Lymphocyte Function in Human Acute Kidney Injury

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Keywords

Acute kidney injury · Lymphocytes · Inflammation · T cells

Abstract

Acute kidney injury (AKI) has been recognised as an inflammatory condition with serious short- and long-term complications. Animal studies primarily using models of ischaemia reperfusion injury or caecal ligation and perforation have clearly demonstrated that inflammatory cells contribute to the initiation, propagation and recovery phase of AKI and that lymphocytes have a key role in these processes. Less is known about their involvement in common types of human AKI. This paper summarises the key findings of experimental AKI studies and limited human data with particular focus on the role of T-lymphocytes.

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Introduction

Acute kidney injury (AKI) is a serious complication of critical illness impacting short- and long-term prognosis. Although it is a heterogeneous syndrome with multiple potential aetiologies, there is increasing evidence that inflammatory processes contribute to the initiation, propagation and recovery phase of renal injury. Experimental studies in animals and preliminary human data have suggested that lymphocytes play a key role.

The aims of this paper are to review the biological roles of different sub-types of lymphocytes (Table 1), to summarise the key findings of experimental AKI studies and to describe the data in human AKI.

Role of Lymphocytes in Experimental AKI

The basic premise that AKI is caused by ischaemia of the vulnerable renal tubular cells has led to the predominant use of ischaemia-reperfusion injury (IRI) models involving clamping and release of renal arteries in experimental models of AKI. This has generated studies involving rodents constitutively deficient in specific immune cells that have demonstrated the important role of lymphocytes in different types and phases of AKI [1–11] (Tables 2, 3). Classically associated with immune responses elicited by specific antigen recognition, these key components of the adaptive immune system have been proven to have a prominent role in experimental AKI both in the absence of antigen and before such time as an antigenic response could be generated.

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Table 1. Potential roles of different lymphocyte subtypes in AKI

Lymphocyte type	Typical mediators	Physiological functions in AKI
Naïve CD4+ T-cell		– Differentiation into effector cells following activation by specific antigens and co-stimulatory signals
CD8+ cytotoxic T-cell	Perforin Granzymes TNF- α IFN- γ	– Destruction of cells – Increased IFN- γ production – Primary response often requires help from CD4+ T-cells
Th1 cell	IL-2 IFN- γ TNF- β	– Promotion of inflammation – Activation of CD8+ cells, macrophages and B-cells
Th2 cell	IL-3 IL-4 IL-5 IL-10 IL-13	– Activation and recruitment of B-cells, mast cells, basophils, eosinophils and macrophages – Inhibition of inflammatory response
Th-17 cell	IL-17 IL-22	– Neutrophil recruitment – Promotion of inflammation
T-regulatory cell (T-reg)	TGF- β IL-35 IL-10 Granzymes	– Inhibition of dendritic cells – Cytotoxic to target cells – Inhibition of inflammatory cells – Depletion of available IL-2
CD4– CD8– DN T-cell	IL-10	– Protective role in ischaemic injury
NK T-cell	IFN- γ IL-2 IL-4 IL-10 IL-18	– Recognition of lipids and glycolipids presented by the CD1 molecule rather than peptide MHCs – Induction of renal inflammation and injury or protection from it depending on the context of activation – Contribution to neutrophil activation
B-cell		– Antibody production – Activation of T-cells
B-regulatory cell	IL-10 TGF- β IL-35	– Skewing of T-cell differentiation in favour of immunosuppressive T-cells – Suppression of Th1 and Th17 differentiation – Decrease of number of pro-inflammatory lymphocytes

Th1, T-helper 1; Th2, T-helper 2; Th-17, T-helper 17; NK, natural killer; AKI, acute kidney injury; CD, cluster of differentiation; DN, double negative; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; TGF, transforming growth factor; TNF, tumour necrosis factor.

Cluster of differentiation (CD) 4+ T-cells and subsequent cell lines, in particular T helper 1 (Th1) and T helper 2 cells (Th2 cells) (Fig. 1) have been shown to contribute to the pathophysiology of AKI. Th1 cells produce pro-inflammatory interferon-gamma (IFN- γ) and interleukin (IL)-2, whereas Th2 cells secrete predominantly IL-4 and IL-10 (both anti-inflammatory) and other cytokines. Both cell types appear to be involved in the early injury phase of IRI [5, 12] (Table 2). Mice deficient in CD4 and CD8 were functionally and structurally protected in IRI

[5]. Reconstitution with transfer of CD4+ restored the injured phenotype but not with CD8+ cells alone. Other experiments confirmed that CD4+ and CD8+ T cells isolated from post-ischaemic kidneys produced more IFN- γ and tumour necrosis factor- α compared to normal or sham-operated kidneys [8], again confirming a key role of T cells in AKI.

