Kidney surveillance in the spotlight: contrast-induced acute kidney injury illuminated

Simon J. Atkinson
Department of Biology, Indiana University – Purdue University Indianapolis, Indianapolis, Indiana, USA.

Acute kidney injury
Acute kidney injury (AKI) is an abrupt decline in kidney function that occurs over a few hours or a few days, is common in people who are already hospitalized, and is associated with significant morbidity and mortality. Multiple factors predispose to development of AKI, and treatment options, other than supportive interventions, are few (1). In addition to being associated with ischemic injury and sepsis, AKI can also result from the toxicity of therapeutic agents, such as aminoglycoside antibiotics or cisplatin chemotherapy. New work from Lau et al. in this issue of the JCI (2) examines the mechanism of contrast-induced AKI (CI-AKI), a form of AKI observed in patients receiving intravascular iodinated contrast media for diagnostic imaging studies. While the risk associated with the use of contrast media is a matter of current debate (3, 4), there is clear evidence for injury resulting from contrast administration in both animal models and humans, especially in patients with risk factors such as underlying chronic kidney disease. The mechanism described by Lau and colleagues is notable for the involvement of multiple cell types, including tubular epithelial cells and both resident and circulating leukocytes, all of which are required for the development of CI-AKI. This is consistent with emerging multifactorial paradigms for the development of AKI from various causes (5) and suggests both opportunities and challenges for the development of rationally designed therapeutic interventions.

Animal models to study pathophysiology of CI-AKI
A major challenge in studies of AKI has been the applicability of animal models of AKI to what is observed in patients (6). Lau et al. use a mouse model of contrast agent administered to volume-depleted animals, chosen since volume depletion has been well documented as a contributing factor to the development of CI-AKI (7). This is clearly not a perfect model, since it (or any animal model, for that matter) cannot include all the complex and variable comorbidities, such as underlying cardiovascular disease, that are inevitable in patients referred for imaging studies. Nevertheless, there is some reassurance to be drawn from their inclusion of data from a prospective study of a small cohort of patients undergoing coronary angiography that are consistent with the mechanisms shown to be active in the mouse experiments.

A variety of explanations have been invoked to account for the pathophysiology of CI-AKI, with proposed mechanisms involving physiological changes such as medullary ischemia, high levels of reactive oxygen species, and toxicity of contrast media when taken up by tubular epithelial cells (8). Although related factors are also implicated in AKI from other causes, the broad AKI field has also embraced the idea that inflammatory processes induced by inappropriately exuberant activation of immune responses are major contributors, and that both resident and infiltrating leukocytes are involved (5). Lau et al. show that this paradigm extends to CI-AKI and, in so doing, show that immune activation happens in distinct compartments and depends on uptake of contrast both by tubular epithelial cells and by resident and infiltrating phagocytes.

Mechanism of contrast-induced immune activation
Their first challenge was to identify a plausible molecular mechanism by which contrast might cause immune activation. Inflammasomes are multisubunit complexes that are now recognized to be important players in both infection and the pathological inflammation that characterizes diabetes, cardiovascular disease, cancer, and a number of kidney diseases. Inflammasomes induce inflammatory responses or cell death by bringing together activator molecules capable of sensing a variety of danger signals such as pathogens that have invaded a cell, or danger-associated molecular patterns (DAMPs) released from dead or dying cells, together with effector proteases of the caspase family (9). One such inflammasome activator, Nod-like receptor pyrin containing 3 (Nlrp3), responds to a variety of stimuli, including ATP, alterations in

Conflict of interest: SJA is a coinventor on patent applications related to the use of hydrodynamic fluid delivery for treatment of kidney injury.

intracellular potassium, and particulate matter, and has previously been shown to be an immune activator in kidney diseases (see, for example, ref. 10). Among the downstream effects induced by Nlrp3 inflammasome is caspase-1–dependent activation of IL-1β via the so-called canonical pathway; noncanonical pathways activate various forms of cell death, including apoptosis. Lau et al. showed that this is also the case in their mouse model: volume-depleted Nlrp3−/− mice were protected against the injury induced by contrast in their Nlrp3+/+ counterparts. But in what cells does Nlrp3 inflammasome activation trigger the initiation of the injury process? Although contrast media have been shown to have direct toxic effects on tubular epithelial cells, and the Nlrp3 inflammasome is able to induce apoptosis via a noncanonical pathway, Nlrp3-dependent apoptosis alone did not account for the cytotoxic effects of contrast media seen in cell culture, and CI-AKI did not result from Nlrp3-dependent mechanisms intrinsic to the epithelial cells alone. However, contrast agent strongly activated the Nlrp3 inflammasome in leukocytes, producing IL-1β activation.

**Lessons from the study**

There are several noteworthy outcomes of this study. First, there are three essential steps in the onset of CI-AKI: activation of the Nlrp3 inflammasome in the kidney’s resident leukocytes, tubular accumulation and reabsorption of contrast, and, finally, recruitment of infiltrating leukocytes and activation of their Nlrp3-dependent canonical signaling. This suggests that there has been some selection against inappropriate activation of these inflammatory mechanisms. Another important outcome is the clear mechanistic explanation for the contribution of volume status to the likelihood of AKI in patients receiving contrast. Volume depletion is necessary for the tubular accumulation and reabsorption, since it allows activation of infiltrating leukocytes, and is therefore necessary for progression to CI-AKI. A
Caveat is that this apparently finely regulated system may well behave differently in patients with the comorbidities that are common in those who are candidates for imaging studies, particularly when these comorbid conditions involve the development of a sterile inflammatory disease state. This may compromise the effectiveness of treatment interventions such as blocking contrast uptake by tubular epithelial cells using dipeptidase-1 inhibitors, as employed by Lau et al. Finally, this study shows that the underlying mechanisms of CI-AKI revolve around dysregulated inflammatory responses in the kidney and thus are consistent with the prevailing thinking on other forms of AKI, perhaps suggesting that there are prospects for new therapeutic approaches that will be effective in AKI broadly.

Address correspondence to: Simon J. Atkinson, 755 W. Michigan Street, UL-1140, Indianapolis Indiana 46202, USA. Phone: 317.274.1020; Email: satkinso@iupui.edu.