The promise of immune cell therapy for acute kidney injury

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Acute kidney injury (AKI) often results from ischemia reperfusion, sepsis, or exposure to nephrotoxins and is associated with a high rate of mortality and morbidity. Advances in understanding the pathophysiology of AKI may lead to the development of specific therapies. Although there is evidence of an important role for immune cells in AKI, the specific relevant populations and the mechanisms of their actions are unclear. In this issue of the *JCI*, Li et al. demonstrate that adenosine manipulates DC responses to kidney injury, raising hope that immunotherapy could be a tangible approach to AKI.

Immune cells in acute kidney injury

Acute kidney injury (AKI) occurs in 3%–7% of patients admitted to tertiary care hospitals in industrialized nations (1). In native kidneys, AKI-associated mortality approaches 50% when occurring in the intensive care unit, and AKI in allograft kidneys worsens short- and long-term kidney function. Ischemia/reperfusion injury (IRI) is a common cause, as are sepsis and nephrotoxins. There is no specific therapy except for supportive care and dialysis. While much of the initial work on AKI pathophysiology focused on the highly abundant epithelial cell, more recent studies have revealed an important role for immune, endothelial, and peritubular resident cells (2). The evidence for the role of immune cells emerged from studies showing that leukocyte adhesion molecules (LAMs) mediated AKI; however, many of the beneficial effects were independent of neutrophils being targeted by LAMs, which was initially confusing (3–5). Further studies demonstrated that T cells were activated during AKI, migrated to kidney, and directly mediated tissue injury (6). This opened up the possibility of other immune populations such as DCs and NKT cells participating in AKI (ref. 7 and Figure 1). Work in other organs, such as lung, liver, and brain, has also revealed the engagement and participation of traditional immune cells in alloantigen-independent acute tissue injury (2, 8).

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Adenosine receptor 2A agonist-induced tolerogenic DCs in AKI

Adenosine, a breakdown product of ATP/ADP metabolism that accumulates in AKI, has been known to regulate lymphocyte responses and is thus an attractive target for modulating immune cells and improving outcomes in AKI (9). In the current issue of *JCI*, Li et al. have elegantly demonstrated that DCs can be modulated by adenosine or selective adenosine receptor agonists to improve the course of AKI when administered prior to or at the time of ischemic injury (10). Li et al. found that kidney dysfunction and inflammation after IRI were accentuated in mice deficient in the adenosine receptor $A_{2A}R$ only on $CD11c^+$ DCs, while selective $A_{2A}R$ agonist ATL313 administration led to tissue protection. Studying bone marrow-derived DCs primed with the glycolipid antigen α-galactosylceramide (αGC) to activate NKT cells led to a worsening of kidney dysfunction after mild (26 minutes) ischemia. Treating DCs that were primed with the NKT agonist αGC with adenosine receptor agonist protected from AKI. The DC therapy was effective if given 2 or 7 days prior to ischemic injury, or at 1 or 6 hours after injury, but not when started 24 hours after IRI. This finding indicates that modified DC cell therapy could be applied for prevention and early treatment; however, most patients are diagnosed well after ischemic injury, so the lack of effect when given 24 hours after ischemia may limit its practical application.

A key mechanism by which adenosine-mediated DC cell therapy works in AKI appears to be via IL-10, a powerful anti-inflammatory cytokine. IL-10 increased in kidney after adenosine-stimulated DC therapy, and blocking endogenous IL-10 reversed the protective effect. Furthermore, administering adenosine-stimulated DC therapy to IL-10–deficient mice led to a loss of the protective effect of the DCs, clearly implicating IL-10 as a protective mechanism (10). This finding is in line with previous reports showing that IL-10 is an important protective cytokine in AKI (11).

Therapeutic implications

The current study is built on a large body of work regarding the promise of tolerogenic DC cell therapy for human disease. Given that the adenosine-induced DCs were effective prior to AKI and up to 6 hours after, this would seem to be a useful approach for prevention of serious injury. However, most patients are diagnosed with AKI at least 12–24 hours after the ischemic insult. The best clinically available marker for AKI is a rise in serum creatinine, which occurs late and can be insensitive. Using improved biomarkers such as KIM-1, NGAL, IL-18, FABP, and Gro-α are potential ways to diagnose AKI early in order to enable timely administration of therapeutic agents (12–14). However, in the absence of earlier markers, cell therapy would be most useful if it could be used during established AKI. Another immune cell population, $CD25^+FoxP3^+$ Tregs, are an exciting candidate for cell therapy, since these cells are effective even when administered 24 hours after the ischemic insult and may also work via IL-10–mediated decreased inflammation and enhanced repair (15). Delivery of exogenous stem cells also shows great promise during established AKI (16). Even though repopulation of tubular epithelial cells after AKI is probably due to division of cells already resident in the kidney rather than from bone marrow–derived cells (17), administration of stem cells could increase the proliferation of the resident cells by paracrine mechanisms and factors including IL-6, SDF-1, and VEGF (18).

