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The innate immune response in ischemic acute kidney injury

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Abstract

Kidney ischemia reperfusion injury is a major cause of morbidity in both allograft and native kidneys. Ischemia reperfusion-induced acute kidney injury is characterized by early, allo-antigen independent inflammation. Major components of the innate immune system are activated and participate in the pathogenesis of acute kidney injury, plus prime the allograft kidney for rejection. Soluble members of innate immunity implicated in acute kidney injury include the complement system, cytokines, and chemokines. Toll-like receptors (TLRs) are also important contributors. Effector cells that participate in ACUTE KIDNEY INJURY include the classic innate immune cells, neutrophils and macrophages. Recent data has unexpectedly identified lymphocytes as participants of early acute kidney injury responses. In this review, we will focus on immune mediators that participate in the pathogenesis of ischemic acute kidney injury.

Keywords

Ischemia reperfusion injury; Innate immunity; Inflammation

Introduction

Acute kidney injury is associated with prolonged hospitalization, higher morbidity and mortality [1]. Ischemia reperfusion injury is a leading cause of acute kidney injury in both transplanted and native kidneys. Ischemia reperfusion-induced acute kidney injury is associated with tubulointerstitial inflammation and a robust inflammatory response to hypoxia and the process of reperfusion [2;3]. In this review, we will discuss the role of the innate immune system in ischemic acute kidney injury, as well as present recent data on a modulatory role for lymphocytes.

In ischemic acute kidney injury, hypoxic and anoxic cell injuries occur early during the ischemic phase, followed by inflammatory responses in the reperfusion phase. During reperfusion, blood containing innate immune component flows through ischemic tissues and accentuates injury. It is well established that a robust inflammatory reaction occurs following ischemia reperfusion [3]. Renal ischemia reperfusion induces renal synthesis or activation of pro-inflammatory cytokines and chemokines, and recruits leukocytes into the post-ischemic kidneys-to be reviewed in more detail in following sections. Several reports demonstrating the reno-protective effects of therapy targeting innate immune components such as complements,

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chemokines (discussed in the following section), or adhesion molecules [4-6], directly support the role of innate immunity in the pathogenesis of acute kidney injury. Functional impairment of kidney during acute kidney injury, leading to retention of fluids and nitrogenous waste products, further aggravates and sustains inflammation.

The initiation signals activating the innate immune system as well as triggering inflammatory response can be classified into 4 categories: 1) factors passively released from injured cells, 2) factors actively synthesized and secreted from the cells that have undergone ischemia, 3) recognition of altered or injured cell structures, and 4) decreased expression of anti-inflammatory factors by injured cells [7]. In acute kidney injury, both endothelium and tubular epithelium participate in innate immune responses. The signaling responses in tubular epithelium during renal injury, such as signaling through toll-like receptors (TLRs), is quite similar with that during ascending urinary infection [8].

Soluble Molecules and Membrane-Associated Receptors

The innate immune response includes soluble molecules such as complement and cytokines. In order to initiate and generate a full-blown innate immune response, TLRs appear required. We will review their roles in ischemic acute kidney injury in this section.

Complement

The complement system is a group of serum and cell membrane proteins that interact with one another and with other molecules of innate and adaptive immunity to carry out key effector functions. Many studies have demonstrated that alternative and mannose-binding lectin (MB-lectin) pathways are associated with ischemic injury. Selective inhibition of the alternative pathway provides protection to the kidneys from ischemic injury [9]. Alternative pathway activation occurs in a microenvironment with higher concentration of its components and lower concentrations of complement inhibitors. In murine acute kidney injury models, C3 (the first component of alternative pathway) production from tubular epithelial cells is stimulated and the complement inhibitor Crry expressed on the tubular basolateral surface is altered after ischemia reperfusion [10]. A recent report showed that C3a plays a crucial role in the CXC chemokine production by tubular epithelial cells after ischemia reperfusion, further demonstrating the role of the alternative complement pathways in post-hypoxic injury and inflammation [11]. Treatment with an inhibitory monoclonal antibody to mouse factor B, necessary for activation of the alternative pathway, protects mice from renal tubular injury and apoptosis following ischemia reperfusion [12]. Gene silencing with small interfering RNA (siRNA) targeting C3 and caspase 3 genes resulted in renal functional and structural protection [13].

