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## Role of immune cells in acute kidney injury and repair

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### Abstract

Acute kidney injury (AKI) is a significant problem in both native and transplant kidneys. There have been significant advances in understanding the role of immune cells in the early injury and repair from AKI. In this brief review, we aim to update information on the pathophysiologic impact of various immune cells in AKI, with special emphasis on repair. An improved understanding of the AKI immunopathology will lead to new therapies that prevent AKI, accelerate repair, and prevent progression of AKI to chronic kidney disease (CKD).

### Keywords

Acute kidney injury; immune cells; inflammation; kidney repair; neutrophil; macrophage; dendritic cells; T lymphocyte; B lymphocyte; double negative T cells; regulatory T cells

### Introduction

Work over the last 20 years has demonstrated important roles for different immune cells in the pathogenesis of early injury during AKI. More recent advances point to their role in recovery and repair from AKI as well. We will briefly update the reader on these advances, with special emphasis on recent literature.

### Immune cells in AKI

#### Neutrophils

Neutrophils traffic into kidney and cause microvascular plugging during AKI. Neutrophils adhere to endothelium and transmigrate into renal interstitium using adhesion molecules like P-selectin and intracellular adhesion molecule-1 (ICAM-1), promoting kidney injury through secretion of cytokines, reactive oxygen species (ROS) and proteases [1]. Because of the traditional view of neutrophils as “first responders”, neutrophils were the main white blood cells investigated in earlier AKI studies. However, discordant results led to

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questioning of the role of neutrophils during early AKI pathogenesis [2]. Recent studies, however, have shown that blocking neutrophil infiltration by inhibition of vascular adhesion protein-1 or leukotriene B<sub>4</sub>-leukotriene B<sub>4</sub> receptor axis had protective effect against ischemia-reperfusion injury (IRI) and cisplatin-induced AKI, respectively [3,4].

### Macrophages and Dendritic cells (DCs)

Resident mononuclear phagocytic cells (MPCs), which are traditionally classified as macrophages based on their phagocytic function or as DCs by their antigen-presenting activity, serve important roles as immune-regulators during steady state as well as a bridge between innate and adoptive cells in tissue injury and repair. During AKI, renal MPCs contribute to expanding the inflammatory cascade and leukocyte recruitment with multiple chemotactic factors. Circulating monocytes infiltrate into kidney following renal injury and differentiate into macrophages or inflammatory DCs depending on the renal microenvironment. Macrophages are divided into two broad subsets, M1 (classically activated, pro-inflammatory) and M2 (alternatively activated, tissue-reparative). M1 phenotype is largely controlled by toll-like receptor ligation and interferon (IFN)- $\gamma$ , whereas interleukin (IL)-4 and IL-13 are responsible for M2 differentiation. [5]. M1 macrophages predominate in early AKI, whereas skewing to M2 macrophages occurs in the later stages. Macrophage ablation in mice before early IRI decreased renal injury, whereas macrophage ablation after established AKI resulted in aggravated tissue injury due to reduced M2 macrophages [6].

DCs also possess functional plasticity governed by different renal interstitial microenvironments. Several studies revealed seemingly disparate roles for DCs that were pathogenic in ischemic AKI and protective in cisplatin-induced AKI [7,8]. This could be because DC function is regulated by injury stimulus and local environment. For these reasons, induction of tolerogenic DCs has received attention to regulate inflammation following AKI.

### T lymphocytes

T lymphocytes accumulate in the kidney within a few hours after AKI, and play important roles in the development and maintenance of AKI [9]. T cell deficient athymic mice are protected from IRI, and have accentuated renal injury after adoptive transfer of T lymphocytes [10]. CD4-deficient mice are more protected than CD8-deficient mice in both ischemia- and cisplatin-induced AKI models [10,11]. Upon activation, CD4<sup>+</sup> T cells differentiate into distinct effector subtypes. Among them, IFN- $\gamma$ -producing T helper 1 (Th1) cells are viewed as pathogenic, whereas IL-4-producing T helper 2 (Th2) cells as protective. Signal transducers and activators of transcription (STAT) 4 and STAT6 regulate development of Th1 and Th2 cells in mice, respectively, and STAT4<sup>-/-</sup> mice are protected from renal IRI, while STAT6<sup>-/-</sup> mice develop severe injury, confirming the respective roles of CD4<sup>+</sup> Th1 and Th2 cells in IRI [12]. IL-17-producing Th17 cells promote renal inflammation by direct tissue damage or by enhancing the pro-inflammatory cytokine secretion from neighboring immune cells.