In the broader context, many patients with AKI harbor infections in addition to a "sterile" systemic inflammation from the kidney dysfunction, leading to inflammation in distant organs (19). Thus, dampen-

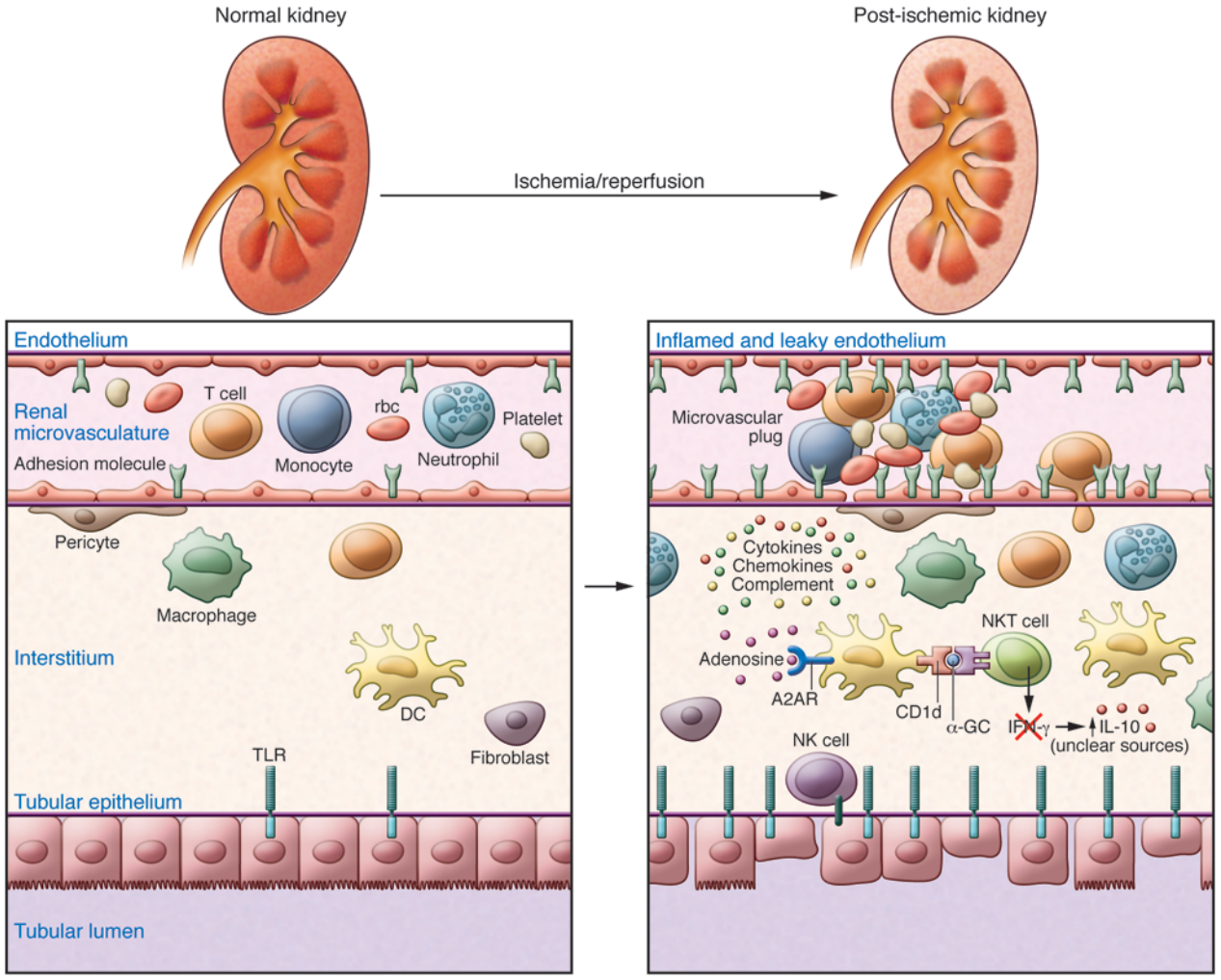

Figure 1

Immune cells in AKI. Immune cells likely mediate AKI while in circulation and when localized in the renal microvasculature, renal interstitium, and lymphoid tissue. While in the renal microcirculation during reperfusion, these cells increase their adhesiveness and adhere to activated endothelium and other cells, accentuating the "plug" that contributes to the no-reflow phenomenon. Some immune cells migrate into the interstitium, but there are also well-described resident renal immune cells. T and B cell, DC, NK and NKT cell, macrophage, and neutrophil crosstalk accentuates the postischemic inflammation. These cells produce and respond to cytokines, chemokines, oxygen free radicals, complement, coagulant factors, and other mediators. Adenosine, acting via $A_{2A}R$, activates DCs, which in turn modulate NKT cell function by decreasing IFN-γ secretion. This triggers increased IL-10 levels, which subsequently downregulate postischemic inflammation. Panels depict the outer medulla. Adapted with permission from the *Journal of Molecular Medicine* (2).

ing the immune system with cell therapy during AKI has to be balanced, as is the case in any immunosuppressive approach, with the risk of increasing the susceptibility to infection. Another possibility that has not been well studied in the experimental literature is that inflammation during AKI, though initially deleterious, could be important in repair. Thus interfering with early inflammation could ironically lead to more fibrosis long term, resulting in increased risk after an episode of AKI for development of chronic kidney disease (CKD) rather than full recovery.

Unanswered questions