The MB-lectin pathway is also activated during acute kidney injury and implicated in tissue injury [14]. Activation of the MB-lectin pathway is triggered by pattern recognition receptors, MB-lectin and ficolin, which bind to carbohydrates expressed on the surface of many pathogens as well as several endogenous ligands expressed on apoptotic and necrotic cells and cytokeratin exposed on hypoxic endothelial cells. MB-lectin recognizes endogenous ligands presented in the post-ischemic kidneys, resulting in complement activation within kidneys during acute kidney injury [14;15]. Decreased C3 deposition in MB-lectin-deficient mice after ischemia reperfusion directly supports the importance of the MB-lectin pathway in complement activation [14]. C5b-9 complex (membrane attack complex, MAC) and C5a also contribute to ischemic acute kidney injury [16;17] and C5a receptor antagonist exhibits renal protective effects [18]. MAC deposition of tubular epithelial cells is known to stimulate production of TNF- α and IL-6 [19]. Decay-accelerating factor (DAF, CD55), a 70 kDa membrane protein on the cell surface blocking the formation of the membrane attack complex, was recently reported to reduce ischemic injury in an acute kidney injury model [20]. Mice deficient in both

DAF and CD59 (a membrane-bound complement regulatory protein) appeared to more sensitive to acute kidney injury [20]. Overall, targeting complement appears like a very fruitful direction for human trials in ischemic acute kidney injury.

Toll-Like Receptor (TLR)

Toll-like receptors (TLRs) are a family of evolutionarily conserved transmembrane receptors and prototype of pattern recognition receptors (PRRs). The signal transduction initiated from TLRs activates effector cells of innate immune system via several kinases and NF- κ B, and generates pro-inflammatory cytokines. Among the 13 known TLRs, some TLRs are activated by the endogenous ligands from damaged tissues such as hyaluronan, fibronectin, heat shock proteins (HSPs), and host DNA, resulting in the stereotypic inflammatory response seen in autoimmune diseases. Of note, TLR-2 and TLR-4 respond to HSP-60 and HSP-70. Renal tubular epithelial cells are known to express both TLR-2 and TLR-4, and expression of both TLRs is increased during acute kidney injury [21;22]. TLR-2-deficient mice and mice treated with TLR-2 antisense oligonucleotides are protected from renal injury both functionally and structurally [23], possibly via production of cytokines and chemokines such as IL-1 β , IL-6, KC and MCP-1, and neutrophil infiltration. Another recent study also showed that TLR-2 is constitutively expressed within the kidney and participates in acute kidney injury through both MyD88 (an adapter protein in the signal transduction pathway mediated by interleukin-1 (IL-1) and TLRs)-dependent and – independent pathways [24]. TLR-4, expressed on macrophages and also reported to be expressed on tubular epithelial cells, has attracted more attention than other TLRs in the study of infectious disease because it recognizes the lipopolysaccharide (LPS) of the gram-negative bacteria by associating with CD14. Recently, TLR-4 activation has been demonstrated in a murine ischemic acute kidney injury model using TLR-4 knockout mice [25]. TLR-4(-/-) mice engrafted with wild-type hematopoietic cells showed significantly less azotemia and less tubular damage compared to wild-type mice reconstituted with TLR-4 (-/-) bone marrow, suggesting that the signaling through TLR-4 in intrinsic kidney cells plays the dominant role in mediating renal damage. Though abundant evidence implicates TLR's in experimental models of ischemic acute kidney injury, application of this knowledge to improve outcome in humans has not started.

Cytokines

Cytokines are low-molecular-weight (approximately 25 kDa) regulatory proteins or glycoproteins released from various cells, mainly from leukocytes, usually by various activating stimuli, and regulate the development and effector functions of immune cells. Most cytokines show autocrine and/or paracrine action and a few of them exhibit endocrine action. Ischemia reperfusion-induced acute kidney injury causes the synthesis of pro-inflammatory cytokines such as IL-1, IL-6, and TNF- α [5;26]. Cytokine production following ischemia reperfusion occurs through the interaction between cytokines and the transcriptional response directly induced by hypoxia itself. For example, generation of IL-1 subsequently stimulates tubular epithelial cells to produce TNF- α and IL-6 [27]. Renal ischemia activates the transcription factors such as NF- κ B, heat shock factor-1, and hypoxia-inducible factor-1 (HIF-1) [28;29]. Direct blockade of a number of cytokines, including IL-1, IL-6, and IL-8 has been shown to attenuate renal injury during ischemic acute kidney injury, while IL-4 and IL-10 modulation can worsen disease [30-32]. Cytokines clearly play an important role in both local and distant organ effects of acute kidney injury.