Several studies have focused on mediators of CD4<sup>+</sup> T cell-induced renal injury. IL-33 promote AKI through enhancing CD4<sup>+</sup> T cell infiltration and CD4<sup>+</sup> T cell-mediated production of chemokine ligand 1 (CXCL1), suggesting therapeutic potential of IL-33 inhibition in AKI [13]. Another study demonstrated that cholinergic stimulation of splenic CD4<sup>+</sup> T cells using ultrasound pretreatment showed renoprotective effect in IRI [14]. Furthermore, activation of type 1 angiotensin II (AT<sub>1</sub>) receptors have tissue-specific effect on cisplatin-induced nephrotoxicity and suggested blocking AT<sub>1</sub> receptors in the kidneys but activating AT<sub>1</sub> receptors on circulating T cell as a promising intervention from cisplatin-induced nephrotoxicity [15]. In addition, T lymphocyte-specific activation of Nrf2, a transcription factor mitigating oxidative stress, also showed functional and histologic protection from ischemic AKI [16]. Further studies are required to elucidate the underlying role of T lymphocytes and their interaction with other neighboring cells in AKI.

## B lymphocytes

B cells play a central role in the pathogenesis of glomerulonephritis and allograft rejection, but only few studies have investigated the role of B cells in renal AKI. B cells infiltrate kidney following IRI and their deficiency in mice showed protection with reduced tubular damage in early phase of IRI and increased tubular proliferation in late phase of IRI, which were reversed by adoptively transferred B cells [17]. Naturally occurring IgM antibodies from B1 cells also protect mice from renal IRI, which is mediated by IgM anti-leukocyte autoantibodies [18].

## Immune cells in AKI repair

### Macrophages and tolerogenic DCs

In addition to their well-established pro-inflammatory effects during early AKI, macrophages also serve a critical role in wound healing and tissue regeneration. M2 macrophages could serve important roles during the repair process by inhibiting progression of AKI to chronic kidney disease (CKD) and fibrosis [6]. Intrinsic IL-10, colony-stimulating factor 1 (CSF1) and granulocyte macrophage colony-stimulating factor (GM-CSF) participate in tissue recovery and immune regulation by M2 macrophages [19]. Recently, a novel role for IL-1 receptor-associated kinase-M (IRAK-M) expressed on macrophages in the regulation of wound healing and tissue regeneration in AKI was reported [20]. In the case of sustained kidney injury, however, M2 macrophages can also participate in maladaptive repair causing renal fibrosis and extracellular matrix deposition.

Tolerogenic DCs serve important parts in peripheral tolerance by inducing regulatory T cells and T cell anergy [21]. Based on the plasticity of DCs, engineering DCs into a tolerogenic type is an attractive therapeutic approach in AKI. For example, treatment of DCs with adenosine 2A receptor (A<sub>2A</sub>R) agonist induced tolerogenic DCs and protected kidney from ischemic IRI by suppressing natural killer T (NKT) cells [21]. A<sub>2A</sub>R-stimulation can also prevent DC migration and promote Th2-skewing of CD4<sup>+</sup> T cells as well as CD8<sup>+</sup> cell anergy [22]. The high plasticity and diversity of macrophage and DCs make them attractive candidates for cell therapy in AKI. Future studies are required to explore their potential for AKI modulation.

## Regulatory T cells (Treg) and Double negative T cells (DNT)

Although T cells are traditionally associated with a deleterious role in tissue injury, certain T cells possess tissue protective activities: CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> regulatory T (Treg) cells and TCR<sup>+</sup>CD4<sup>-</sup>CD8<sup>-</sup> double negative (DN) T cells. Tregs suppress pro-inflammatory response by direct cell-contact and through soluble factor-mediated mechanisms [23]. Treg-mediated tissue protection have been confirmed in both ischemic- and nephrotoxic AKI by multiple studies using depletion and expansion approaches. [23]. Therapeutic potential of Tregs in AKI has been actively pursued, including adoptive transfer of Treg cells which enhanced the repair process and reduced pro-inflammatory cytokine production by other T cell subsets [24]. Diverse Treg enhancing drugs, including A<sub>2A</sub>R, bee venom or dimethylsphingosine are also showing promising results of the Treg-driven immunotherapy [23].

DN T cells are rare in the peripheral blood and lymphoid organs but comprise a significant component of renal T cells accounting for 18 to 32% of resident T cells in both mouse and humans [25]. Renal DN T cells expand significantly in early phase of AKI, express higher level of IL-10 and IL-27 compared to conventional T lymphocytes, and adoptive transfer of DN T cells reduce ischemic AKI in mice. There is very little information on DN T cells in kidney despite their significant numbers.