There is also evidence that activated CD4+ and CD8+ T cells are present in the recovery phase at 6 weeks post-IRI and may be implicated in ongoing damage [10].

Table 2. Role of lymphocytes in acute kidney injury in selected experimental murine models

Publication	Experimental murine model	Key findings	Phase of AKI
Burne et al. [5]	Aseptic bilateral IRI	<ul style="list-style-type: none"> – CD4+ T-cell deficiency was renoprotective – CD8+ T-cell deficiency was not renoprotective – The effect of CD4+ T-cells was dependent on CD28 and IFN-γ 	Injury: 24 and 48 h
Ascon et al. [6]	Aseptic bilateral IRI	<ul style="list-style-type: none"> – Role of CD3+ T-cells and NK T-cells in early IRI – Increased production of TNF-α and IFN-γ at 24 h – Transfer of infiltrating lymphocytes to T-cell deficient mice was renoprotective at 24, 48, and 72 h 	Injury: 24, 48, and 72 h
Wang et al. [7]	Aseptic unilateral IRI and contralateral nephrectomy	<ul style="list-style-type: none"> – Reduced CD4+ T-cell infiltration following IRI in IL-16 deficient mice 	Injury: 48 h
Zhang et al. [20]	Aseptic unilateral IRI and contralateral nephrectomy	<ul style="list-style-type: none"> – NK T-cells induced apoptotic death of tubular epithelial cells and contributed to effects of IRI 	Injury: 48 h
Ascon et al. [8]	Healthy mice and aseptic bilateral IRI	<ul style="list-style-type: none"> – Identification of resident CD4+, CD8+ and CD4– CD8– DN T-cells in healthy mouse kidney – Increased production of IFN-γ and TNF-α by CD4+ and CD8+ T-cells after IRI – Suggestion that cells harbored in the kidney are implicated in the immune response of IRI 	Injury: 0, 3, and 24 h
Kinsey et al. [3]	Bilateral IRI	<ul style="list-style-type: none"> – T-regs modulate kidney injury after IRI – Depletion of T-regs resulted in more neutrophil and macrophage infiltration after IRI but did not affect CD4+ T-cells or B-cells – Renoprotective effects of T-regs was IL-10 dependent 	Injury: 24 h
Lee et al. [13]	Septic caecal ligation and puncture versus IRI	<ul style="list-style-type: none"> – Septic injury was associated with increased IL-10, massive immune cell apoptosis and increased T-regs – T-reg depletion was renoprotective before caecal ligation and puncture but aggravated injury in IRI – Blocking IL-10 was renoprotective in septic mice but had no effect in IRI 	Injury: 24 h
Liu et al. [21]	Acute cisplatin nephrotoxicity	<ul style="list-style-type: none"> – CD4+ and CD8+ T-cells were direct mediators of experimental cisplatin nephrotoxicity 	Injury: 24 h
Burne-Taney et al. [9]	Aseptic bilateral IRI	<ul style="list-style-type: none"> – B-cell deficient mice were protected from effects of IRI at 24, 48 and 72 h despite similar levels of CD4+ cell infiltration 	Injury: 24–72 h
Martina et al. [4]	Bilateral IRI	<ul style="list-style-type: none"> – DN T-cells are a subset of the resident T-cell population in the kidney and have an anti-inflammatory role in early IRI – The role of DN T-cells is IL-10 dependent 	Injury: 0–72 h
Gandolfo et al. [2]	Unilateral and bilateral IRI	<ul style="list-style-type: none"> – Significant trafficking of T-regs at day 3 and 10 post-IRI promoting repair through modulation of pro-inflammatory cytokine production of other T-cell subsets 	Repair: 3–10 days
Jang et al. [11]	Aseptic unilateral IRI	<ul style="list-style-type: none"> – B-cells limited the repair process after IRI 	Repair: 3–28 days
Ascon et al. [10]	Aseptic bilateral and unilateral IRI	<ul style="list-style-type: none"> – Increase of CD8+ T-cells 2 weeks after IRI – Infiltration of CD4+ and CD8+ T-cells 6 weeks after IRI – Decrease of CD4+ NK T-cells and CD19+ B cells 6 and 11 weeks post IRI – Depletion of CD4+ and CD8+ T-cells before IRI resulted in less medullary damage and cytokine expression 	Long term: 2, 6, and 11 weeks post-injury

AKI, acute kidney injury; ATN, acute tubular necrosis; CD, cluster of differentiation; DN, double negative; IFN, interferon; IRI, ischaemia reperfusion injury; NK, natural killer; TNF, tumour necrosis factor.