Given the rapid emergence of the field of chemokines and acute tissue injury, we will expand on this area in more detail. Chemokines are a subgroup of cytokines, which are released by tissues and composed of 90 to 130 amino acid residues. Their basic functions are chemotaxis and activation of leukocytes. Chemokines have three subtypes according to the number of amino acids between the first two cysteines; CC, CXC, and CX3C families. Chemokine

induction during the inflammatory response after ischemia reperfusion injury has been reported in several organs such as brain, heart, liver, and kidney [32]. In post-ischemic tissues, chemokines are induced by reactive oxygen species (ROS), cytokines, complement activation, TLR-mediated pathways, and the NF- κ B system. Regarding the role of ROS in chemokine induction, ROS has been reported to induce chemokine production in brief myocardial ischemia in a murine model [33] and a canine model [34] although there are still few reports in ischemia reperfusion-induced acute kidney injury models. ROS is known to trigger cytokine and chemokine cascades through NF- κ B activation. Pro-inflammatory cytokines, such as tumor-necrosis factor (TNF)- α and interleukin (IL)-1 β , stimulate chemokine production in post-ischemic tissues of myocardial ischemia reperfusion injury models [35] and hepatic ischemia reperfusion injury models [36]. Complement activation can also stimulate chemokine induction. There was a report demonstrating that a specific C5a receptor antagonist abolished up-regulation of CXC chemokines and diminished neutrophil infiltration to less than 50% of control group in an ischemic acute kidney injury model [17].

IL-8/CXCL8, an ELR-containing CXC chemokine, plays a crucial role in neutrophil recruitment in the post-ischemic kidney mediating tissue injury via cytokines, free radical intermediates, and proteases [37;38]. IL-8 was reported to be increased during reperfusion of living and cadaveric donor kidney allografts in a clinical study and its expression correlated with the ischemic time imposed on the allograft [38]. Growth-related oncogene (GRO)- α /keratinocyte-derived chemokine (KC, a mouse analog of human IL-8) was induced in a murine ischemic acute kidney injury model [39]. Neutralization of GRO- α /KC and macrophage inflammatory protein (MIP)-2 was reported to attenuate acute kidney injury [37]. KC is also an attractive early biomarker of acute kidney injury based on both murine and human studies [40]. Inhibition of CXCR2, one of two specific receptors for the ELR-containing CXC chemokines, was reported to mitigate renal injury in a rat model of cold ischemia followed by kidney transplantation [41].

CXCR3 receptor is predominantly expressed on activated Th1-cells and binds three non-ELR-containing CXC chemokines; monokine, interferon- γ inducible protein (IP)-10/CXCL10, and interferon-inducible T cell alpha chemoattractant (ITAC/CXCL11). CXCR3 expression was increased in the post-ischemic kidney of a murine acute kidney injury model and renal protection is reported in CXCR3-deficient mice [42]. Stromal cell-derived factor (SDF)-1/CXCL12, non-ELR-containing CXC chemokine with a critical role in cardiovascular development and angiogenesis, was recently reported to be increased in the post-ischemic kidney [43], however its functional role in acute kidney injury is still unclear. Monocyte chemoattractant protein-1 (MCP-1)/CCL2, one of CC chemokines, is a potent chemoattractant for monocytes, T cells, and NK cells. MCP-1/CCL2 upregulation has been implicated in diseases with monocyte infiltration as well as ischemia reperfusion injury models of kidney [44], heart [45], and brain [46]. CCR2 (the receptor of CCL2)-null mice showed diminished tubular injury and decreased macrophage infiltration during acute kidney injury [44]. RANTES (regulation upon activation, normal T cell expressed and secreted), a chemoattractant for monocytes, eosinophils, and T cell subsets, was found to be significantly increased in the serum of acute myocardial infarction patients in a small clinical study [47], though not increased in a murine ischemia reperfusion-induced acute kidney injury model [48]. Fractalkine/CX3CL1, a member of the CX3C chemokine subfamily and expressed on NK cells, monocytes and T cells, plays a role as a leukocyte chemoattractant and an adhesion molecule. CX3CL1 is constitutively expressed in the kidney and its expression is known to be redistributed to the outer medulla after ischemia reperfusion injury. Inhibition of CX3CR1, the receptor of CX3CL1, attenuated interstitial fibrosis in the post-ischemic kidney, suggesting that CX3CR1 signaling regulates macrophage infiltration and fibrosis in ischemia reperfusion-induced acute kidney injury [49]. Although CX3CL1 was also reported to be related with cerebral ischemia reperfusion