In addition to these well studied cell types, other immune cell subsets like NK T cells,  $\gamma\delta$  T cells are also being actively studied for their role in AKI. Future studies are required to further ascertain their specific pathophysiologic and therapeutic functions.

## Conclusion

A more in-depth understanding of the role of immune cells, particularly in view of successful immunotherapy for cancer, is expected to lead to novel therapeutic approaches to prevent and treat AKI.

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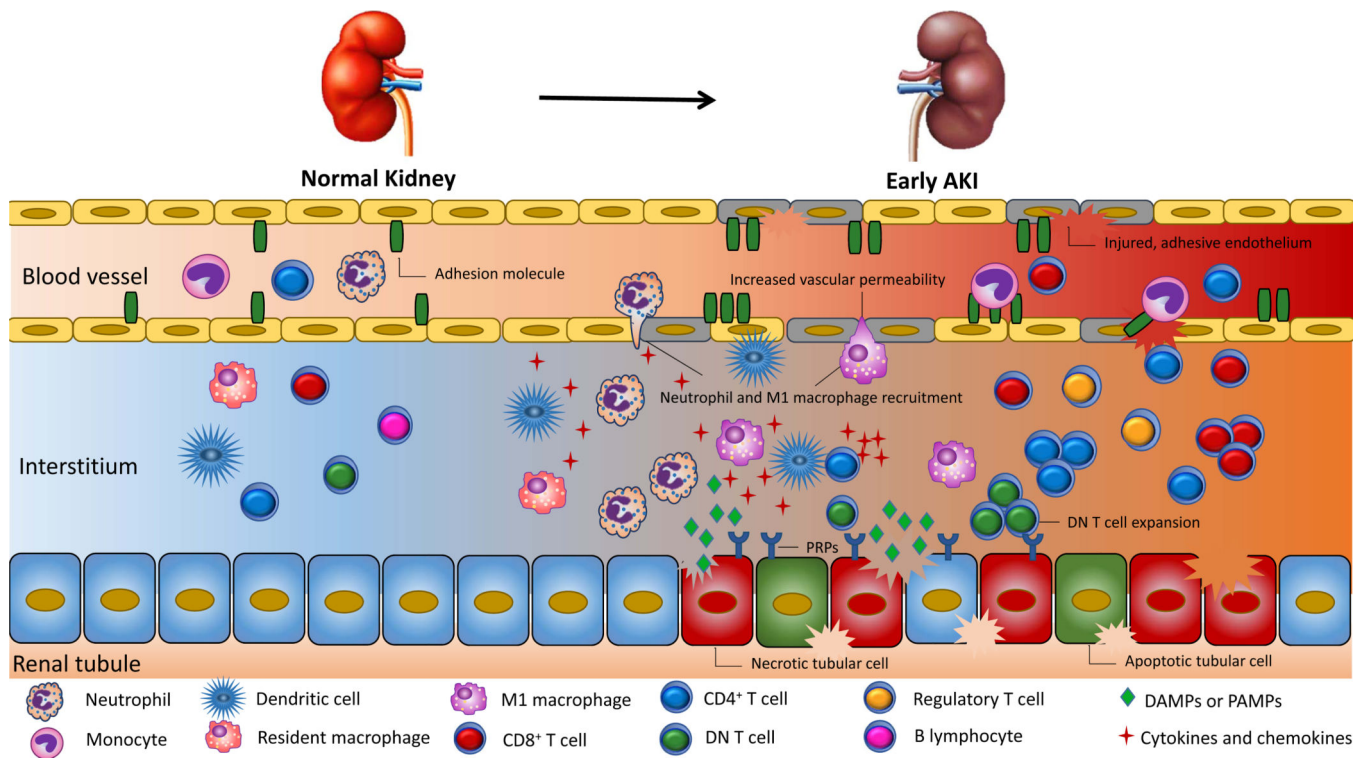
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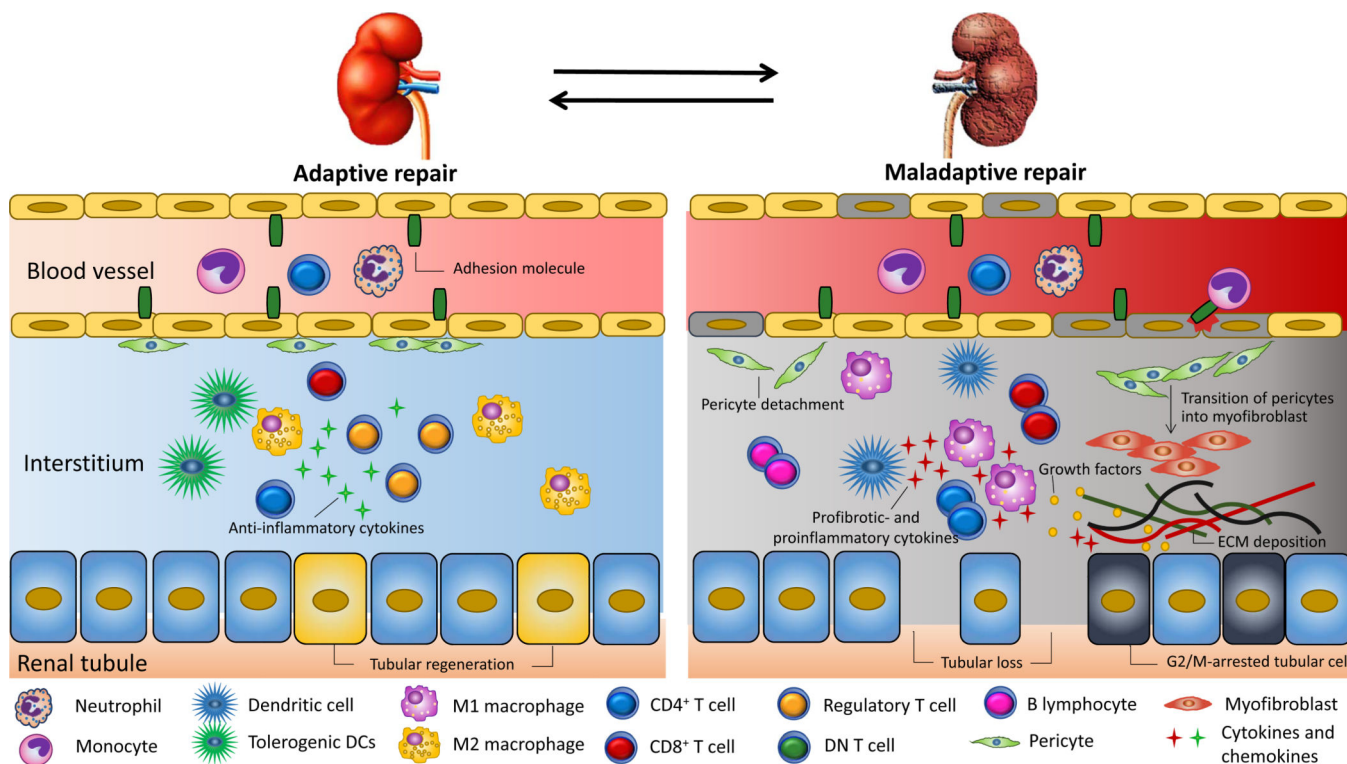
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**Figure 1.**

