The Role of Myeloid Cells in Acute Kidney Injury and Kidney Repair

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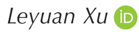

Abstract

AKI remains highly prevalent, yet no optimal therapy is available to prevent it or promote recovery after initial insult. Experimental studies have demonstrated that both innate and adaptive immune responses play a central role during AKI. In response to injury, myeloid cells are first recruited and activated on the basis of specific signals from the damaged microenvironment. The subsequent recruitment and activation state of the immune cells depends on the stage of injury and recovery, reflecting a dynamic and diverse spectrum of immunophenotypes. In this review, we highlight our current understanding of the mechanisms by which myeloid cells contribute to injury, repair, and fibrosis after AKI.

KIDNEY360 2: 1852–1864, 2021. doi: https://doi.org/10.34067/KID.0000672021

Introduction

Kidneys maintain fluid, electrolyte and acid-base balance, excrete waste products, and regulate BP with high metabolic activity, which renders them susceptible to injury from aseptic insults to asepsis. These insults cause AKI characterized by a rapid decline in renal function. AKI is common in patients who are hospitalized, especially those in the intensive care unit. Patients who survive AKI are at an 8.8-fold increased risk for developing CKD and a 3.3-fold increased risk for ESKD (1–3). However, optimal therapy has not yet been developed to prevent such injury or promote recovery after AKI. Understanding the underlying mechanism(s) of AKI will help identify novel targets and develop therapeutic strategies for AKI to mitigate the burden of this disease.

The pathophysiology of AKI ranges from diminished renal perfusion with no structural damage to intrinsic kidney disease, including vascular endothelial injury, GN, acute interstitial nephritis, acute tubular injury, and obstruction of urinary outflow with associated apoptosis of tubular cells. Recently, the advanced technology of single-cell RNA sequencing (scRNA-seq) or single-nucleus RNA-seq allows researchers to unbiasedly map the cellular complexity of the kidneys, in both human and mice, and to study the mechanism(s) of AKI at the single-cell level. For instance, unsupervised clustering of scRNA-seq data from the allograft biopsy specimen (histologically read as mixed rejection) reveals most native kidney cell types and all of the major immune cells, including monocytes, mast cells, T cells, B cells, and plasma cells (4). Consistently, the data from mouse models of AKI (*i.e.*, ischemia-reperfusion injury [IRI], reversible unilateral ureter obstruction) show most cell types that comprise the kidney with a multitude of resident and infiltrating immune cells, including monocytes/macrophages, neutrophils, dendritic cells (DCs), T cells, B cells, and natural killer cells (5–8). The clinical and experimental evidence suggest that both myeloid and lymphoid cells are involved in immune-mediating damage to renal tubular cells and in recovery from AKI (9–12). This review will focus on the role(s) of myeloid cells in the course of AKI and kidney repair (briefly summarized in Figure 1).

The Origins and Plasticity of Myeloid Cells in the Kidney

One of the hallmarks of most immune cells is their continuous replenishment from precursors that are ultimately derived from bone marrow–derived hematopoietic stem cells (HSCs) (13). In kidney, all myeloid cells, including granulocytes (neutrophils, eosinophils, basophils, and mast cells [in a small number]), monocytes, and DCs are derived from HSCs, except tissue-resident macrophages (Table 1). Studies also show that kidney-resident mononuclear phagocytes are derived from the yolk sac at the embryogenesis stages. The kidney macrophages are originated from HSCs and replaced continually from DC precursors (21–23).

Regardless of the initial cause of injury, sepsis or kidney damage *via* aseptic insult, the innate immune system is first activated not only by the resident immune cells but also by a rapid influx of myeloid cells from systemic immune factors during AKI. Injury leads to oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction in both endothelial and tubular epithelial cells, in which c-Jun N-terminal kinase, caspase cascade, and receptor-interacting protein kinase 1 pathways are activated to induce apoptosis (predominantly) and necrosis, and downstream proinflammatory cytokines are also activated to promote the inflammatory milieu (24,25).