injury [50], the precise role of this chemokine in ischemic acute kidney injury has not been fully elucidated.

Cellular Mediators of Innate Immunity

Macrophages, neutrophils, natural killer (NK) cells, and dendritic cells are important cells involved in innate immune responses. In addition, newer data also implicates lymphocytes during these early injury responses.

Macrophages

Macrophages play roles in both innate and adaptive immunity. Activated macrophages exhibit potent phagocytic activity and secrete several important cytokines such as IL-1, IL-6, IL-8 (CXCL8), IL-12, and TNF- α . Monocyte adherence at the level of the renal microvessel, the ascending vasa recta, is observed after 2 hours following reperfusion, and inhibition by anti-B7-1 antibody attenuated renal injury [51]. Macrophages infiltrate into the outer medulla of the post-ischemic kidneys and remain into the recovery phase [52]. Early monocyte/macrophage influx could be mediated by microvascular basement membrane heparin sulfate proteoglycans binding to L-selectin and monocyte chemoattractant protein-1 (MCP-1) [53]. Although macrophages are suspected to play a role in renal repair after acute kidney injury, their precise role is yet to be elucidated. One study demonstrated that osteopontin (a macrophage chemoattractant) knockout mice revealed fewer infiltrating macrophages and less fibrosis compared to wild-type mice [54]. There are several recent reports implicating macrophages in the recovery phase of ischemia reperfusion-induced acute kidney injury and contributing to the development of renal fibrosis [55;56]. However, macrophages clearly have a role in the early injury phase of ischemia reperfusion-induced acute kidney injury [57;58]. Macrophage production of heme-oxygenase-1 has been shown to underlie the protective effects of statins in acute kidney injury, though statins have quite diverse effects [59].

Neutrophils

Neutrophils play key roles in innate immune response by phagocytosis, producing reactive oxygen, nitrogen species and antimicrobial peptides. Although neutrophil infiltration is found in ischemic acute kidney injury models [60;61] and biopsies from patients with early acute kidney injury [2;62], the precise role and kinetics of neutrophil trafficking into the post-ischemic kidneys are not fully defined [52]. Some reports demonstrated that renal injury was reduced after ischemia reperfusion when treatments inhibiting neutrophil infiltration or activity were applied [4], while other studies failed to find a protective effect of neutrophil blockade or depletion [63;64]. Although neutrophils are less likely to cause direct renal injury compared to their effect during cardiac or skeletal muscle ischemia reperfusion injury, they likely have a contributory role by plugging renal microvasculature and releasing oxygen free radicals and proteases [62].

Despite inconsistent conclusions during studies directly targeting neutrophils, treatments targeting several adhesion molecules involved in neutrophil (as well as other leukocytes) migration, such as selectins, intercellular adhesion molecule 1 (ICAM-1), and CD11/CD18, have had protective effects in rodent acute kidney injury models [4;61;64]. A phase I human trial blocking ICAM-1 showed lower rates of transplant ischemic injury (delayed graft function) in treated group [65]. However, a randomized controlled trial of anti-ICAM-1 monoclonal antibody in recipients of cadaveric renal transplants failed to show beneficial effects on the rate of delayed graft function or acute rejection [66]. Blockade of platelet-activating factor (PAF), known to play a role in neutrophil adherence to endothelium, also had a protective effect in a rat cold ischemia reperfusion injury model [67]. Alpha-melanocyte-stimulating hormone (α -MSH), an inhibitor of IL-8 (a murine neutrophil chemokine) and

ICAM-1, significantly reduced renal injury following ischemia reperfusion in both wild-type and neutrophil-depleted murine models, suggesting that the beneficial role of α -MSH may occur by acting on renal tubular cells [60;62;68]. Many substances affecting neutrophil influx or activation, such as neutrophil elastase, tissue-type plasminogen activator, activated protein C, hepatocyte growth factor, and CD44 have been suggested to participate in inducing renal injury [69-73].