T-regulatory cells (T-regs) are a subset of CD4+ T cells. Activated T-regs can directly suppress the activation and proliferation of T cells and even induce apoptosis via secretion of anti-inflammatory cytokines (IL-10, IL-35 and transforming growth factor-beta) and depletion of available IL-2. There is compelling data that

they play an important role in experimental AKI. Aseptic IRI models showed that T-regs attenuated injury in the initial phase and enhanced repair (Table 2). Depletion of T-regs using an anti-CD25 monoclonal antibody exacerbated renal tubular damage, reduced tubular proliferation and increased pro-inflammatory cytokine produc-

Table 3. Role of lymphocyte subsets in different AKI phases based on experimental models

Lymphocyte subset	Early injury	Late injury/recovery phase	Key interactions
Cytotoxic T-cells	<ul style="list-style-type: none"> – CD8+ cells up-regulate IFN-γ 24 h post IRI [6] – The absence does not protect against AKI [5] 	<ul style="list-style-type: none"> – Infiltration may persist for several weeks post AKI and may be implicated in chronic damage [10] 	<ul style="list-style-type: none"> – Likely to act synergistically with multiple cell lines through cytokine production and co-stimulation
T-helper cells	<ul style="list-style-type: none"> – Critical role in early AKI – Deficiency or depletion before IRI is protective [5, 12] 	<ul style="list-style-type: none"> – Infiltration may persist for several weeks post AKI [10] 	<ul style="list-style-type: none"> – Promote infiltration by neutrophils, macrophages and dendritic cells in the injured kidney
T-regs	<ul style="list-style-type: none"> – Attenuation of renal injury through IL-10 mediated suppression of the innate immune system [3] 	<ul style="list-style-type: none"> – Likely to be a key modulator. – Associated with enhanced tubular recovery and repair 	<ul style="list-style-type: none"> – Inhibit pro-inflammatory cytokines from T-helper cells [2] – Likely to help switching of macrophages to an anti-inflammatory M2 phenotype in recovery phase
DN T-cells	<ul style="list-style-type: none"> – Early expansion post-IRI. – Adoptive transfer is protective and mediated via IL-10 [4] 	<ul style="list-style-type: none"> – No data available 	<ul style="list-style-type: none"> – Likely to act synergistically with multiple cell lines through cytokine production and co-stimulation
B-cells	<ul style="list-style-type: none"> – Attenuation of IRI in B-cell-deficient mice [9] 	<ul style="list-style-type: none"> – Infiltrating cells mature to plasma cells and have a deleterious effect on tubular recovery [11] 	<ul style="list-style-type: none"> – Likely to act synergistically with multiple cell lines through cytokine production and co-stimulation
NK T-cells	<ul style="list-style-type: none"> – Very early infiltration and IFN-γ production appear to have deleterious effects [6, 18]. – Type II NK T-cell subtype may be protective [28] 	<ul style="list-style-type: none"> – No data available 	<ul style="list-style-type: none"> – May have a positive feedback loop of activation and IFN-γ production with neutrophils

AKI, acute kidney injury; CD, cluster of differentiation; DN, double negative; IFN, interferon; IL, interleukin; IRI, ischaemia reperfusion injury; NK, natural killer.

tion after IRI [2]. Adoptive transfer of T-regs improved repair and reduced the generation of pro-inflammatory cytokines.

Interestingly, there is also evidence of a possible opposing role in relation to the role of T-regs in IRI and sepsis. Their depletion pre-injury was found to aggravate renal injury in a murine IRI model, whereas their depletion in a septic model using caecal ligation and puncture was reno-protective [13].

It has been suggested that CD4/CD8 double negative (DN) T cells are also involved in the pathogenesis of IRI. In a murine bilateral IRI model, DN T cells expanded early to become dominant subsets and maintained dominance until 24 h after IRI [4]. Global gene expression analysis of DN T cells before and after IRI revealed 16-fold upregulation of the gene encoding the anti-inflammatory cytokine IL-10 suggesting a protective role. This beneficial effect was elegantly demonstrated by adoptive transfer of DN T-cells into wild-type mice 24 h before IRI. The animals were significantly protected

from AKI compared to control mice transfused unseparated T cells. The administration of a monoclonal antibody that blocked IL-10 receptors inhibited the protective effect.

Although B cells are classically associated with antibody production, they have an important role in the cellular response via T-cell activation and cytokine generation too [14]. They have been implicated in the injury phase of septic AKI and also been shown to impair recovery after ischaemic AKI [9, 11]. Following IRI, B cells comprised important constituents of the immune cell infiltrate, and B-cell deficiency conferred protection from IRI [9]. B-cell-deficient mice had attenuated renal injury, increased tubular proliferation and higher IL-10 expression [9, 11]. Adoptive transfer of serum into B-cell-deficient mice partially restored the ischemic phenotype [9] and transfer of B cells reduced tubular proliferation and increased tubular atrophy [11].