Several types of resident immune cells are present in the normal kidney. After renal injury, very early inflammation is likely initiated by the resident immune cells, which is followed by rapid infiltration of circulating immune cells in response to the inflammatory cytokines and chemokines secreted from activated/damaged resident cells. DAMPs and PAMPs secreted from damaged cells enhance immune cell recruitment to injured kidney tissue and participate in the establishment of initial tissue injury in early AKI. Abbreviations: AKI, acute kidney injury; DN T cell, double negative T cell; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; PRP, pattern recognition receptor. Modified from Jang, H.R. & Rabb, H. Immune cells in experimental acute kidney injury, *Nature reviews Nephrology*. 2015;11:88-101





**Figure 2.** The regional immunologic response after AKI determines the consequence of renal injury, either in tissue repair and regeneration or in chronic inflammation with renal fibrosis. During adaptive repair, reparatory responses occur to restore the normal structure and tissue homeostasis in the kidney. Tolerogenic DCs, M2 macrophages and regulatory T cells modulate the renal immune response by direct cell-cell contact or by humoral mediators, leading to endothelial and renal tubular repair and regeneration. However, when there is prolonged or severe AKI, maladaptive repair process begins resulting in chronic inflammation and tissue fibrosis. Inflammatory cells continue to infiltrate into renal interstitium with secretion of pro-inflammatory/pro-fibrotic cytokines. Growth-arrested tubular cells also participate in the formation of pro-fibrotic renal microenvironment with secretion of profibrotic cytokines and growth factors. The interaction of pericyte and endothelial cells is impaired due to endothelial injury during AKI, which leads to activation and proliferation of pericytes. Active pericytes evolve into scar-producing myofibroblasts, which induces renal fibrosis and clinically leads to chronic kidney disease. Abbreviations: AKI, acute kidney injury; DCs, dendritic cells; DN T cell, double negative T cell. Modified from Jang, H.R. & Rabb, H. Immune cells in experimental acute kidney injury, *Nature reviews Nephrology*. 2015;11:88-101