Immune Modulation of Acute Kidney Injury

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Acute kidney injury (AKI), inclusive of clinical terms such as acute renal failure, acute tubular necrosis, and delayed graft function, is being defined as functional or structural abnormalities or markers of kidney damage, including abnormalities in blood, urine, or tissue tests or imaging studies present for \(<3\) months (Acute Kidney Injury Network group proposed consensus definition; personal communication, Mehta R., University of California San Diego, January 16, 2006). AKI occurs in 5 to 10% of patients in tertiary care hospitals and in virtually all patients early after kidney transplantation (1). The leading cause of AKI is ischemia reperfusion injury (IRI), while nephrotoxins and obstruction are other common etiologies. AKI in the native kidney is associated with high mortality rates, while AKI in transplants is associated with increased frequency of rejection and decreased short-term and long-term allograft function (2). The lack of specific therapies for AKI has led to intense investigation of the pathophysiology with the promise that targeted therapies will emerge. The role of innate immunity in acute tissue injury is well established, with engagement of complement, cytokines, and neutrophils. However, studies examining blockade of neutrophils in experimental AKI, unlike in acute injury to heart or gut, led to mixed results, whereas blockade of leukocyte adhesion molecules in experimental AKI models, supposedly targeting neutrophils, were usually highly protective (reviewed in 3). This seeming inconsistency led to the consideration that leukocyte adhesion molecule blockade was working through nonneutrophil leukocytes that expressed these receptors, like lymphocytes and macrophages. Although unexpected according to traditional immune models, lymphocytes, particularly CD4 T cells, have been found to directly mediate AKI as well as IRI injury to liver, lung, and intestine (4–8). Lymphocytes have recently been implicated in the pathogenesis of cardiac ischemia and stroke (9,10). The recognition of this important finding was delayed by limited data on early lymphocyte infiltration soon after kidney injury, plus absence of a conceptual model to explain how lymphocytes could be involved in acute, alloantigen-independent, tissue injury.

However, studies performed \(>30\) yr ago on human AKI biopsies demonstrated mononuclear leukocytes rather than neutrophils (11). Subsequent studies in humans have shown that these mononuclear leukocytes include CD3 cells in the vasa recta (12). While pursuing the identify of pathogenic lymphocytes in experimental kidney IRI in mice, a surprise finding was that not only were IFN\(\gamma\) producing T cells injurious, but lymphocytes producing Th2 cytokines, including IL-4, were protective (13). A complex model began to emerge where lymphocytes could not only be deleterious, but also have some protective properties in kidney IRI—now more consistent with classic immunologic models of balancing roles for lymphocytes in disease. Similar finding of both deleterious and potentially protective lymphocytes were found in a model of liver IRI (14).

Thus, a model of a modulatory role of the lymphocyte in IRI has emerged, rather than a purely pathogenic one.

In the context of this work, Fiorina and colleagues at Harvard have studied the role of the CXC chemokine receptor 3 (CXCR3) in kidney IRI in mice (15). CXCR3 is mainly expressed on activated Th1 T cells and mediates recruitment of T cells to sites of inflammation, adhesion and activation. In a unilateral clamp model of kidney IRI, an early increase in the CXCR3 ligands IP-10/CXCL10 and MIG/CXCL9 in posts ischemic tissue was observed using real-time PCR, but little expression of another ligand-ITAC. CXCR3 expression was observed at 6 h of clamping, but not later, demonstrating the importance of studying very early times after ischemia reperfusion to kidney. A marked attenuation of kidney dysfunction, tubular injury, and mortality was observed in the CXCR3-deficient mouse compared with age-, sex-, and strain-matched controls. However, actual littermate controls were not used and controls derived in different environments could have other factors that alter response to injury. Given that CXCR3 could be mediating AKI through nonlymphocyte cells, an important mechanistic experiment was performed: Adoptively transferring purified CD3 cells into CXCR3-deficient mice before induction of IRI, which restored the expression of kidney injury and mortality. Thus, CXCR3 was indeed mediating AKI through T cells. To evaluate whether CXCR3 deficiency was protective via polarizing lymphocytes toward a “protective” Th2 phenotype, kidney infiltrating CD4 cells were extracted, and Th2 producing anti-inflammatory IL-4 and IL-10 were enhanced in CXCR3-deficient mice. Furthermore, enhanced protective genes superoxide dismutase and heme oxygenase, additional candidate mediators of the protected phenotype, were found in CXCR3−/− mice. The important role for CXCR3 in kidney IRI is consistent with its recently described role in experimental lower limb IRI (16).

The study by Fiorina et al. provides strong additional data supporting the role for immune cells as modulators of AKI;
more importantly, the study identifies a viable target, CXCR3 and its ligands, for future translational studies in humans. This work also highlights the importance of examining very early time points after IRI, as most groups have looked later on after IRI, and thus likely missed important, early, pathophysiologic processes. A related study in this same issue of JASN expands the role of lymphocytes in AKI by demonstrating that cisplatin-induced nephrotoxicity is, in part, lymphocyte-mediated (17). An unexpected early, not late, trafficking of CD3 cells into kidney was seen after cisplatin, a “hit and run” phenomenon. The decreased TNF production observed in the T cell–deficient mice with associated protection from cisplatin nephrotoxicity is also consistent with the reported role for TNF as a mediator of cisplatin injury (18). Lymphocytes have also recently been demonstrated to mediate sepsis-induced AKI (19).

How can this information benefit our patients? One of the exciting ramifications of identifying a role for immune cells in AKI is that there is already a large armamentarium in humans of effective agents targeting lymphocytes for more classic immunologic diseases. Given that small numbers of lymphocytes are sufficient to modulate full expression of AKI, it is unlikely based on preclinical studies that peripheral lymphocyte depletion with a single monoclonal antibody will be sufficient to significantly attenuate AKI in humans (20,21). However, combinations of antibodies have been shown both in vivo in murine IRI (20) and in a small study in human transplant IRI to decrease the full extent of kidney injury after ischemia (22). This polyclonal approach needs to be evaluated more rigorously in humans. Promising data from T cell co-stimulatory blockade in rodents lays the groundwork for targeting human IRI with this agent in combating their cancer. Recently, more conventional approaches to IRI have intersected with the lymphocyte story with the surprise finding that the adenosine 2A receptor agonist, which is renoprotective during kidney IRI, is working primarily through CD4 cells (26). Given the modulatory role of lymphocytes in experimental AKI, and the possible role of lymphocytes after AKI in wound repair and fibrosis (27), it will be important to carefully dampen deleterious rather than protective lymphocyte responses.

References
depletion is not sufficient to prevent ischemic acute renal failure. *Transplantation* 5: 269–287, 2005


See related articles “Role of CXC Chemokine Receptor 3 Pathway in Renal Ischemic Injury,” on pages 716–723, and “A Pathophysiologic Role for T Lymphocytes in Murine Acute Cisplatin Nephrotoxicity,” on pages 765–744.