Conversely, a protective antibody-mediated role for B-cell involvement in AKI has also been identified via

Fig. 1. Differentiation of T cells. Th, T-helper; DN, double negative; T-reg, T regulatory cell.

natural immunoglobulin (Ig) M – anti-leukocyte antibodies (ALA), which are characteristically increased early during inflammatory and infective conditions [15]. Natural IgM-ALA inhibits pro-inflammatory T cells from proliferating and producing IFN- γ and IL-17 in response to noxious stimuli. In IgM knock-out mice, natural IgM enriched in ALA protected against IRI [15].

In the last decade, B-regulatory cells (B-regs) have been appreciated as important types of B cells with distinct and contrasting suppressive and tolerogenic properties [16]. They are able to suppress Th1 and Th17 cell differentiation [16]. Their exact role in human AKI remains unclear.

Natural killer (NK) T cells are a heterogeneous group of T cells that share properties of both T cells and NK cells. Many of these cells recognize lipids and glycolipids from organisms presented by the non-polymorphic CD1d molecule, an antigen-presenting molecule rather than peptide-major histocompatibility complexes. The

clinical potential of NK T cells lies in the rapid release of cytokines (such as IL-2, IFN- γ , tumour necrosis factor- α , and IL-4) and the ability to induce renal inflammation and injury or protect from it depending on the context of their activation [17]. Post IRI, infiltrating NK T-cells have been shown to stimulate IFN- γ production and neutrophil infiltration [18]. Importantly, neutrophils may cause further activation of NK T-cells via IL-17, which ultimately creates a deleterious positive feedback loop and significant IFN- γ production in ischaemic kidneys [19].

Role of Lymphocytes in Specific Forms of AKI

A major pitfall of experimental AKI is the inherent difference between the rodent and human immune system and kidneys themselves. In addition, most experimental models entail a single insult (often IRI) with a clearly defined time of onset using animals without any comorbid

conditions. Therefore, it remains uncertain whether these findings can be applied to humans.

However, there is evidence that lymphocytes play a role in specific types of human AKI, including interstitial nephritis, lupus nephritis and transplant rejection. This is perhaps not surprising given that the uninjured kidney contains several types of T cells in the renal interstitium that can be activated locally.

Interstitial Nephritis

Acute interstitial nephritis is an important cause of AKI resulting from immune-mediated tubule-interstitial injury, typically triggered by drugs, infection or immune disorders. The hallmarks of drug-induced acute interstitial nephritis are interstitial oedema and interstitial inflammation with an inflammatory infiltrate typically composed of CD4+ T cells and mononuclear cells with a variable number of plasma cells and eosinophils. It is thought that the T cells orchestrating injury are activated locally in the kidney by APCs or migrate from neighbouring lymph nodes and cause a cascade of inflammatory interstitial reactions marked by cytokine release and subsequent tubule-interstitial injury [22].

Lymphocytic infiltrates are also regular features of infection-associated interstitial nephritis, for instance, HIV-associated nephropathy [23].

Lupus Nephritis

Lupus nephritis is an important cause of AKI and chronic kidney disease. Accumulating evidence suggests that anti-double-stranded DNA antibodies play a critical role in the pathogenesis. Typically, immune complex deposition is accompanied by complement activation, infiltration of immune cells, cytokine release and oxidative damage [24]. Both, B and T lymphocytes and their mediators participate at all levels in disease pathogenesis from initiation, perpetuation to tissue destruction and disease relapse [25].

Transplant Rejection

T cells are central to the process of AKI due to transplant rejection through allorecognition of foreign antigens and the induction of inflammatory processes leading to organ damage [26].

Potential Role of Lymphocytes in AKI during Critical Illness

The main causes of AKI in critically ill patients are sepsis, haemodynamic instability, volume depletion and nephrotoxicity, often in combination and succession. The exact role of lymphocytes in this setting is not known especially since renal biopsies are rarely performed.

Limited data from humans showed that patients with septic AKI had significantly higher serum levels of soluble CD25, a marker that is representative of T-regs compared to septic patients without AKI and non-septic patients [27]. The results of an active study exploring immune function in human AKI are awaited (ClinicalTrials.gov Identifier: NCT02470507).

Conclusions

There is overwhelming evidence that lymphocytes play a key role in experimental AKI. Their role is also well established in acute interstitial nephritis, lupus nephritis and transplant rejection. However, the contributions of different lymphocyte subsets in human AKI in the setting of critical illness are not fully established and results of ongoing studies are awaited.

Disclosure Statement

The authors have no conflicts of interest to declare.

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