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Editorial

Experimental evidence that preexisting chronic kidney disease is a risk factor for acute kidney injury



Acute kidney injury (AKI) is defined by a rapid decline in glomerular filtration rate. AKI is a worldwide health problem; it has a high mortality rate and can progress toward chronic kidney disease (CKD). Rates of mortality, morbidity, and hospitalization following AKI, which is induced by various medical complications, are higher in patients with CKD [1,2]. CKD is reported in approximately 30% of AKI patients in intensive care units [2]. Accumulating epidemiological evidence has demonstrated that CKD is a risk factor for the development of AKI and that the prevalence of CKD is increasing worldwide [1,2]. However, the role and underlying mechanisms of CKD in the development of AKI remain unclear owing to the limitation of clinical studies and the lack of useful animal models. Furthermore, researchers have not focused on defining the underlying mechanisms of CKD in the development of AKI, most likely because they believe it is biologically plausible that preinjured organs are more vulnerable to further injury [1].

AKI rarely happens as an isolated event, but generally occurs in various clinical situations, including intestinal, hepatic, and cardiac surgery, exposure to radio-contrast, and sepsis. One of the typical characteristics of AKI is damage to tubular epithelial cells. Chronic inflammation is frequently noted in patients with CKD. Growing bodies of evidence indicate that the inflammatory response in AKI contributes to tubular epithelial cell injury through various cellular and molecular events: production of adhesion molecules by injured endothelium leading to leukocyte infiltration, production of inflammatory cytokines and chemokines leading to tubular epithelial cell death and enhancement of inflammatory responses, and production of hemodynamic regulators inducing an alteration in renal blood flow [3,4]. A preexisting injury produces two opposing consequences for subsequent injury, one beneficial and the other harmful. A preexisting injury either increases or reduces the vulnerability of the organ to subsequent injury, and this is the case even for remote organs. These effects are associated with a number of systemic and local factors (e.g., cytokines, chemokines, and hemodynamic regulators) that can influence the functions and microenvironments of the organs. Therefore, it is presumed that preexisting mild inflammation makes kidney epithelial cells more vulnerable to subsequent injury.

In the current issue of *Kidney Research and Clinical Practice*, Skott and colleagues [5] investigated the response of organs (kidney, liver, and lung) after intestinal ischemia/reperfusion (I-IR)-induced AKI in rats with or without CKD. To mimic AKI in patients with CKD, the authors established a two-stage rodent model. This model involved a 5/6 nephrectomy-induced CKD followed by an I-IR-induced AKI. In this study, Skott et al [5] delineated CKD based on an increased serum creatinine concentration at the beginning of I-IR, as serum creatinine concentration is generally used as a marker of preexisting CKD. The authors found that the serum creatinine levels after I-IR were higher in the 5/6 nephrectomized rats than in the nonnephrectomized rats. This finding is consistent with previous reports by that group, which showed that preexisting CKD induced by 5/6 nephrectomy worsens the outcome of AKI induced by I-IR [6]; this supports the notion that CKD is a risk factor for AKI.

Patients suffering from CKD present notable inflammatory features, such as higher levels of proinflammatory cytokines and fibrotic lesions in the kidney and plasma in comparison to healthy individuals [4]. Skott et al [5] observed higher levels of cytokines in the kidneys of 5/6 nephrectomized rats prior to I-IR than in nonnephrectomized rats. After I-IR, in the kidneys of 5/6 nephrectomized rats (but not in their livers or lungs), they observed higher levels of interleukin (IL)-1 β and RANTES (but not IL-10 or monocyte chemoattractant protein-1) compared to nonnephrectomized rats [5]. These results suggest that the local inflammatory response in CKD kidneys differs from that in healthy kidneys. In addition, they found that α -melanocyte-stimulating hormone (a neuropeptide with broad anti-inflammatory properties) treatment did not prevent I-IR-induced increases of serum creatinine or cytokine production in the kidney [5]. This is in contrast to previous studies, which demonstrated that α -melanocyte-stimulating hormone prevented AKI induced by kidney injury as well as AKI induced secondarily by sepsis or endotoxins [1,5,7]. As discussed by Skott et al [5], the difference between their results and those of other researchers [6] may be associated with differences in their experimental settings. However, this study raised questions about the role of the preexisting local inflammatory response in the enhanced vulnerability of CKD kidneys to subsequent AKI-inducing injury.

In conclusion, the work of Skott et al [5] has taken an important step toward understanding the relationship between CKD and AKI. However, the mechanisms underlying the influence of preexisting CKD on AKI remain unclear. This may be attributable to the variety of definitions for CKD, the complexity of CKD progression, which makes it difficult to compare results between clinical studies, and the dearth of experimental models for CKD. To better understand the role of CKD as a risk factor for AKI and the underlying mechanisms of AKI development in patients with CKD, we must develop a better model to overcome the differences between clinics and experiments.

Conflicts of interest

The author has no conflicts of interest for this manuscript.

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