Natural Killer (NK) cells

Natural Killer (NK) cells are a class of large, granular, cytotoxic lymphocytes that lack T- or B-cell receptors. They target and kill infected cells directly as well as produce a variety of cytokines including interferon (IFN)- γ and TNF- α . Little is known about the role of NK cells in acute kidney injury. However, NK cells are predicted to play a role in inducing renal injury following ischemia reperfusion because they secrete major cytokines that facilitate the inflammatory process including activation of neutrophils and macrophages.

Dendritic cells

Dendritic cells have been shown to participate in ischemic acute kidney injury in a number of studies. In a rat transplant ischemia reperfusion model, recruitment of recipient MHC class II-positive leukocytes into the kidney was demonstrated despite no sign of acute rejection, and some of them were identified as dendritic cells [74]. Both total number and MHC class II expression of renal dendritic cells are increased after ischemia reperfusion injury [22].

Dendritic cell-endothelial cell binding and migration seem to be facilitated during the initial inflammatory response [75]. Resident dendritic cells are the predominant TNF-secreting cell in early ischemia reperfusion-induced acute kidney injury [76] and ischemia reperfusion causes abnormal dendritic cell trafficking into the transplanted kidney, which might be predisposed to delayed graft function and acute rejection [77].

Other Leukocytes Participating in Early Injury Responses (“Innate-Like”)

There are several minor lymphocytes subsets which express receptors with very limited diversity and do not undergo clonal expansion before responding effectively to the antigens. Therefore, they are known as innate-like lymphocytes (ILLs). Three main classes of ILLs are NK T cells, intraepithelial $\gamma\delta$ T cells, and B-1 subset of B cells (B-1 cells).

Natural Killer T cells (NK T cells)

NK T cells, also known as NK1.1 T cells, are lymphocytes with some of the characteristics of T cells as well as those of natural killer (NK) cells, existing both in the thymus and peripheral lymphoid organs. NK T cells exert regulatory functions by secreting cytokines such as IL-4, IL-10, and IFN- γ . NK T cells are known to traffic into the post-ischemic kidneys as early as 3 hours after ischemia reperfusion injury and begin to decrease at 24 hours after ischemia reperfusion injury compared to normal and sham operated kidneys [78]. Isoflurane anesthesia significantly attenuated ischemia reperfusion-induced acute kidney injury in mice by reducing inflammation and modulating infiltration of NK T cells as well as neutrophils and macrophages [79]. Recently, NK T cell activation was reported to contribute to acute kidney injury by mediating neutrophil IFN- γ production [80].

Intraepithelial $\gamma\delta$ T cells

The $\gamma\delta$ T cells are a minor subset of T cells with TCR composed of a γ chain and a δ chain, while TCR of majority T cells is composed of α and β chains. The $\gamma\delta$ T cells recognize phospholipids or intact protein instead of peptide antigen carried on MHC, and are divided into two highly distinct sets of cells according to primary residing location and function. One set

of $\gamma\delta$ T cells is found in the lymphoid tissue of all vertebrates and exhibit highly diversified TCR such as $\alpha\beta$ T cells. By contrast, intraepithelial $\gamma\delta$ T cells occur variably in different vertebrates and express very limited diversity, particularly in the skin and the female reproductive tract of mice. Two recent reports demonstrated that $\gamma\delta$ T cell-deficient mice were protected from early renal tubular injury after ischemia reperfusion as well as $\alpha\beta$ T cell-deficient mice [81;82].

B-1 cells

B-1 cells are a minor subset of B cells and distinguished from conventional B-2 cells by the cell-surface protein CD5 and primary residing location. They are distributed in the peritoneal and pleural cavities. Although production of natural antibodies, immunoglobulins which arise without specific antigenic stimulation, is suggested as a primary role of B-1 cells, their precise role still remains to be defined. Natural IgM from B-1 cells has been reported to be involved in initiation of injury in murine intestinal ischemia reperfusion injury models [83]. In a murine ischemic acute kidney injury model, μ chain-deficient mice (lacking mature B cells) were protected from renal injury, suggesting possible roles of B cells [84]. However, there are no reports that directly reveal the role of B-1 cells in ischemia reperfusion-induced acute kidney injury.