The current study by Li et al. sheds light on exciting mechanistic pathways during ischemic AKI and stimulates many other questions. The location of the effect of the adenosine-stimulated DCs could be intrarenal or extrarenal, including in lymph nodes. The recognition of IL-10 as a key mediator of these effects raises the question of the identity of the cell producing IL-10, since it is probably not the DCs themselves. Are all of the effects due to IL-10, and if so, could IL-10 be infused at an appropriate dose and time in the place of cell therapy? Furthermore, what are the early signals that engage DCs in AKI as well as activate the other related immune pathways? Since T cells are known to modulate outcomes in AKI, either in a deleterious or protective way, depending on their functional subtype (20), a key question is what the initial stimulus is for such a rapid response in the absence of alloantigen. To date, no AKI antigen has been identified as driving immune responses. One of the confusing findings has been that many different immune cells are known to mediate AKI, but their relationships with each other, their redundancies, and molecular mecha-

nisms underlying their roles in kidney injury and repair are largely unknown.

Furthermore, ischemic injury, the focus of the Li et al. paper, may not have the same pathophysiologic pathways as nephrotoxic injury or sepsis. Another key step will be to understand why so many mechanistic studies in rodents have shown protection while clinical studies targeting the same pathways have failed. Does ischemic injury in native kidneys have a different pathophysiology than IRI in allografts when additional factors such as brain death, cold transport, and immunosuppressive treatment are superimposed? Finally, a recent surge of data has identified AKI as an important risk factor for CKD (21–23), and immune cells are likely important mediators between these two diseases, possibly related to autoimmunity (24). The type of immune cells involved in AKI-to-CKD transition and the details of how they function will be important to elucidate.

