigational drugs targeting soluble guanylyl cyclase, particulate guanylyl cyclase A receptor, vitamin D receptor, CD28 receptor, p53 pathway, hepatocyte growth factor, and *N*-acetylcysteine are under way, with most of the studies centered on AKI prevention and treatment in patients undergoing cardiac surgery. In regard to biomarker studies, newly discovered noninvasive urinary biomarkers include c-type natriuretic peptide (2), liver fatty acid binding protein (6), and matrix metalloprotease 7 (7), which have demonstrated powerful predictive value in experimental or human studies.

The interconnecting pathophysiology and close interactions between the heart and kidney inevitably generate the challenge of cotargeting both organs for AKI. Previously, our laboratory reported that renal insufficiency induced myocardial apoptosis, fibrosis, and diastolic dysfunction (8). Similarly, as advanced by Prud'homme et al. (1), AKI, through circulating hormones or mediators, induces cardiac injury and dysfunction. The current Gal-3 inhibition studies, however, did not demonstrate noticeable improvement on renal function (creatinine and blood urea nitrogen levels) or renal hypertrophy, although significant improvements were observed in cardiac parameters. Optimizing the benefits of targeting both organs such as therapies activating particulate guanylyl cyclase A receptor and soluble guanylyl cyclase receptors can exert beneficial effects in both organs, as demonstrated by glomerular filtration rate elevation, vasorelaxation, and cardiac and renal antiremodeling (2,9). Further investigations to discover novel therapeutic targets or optimize the current drug targets are critical for the success of this cotargeting strategy.

This newly published study has several strengths. First, it elucidates the connection between AKI and remote cardiac damage, which is mediated by bone marrow Gal-3 upregulation. This new mechanism helps to understand the pathophysiology of the cardiorenal syndrome in such a setting and provides a promising new route of treating cardiorenal syndrome in AKI. Second, this study includes both acute and chronic intervention studies. Specifically, the acute study served to investigate the acute renal effects and the chronic study explored the long-term pharmaceutical feasibility of Gal-3 blockade. Furthermore, the study includes both mechanistic and biomarker studies, which conclude that Gal-3 not only is a mediator for AKI-induced cardiac injury but also may be a biomarker for AKI severity.

It is unclear what is the deleterious signal transmitted to the bone marrow from the injured kidney. Therefore, it will be of interest to investigate the hormonal or neural signals generated by the kidney and the causal relationship between the unknown signals and bone marrow Gal-3 formation. Furthermore, the authors did not mention the effect of modified citrus pectin or Gal-3 KO on cardiovascular hemodynamics such as blood pressure in the mice. This key information may further contribute to the cardiac improvement observed in the current study and should be studied. Additionally, future studies to investigate renin-angiotensin-aldosterone system modulation by Gal-3 suppression will be important because studies have previously documented the critical role of the system in inflammation and cardiac injury, with AKI initiation (2,10).

Gal-3 inhibition exerted potent cardiac protective effects in 2 kidney injury models but did not improve renal function or reduce renal structural abnormalities, which consequently may limit its use for AKI prevention or treatment itself. Thus, optimizing the dose, potency, and organ selectivity of a Gal-3 inhibitor to improve renal function such as increasing glomerular filtration rate or urine output is critical for the future development of a Gal-3 blockade strategy for AKI management. Additionally, from a therapeutic perspective, the authors may want to consider investigating disease models that focus on myocardial therapeutics with the use of Gal-3 inhibition. Future directions also include validating the therapeutic potential of Gal-3 inhibition in a large-animal model such as canines or porcines, which constitute a higher functional similarity and genetic homogeneity with humans.

Biomarker studies measuring plasma Gal-3 at admission (in addition to discharge) for critically ill patients may also help to identify patients who will later develop AKI. Additionally, given the distribution of Gal-3 in renal tubules and macrophages, it will be interesting to evaluate urinary Gal-3 levels in AKI patients. Effective preventive strategies and interventions can then be used to treat these patients at

an early stage of AKI. Considering the critical role of Gal-3 in cardiac injury, it is thus highly relevant to assess its predictive value for cardiovascular adverse outcomes in AKI patients.

Congratulations to the authors for such a well-designed, solid study and the novel findings of Gal-3 as a pathophysiologic mediator, a therapeutic target, and a biomarker for cardiorenal syndrome and AKI, and of the key role of bone marrow. These results highlight the essential role of Gal-3 in stimulating cardiac inflammation and fibrosis as a result of AKI. Indeed, this insult to the heart is independent of the type of renal injury. A Gal-3 suppression strategy may emerge as an effective, next-generation therapy for AKI-induced cardiac injury and related cardiorenal syndrome. Still, a need that remains is protecting the kidney and preserving renal function in AKI, in which a novel kidney-bone marrow-heart connection plays a key role.

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