CD4 T Cells

CD4 T cells have been identified as an unexpected (based on traditional functions of CD4 T cells) mediator of acute kidney injury, functioning very early like traditional innate immunity members. The pathophysiologic role of T cells has been elucidated in the initiation phase of ischemic acute kidney injury in many studies, both directly and indirectly [51;78;85-87]. FK506 and mycophenolate mofetil, T cell targeting medications, significantly attenuated renal injury in ischemia reperfusion-induced acute kidney injury [88;89]. Blockade of the T cell CD28-B7 costimulatory pathway with CTLA4Ig (a recombinant fusion protein containing a homolog of CD28 fused to an IgG1 heavy chain) also showed a significant reduction in early injury after cold renal ischemia reperfusion injury [90]. Furthermore, CTLA4Ig treatment both on the day of ischemia reperfusion injury and during the first week after ischemia reperfusion injury reduced proteinuria in a long-term model of progressive proteinuria in uninephrectomized rats that underwent cold ischemia reperfusion injury [91]. More direct involvement of T cells in acute kidney injury was demonstrated in murine ischemia reperfusion-induced acute kidney injury using mice deficient in CD4 and CD8 [85]. In this work, CD4 and CD8 double knockout mice were significantly protected from early renal injury in vivo, while T cells showed a two-fold increased adherence to renal tubular epithelial cells after in vitro hypoxia reoxygenation. Another T cell knockout mouse strain, athymic *nu/nu* mice, was also protected from acute kidney injury and adoptive transfer of T cells into these mice reconstituted renal injury following ischemia reperfusion, demonstrating that it was indeed the T cell deficiency that conferred protection from acute kidney injury in this strain [86]. CD4 knockout mice, but not CD8 knockout mice, were markedly protected from renal injury with significantly lower mortality, and adoptive transfer of CD4 T cells into CD4 knockout mice restored renal injury. CD28 on T cells, as well as T cell IFN- γ production, was a key factor in the CD4 T cells' effects on acute kidney injury. However, in this work, very few infiltrating T cells were found in early (within 24 hours) post-ischemic renal tissues. A "hit-and-run" hypothesis was proposed to explain the paucity of T cells during the insult phase of ischemic acute kidney injury, that T cells would rapidly infiltrate within hours, initiate damage, and then disappear soon after [62]. This hypothesis is directly supported by two recent reports revealing early trafficking of lymphocytes into post-ischemic kidneys [78;92].

A study on CD4 T cell subsets in a murine ischemia reperfusion-induced acute kidney injury model revealed that CD4 T cells of the Th1 phenotype are pathogenic and the Th2 phenotype

can be protective [93]. This work was performed using mice with targeted deletions in the enzymes signal transducers and activators of transcription (STAT) 4 and STAT6, which regulate Th1 (IFN- γ producing) or Th2 (IL-4 producing) differentiation and cytokine production, respectively. STAT6-deficient mice had markedly worse renal function and tubular injury, whereas STAT4-deficient mice had a mildly improved renal function. Furthermore, IL-4-deficient mice showed similar post-ischemic phenotype with STAT6-deficient mice, suggesting that IL-4 mediates protective effect of the STAT6 pathway. One recent report supports the importance of CD4 T cells in early renal injury after ischemia reperfusion by demonstrating that inactivation of IL-16 (a T cell chemoattractant, strongly expressed in distal and proximal straight tubules of the post-ischemic kidney) by antibody therapy and IL-16 deficiency led to less CD4 T cell infiltration and prevented renal injury [94].

Despite ample data on the role for CD4 T cells in kidney ischemia reperfusion injury, as well as ischemia reperfusion injury of other organs like liver, lung, brain, and gut, the precise mechanisms underlying the role of T cells in acute kidney injury still need to be elucidated. Although T cell depletion with thymectomy followed by T cell depleting antibody administration improved the course of experimental ischemia reperfusion-induced acute kidney injury [95], mice deficient in both T and B cells were not protected from ischemia reperfusion-induced acute kidney injury [96]. TCR appears to play a role in establishing the full injury after ischemia reperfusion, though alloantigen-independent activation in acute kidney injury could also participate [78]. This is an area of active investigation with important translational potential for human acute kidney injury.