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1. Clarkson MR, Friedewald JJ, Eustace JA, Rabb H. Acute kidney injury. In: Brenner BM, ed. *Brenner & Rector's The Kidney*. 8th ed. Philadelphia, Pennsylvania, USA: Saunders, Elsevier; 2008:943–986.
2. Jang HR, Ko GJ, Wasowska BA, Rabb H. The interaction between ischemia-reperfusion and immune responses in the kidney. *J Mol Med*. 2009;87(9):859–864.
3. Thornton MA, Winn R, Alpers CE, Zager RA. An evaluation of the neutrophil as a mediator of in vivo renal ischemic-reperfusion injury. *Am J Pathol*. 1989;135(3):509–515.
4. Rabb H, et al. Role of CD11a and CD11b in ischemic acute renal failure in rats. *Am J Physiol*. 1994;267(6 pt 2): F1052–F1058.
5. Kelly KJ, et al. Intercellular adhesion molecule-1-deficient mice are protected against ischemic renal injury. *J Clin Invest*. 1996;97(4):1056–1063.
6. Burne MJ, et al. Identification of the CD4(+) T cell as a major pathogenic factor in ischemic acute renal failure. *J Clin Invest*. 2001;108(9):1283–1290.
7. Dong X, Swaminathan S, Bachman LA, Croatt AJ, Nath KA, Griffin MD. Resident dendritic cells are the predominant TNF-secreting cell in early renal ischemia–reperfusion injury. *Kidney Int*. 2007;71(7):619–628.
8. Zhai Y, Busuttil RW, Kupiec-Weglinski JW. Liver ischemia and reperfusion injury: new insights into mechanisms of innate-adaptive immune-mediated tissue inflammation. *Am J Transplant*. 2011;11(8):1563–1569.
9. Huang S, Apasov S, Koshiba M, Sitkovsky M. Role of A2a extracellular adenosine receptor-mediated signaling in adenosine-mediated inhibition of T-cell activation and expansion. *Blood*. 1997;90(4):1600–1610.
10. Li L, et al. Dendritic cells tolerized with adenosine A_{2A}R agonist attenuate acute kidney injury. *J Clin Invest*. 2012;122(11):3931–3942.
11. Deng J, et al. Star Interleukin-10 inhibits ischemic and cisplatin-induced acute renal injury. *Kidney Int*. 2001;60(6):2118–2128.
12. Bonventre JV, Vaidya VS, Schmouder R, Feig P, Dieterle F. Next-generation biomarkers for detecting kidney toxicity. *Nat Biotechnol*. 2010;28(5):436–440.
13. Mishra J, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet*. 2005; 365(9466):1231–1238.
14. Molls RR, et al. Keratinocyte-derived chemokine is an early biomarker of ischemic acute kidney injury. *Am J Physiol Renal Physiol*. 2006;290(5):F1187–F1193.
15. Gandolfo MT, et al. Foxp3+ regulatory T cells participate in repair of ischemic acute kidney injury. *Kidney Int*. 2009;76(7):717–729.
16. Tögel F, Hu Z, Weiss K, Isaac J, Lange C, Westenfelder C. Administered mesenchymal stem cells protect against ischemic acute renal failure through differentiation-independent mechanisms. *Am J Physiol Renal Physiol*. 2005;289(1):F31–F42.
17. Humphreys BD, et al. Intrinsic epithelial cells repair the kidney after injury. *Cell Stem Cell*. 2008;2(3):284–291.
18. Huang Y, et al. Kidney-derived stromal cells modulate dendritic and T cell responses. *J Am Soc Nephrol*. 2009;20(4):831–841.
19. Grams ME, Rabb H. The distant organ effects of acute kidney injury. *Kidney Int*. 2012;81(10):942–948.
20. Yokota N, Burne-Taney M, Racusen L, Rabb H. Contrasting roles for STAT4 and STAT6 signal transduction pathways in murine renal ischemia-reperfusion injury. *Am J Physiol Renal Physiol*. 2003;285(2):F319–F325.
21. Ishani A, et al. Acute kidney injury increases risk of ESRD among elderly. *J Am Soc Nephrol*. 2009;20(1):223–228.
22. Macedo E, Bouchard J, Mehta RL. Renal recovery following acute kidney injury. *Curr Opin Crit Care*. 2008;14(6):660–665.
23. Cohen SD, Kimmel PL. Long-term sequelae of acute kidney injury in the ICU [published online ahead of print August 29, 2012]. *Curr Opin Crit Care*. doi:10.1097/MCC.0b013e328358d3f5.
24. Burne-Taney MJ, Liu M, Ascon D, Molls RR, Racusen L, Rabb H. Transfer of lymphocytes from mice with renal ischemia can induce albuminuria in naive mice: a possible mechanism linking early injury and progressive renal disease? *Am J Physiol Renal Physiol*. 2006;291(5):F981–F986.

New mechanisms of glucocorticoid-induced insulin resistance: make no bones about it

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Glucocorticoids are a powerful tool used to treat a range of human illnesses, including autoimmune diseases and cancer, and to prevent rejection following organ transplantation. While lifesaving for many, they come with a steep price, often leading to obesity, insulin resistance, diabetes, and osteoporosis. In this issue of the *JCI*, Brennan-Speranza and colleagues provide evidence that the osteoblast-derived peptide osteocalcin is one of the drivers of the metabolic derangements associated with glucocorticoid therapy. This novel mechanism could open up new avenues for the treatment of these disorders.

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Glucocorticoids act by binding to the glucocorticoid receptor and promoting binding of the receptor to glucocorticoid response elements or association with other transcription factors, such as AP1, leading to either transactivation or transrepression of target genes. At physiological concentrations, glucocorticoids have effects on multiple metabolic, cardiovascular, and immunologic functions. Pharmacologic concentrations produce their therapeutic benefit of immune modulation by inducing antiinflammatory cytokines, inhibiting inflammatory cytokines, and inducing apoptosis of T-lymphocytes (1) but also cause many undesirable side effects, including increased susceptibility to infection, weight gain, glucose intoler-