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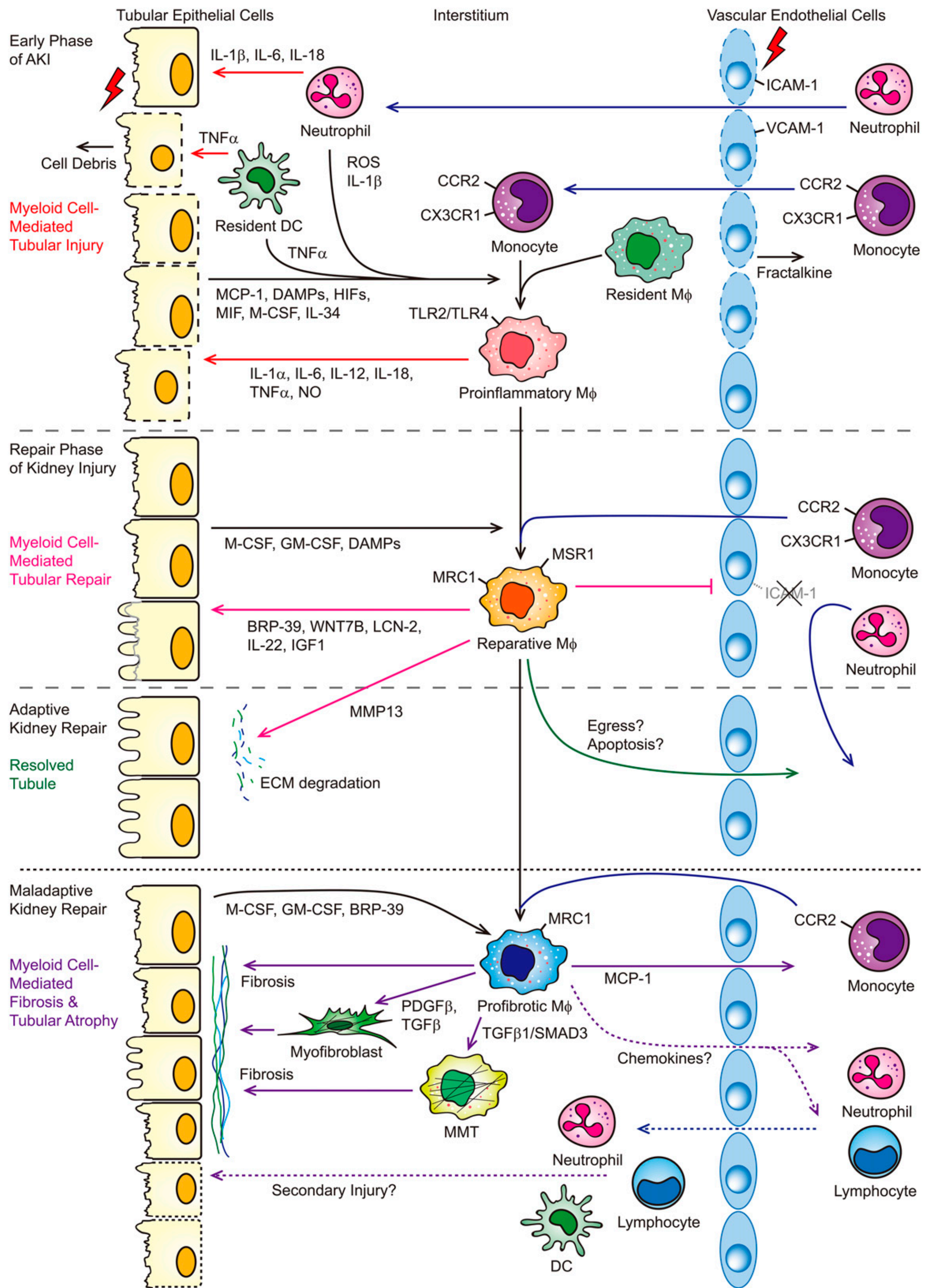

Figure 1. | Myeloid cells mediate tubular injury and repair following AKI. In response to AKI, endothelial cells express fractalkine (CX3CL1) and ICAM-1 and VCAM-1 to recruit neutrophils and monocytes into the injured kidney and promote leukocyte-endothelial cell adhesion, respectively. IL-1β, IL-6, IL-18, and TNF-α released from neutrophils/dendritic cells induce apoptosis and/or necrosis of tubular epithelial cells. Proinflammatory cytokines, ROS, HIFs, and DAMPs released by degranulating PMNs and injured or dying tubular cells lead to the proinflammatory activation of macrophages. These proinflammatory macrophages then subsequently produce proinflammatory cytokines and NO, which lead to further tubular injury. The inflammatory milieu in the early phase is later reversed during the repair phase. Downregulation of ICAM-1 and VCAM-1 limits inflammatory cell infiltration. Macrophage growth and differentiation factors M-CSF