Conclusion

Robust early inflammatory responses occur in post-ischemic kidneys, facilitating the full expression of tissue damage and organ dysfunction in acute kidney injury. Numerous experimental studies have revealed the importance of innate immune responses following ischemia reperfusion injury. Based on this information about the role of immune component of ischemic acute kidney injury, there is an opportunity to further dissect the underlying mechanisms. It will be important to study how early immune responses link transplant rejection and poor long term outcomes, and how we can intervene to improve outcomes from acute kidney injury with novel immune therapeutics.

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Figure 1. Overview of early immune response occurring in post-ischemic kidneys

In experimental ischemia reperfusion-induced acute kidney injury models, ischemic insult occurs first and then reperfusion initiates inflammation in post-ischemic kidneys with entry of blood containing major cellular components of innate immunity, plus lymphocytes. Leukocytes including neutrophils, macrophages and lymphocytes traffic into post-ischemic kidneys. Cytokines and complement system also contribute to renal injury. Early injury events take place both at the level of the microvasculature, and then in the tubular interstitial space. Renal microcirculation is interfered by plugging with leukocytes and platelets and each immune component act in concert causing robust inflammatory responses in the tubular interstitial space.

Table 1

Summary of data on effector cells of innate immune system in ischemic acute kidney injury

Cells	Major findings in post-ischemic kidneys	Reference
Macrophages	<ul style="list-style-type: none"> • Infiltration into the outer medulla, remaining until the recovery phase • Less renal fibrosis in osteopontin knockout mice, suggesting possible role of macrophages in the recovery phase • Roles in the early injury phase 	Ysebaert, 2000 [52] Persy, 2003 [54] Day, 2005 [57] Jo, 2006 [58]
Neutrophils	<ul style="list-style-type: none"> • Infiltration into post-ischemic kidneys • Protective effects of inhibiting neutrophil infiltration • No protection in neutrophil blockade or depletion • Protective effects of several adhesion molecules, PAF, CD44, and activated protein C, which are involved in neutrophil infiltration or activation 	Chiao, 1997 [60] Kelly, 1996 [4] Thornton, 1989 [63] Rabb, 1994 [64] Nemoto, 2001 [61] Rabb, 1994 [64] Riera, 1997 [67] Rouschop, 2005 [73] Turunen, 2005 [71]
Dendritic cells	<ul style="list-style-type: none"> • Increased total numbers and MHC class II expression of renal dendritic cells during ischemia reperfusion-induced acute kidney injury • TNF secretion from resident dendritic cells in early renal injury following ischemia reperfusion • Abnormal dendritic cell trafficking into transplanted kidneys 	Kim, 2005 [22] Dong, 2007 [76] Loverre, 2007 [77]

Table 2

Summary of data on lymphocytes participating in early injury responses of ischemic acute kidney injury

Cells	Major findings in post-ischemic kidneys	Reference
NK T cells	<ul style="list-style-type: none"> Trafficking as early as 3 hours and decreasing at 24 hours after ischemia reperfusion injury Mediating IFN-γ production by neutrophil in post-ischemic kidneys 	Ascon, 2006 [78] Li, 2007 [80]
$\gamma\delta$ T cells	<ul style="list-style-type: none"> Protective effect of $\gamma\delta$ T cell deficiency as well as $\alpha\beta$ T cell deficiency Mediating renal injury only in the first 72 hours of renal ischemia reperfusion injury 	Savransky, 2006 [81] Hochegger, 2007 [82]
CD4 T cells	<ul style="list-style-type: none"> Increased percentage of total T cells at 3 hours, then decreased at 24 hours after ischemia reperfusion injury, supporting "hit-and-run" theory Increased infiltration of T cells within 1 hour after ischemia reperfusion injury Protective effect of CD4 knockout mice Pathogenic role of Th1 phenotype and protective role of Th2 phenotype Protective effect with less infiltration of CD4 T cells in IL-16 inactivation by antibody and IL-16-deficient mice 	Ascon, 2006 [78] Lai, 2007 [92] Burne, 2001 [86] Yokota, 2003 [93] Wang, 2007 [94]