Figure 1 | *Continued*. and GM-CSF and DAMPs released from the tubular epithelial cells lead to the reparative activation of macrophages. BRP-39, WNT7B, LCN2, IL-22, and IGF1 secreted from reparative macrophages promote tubular cell proliferation and/or repair. In the setting of adaptive kidney repair, macrophages release MMP13 to facilitate degradation of ECM, which is initially deposited after injury to aid repair, and macrophage egress and/or apoptosis after the injury is resolved. However, in the setting of maladaptive kidney repair, macrophages persist within the kidney. Macrophage growth factors, M-CSF, GM-CSF, and BRP-39 released from sustained injured tubular epithelial cells promote further recruitment and/or retention of macrophages and polarize macrophages into a profibrotic phenotype. Profibrotic macrophages or MMTs can promote kidney fibrosis directly and indirectly by activating interstitial myofibroblasts and contribute to the secondary tubular injury. BRP-39, breast regression protein 39; DAMP, damage-associated molecular pattern; DC, dendritic cell; ECM, extracellular matrix; HIFs, hypoxia-inducible factors; ICAM-1, intracellular adhesion molecule 1; LCN-2, lipocalin-2; Mϕ, macrophage; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage colony-stimulating factor; MIF, macrophage migration inhibitory factor; MMP13, matrix metallopeptidase 13; MMT, macrophage-to-myofibroblast transition; MRC1, mannose receptor 1; MSR1, macrophage scavenger receptor 1; NO, nitric oxide; PDGFβ, platelet-derived growth factor subunit B; ROS, reactive oxygen species; SMAD3, mothers against decapentaplegic homolog 3; TLR, Toll-like receptor; VCAM-1, vascular cell adhesion molecule-1, WNT7B, Wnt family member 7B.

Injured or necrotic tubular cells, in turn, release damage-associated molecular patterns (DAMPs) and hypoxia-inducible factors, which are responsible for recruiting the circulating immune cells to the injured kidney. Both resident macrophages and DCs ensure inflammation by releasing proinflammatory cytokines, such as TNF-α, which is amplified by infiltrated myeloid cells through chemokines and cytokines (26,27).

Because of their heterogeneity and inherent plasticity, monocytes/macrophages may adopt different phenotypes in response to the microenvironmental stimuli, such as injury, cell debris, DAMPs, and extracellular matrix (ECM). For instance, using fate mapping, four subsets of mononuclear phagocytes (macrophages and DCs) found in the kidneys from adult mice are phenotypically, functionally, and transcriptionally distinct from each other (28). These mononuclear phagocytes exhibit unique age-dependent developmental heterogeneity. A recent scRNA-seq analysis identifies 13 subtypes of myeloid cells, and the pseudotime analysis reveals a dynamic change in monocyte and macrophage phenotypes during AKI progression after ureter obstruction and AKI regression after reversible ureter obstruction (7).

Myeloid Cell–Mediated Inflammation during Initial Kidney Injury

In the obstructive kidney or ischemic kidney after reperfusion, neutrophils are first recruited followed by expansion of macrophages and T cells, which persist beyond the reversal of obstruction or in the repair phase after IRI. In response to ischemic injury, endothelial cells increase expression of intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1, which are important determinants of leukocyte-endothelial cell adhesion (29,30). The infiltrated neutrophils release reactive oxygen species (ROS), cytokines, and proteases, which promote kidney injury (31). Genetically knocking out *Icam1*, using neutralizing antibody against ICAM-1, or directly depleting neutrophils, using anti–mouse neutrophil serum, protects mice against ischemic injury (32). In addition, histone secretion from ischemically injured tubular epithelial cells primes neutrophils to form neutrophil extracellular traps (NETs), which further induce tubular epithelial cell death and accelerate NETs production in fresh neutrophils (33). Pretreatment with inhibitors of NETs formation protects kidney from injury, which can be enhanced by dual inhibition of NETs formation and tubular cell necrosis (33). After cisplatin-induced AKI, neutrophil infiltration into kidneys is mediated by caspase-1–dependent proinflammatory cytokines, including IL-1β, IL-18, and IL-6. Knocking out caspase-1 protects mice against cisplatin-induced acute renal failure (34). However, individually inhibiting these cytokines or blocking neutrophil infiltration is insufficient to protect against cisplatin-induced acute renal failure (Table 2) (35), suggesting neutrophils are not essential for cisplatin-induced AKI.

One of the major cell types that accumulate around injured tubules in the kidney after AKI is the mononuclear phagocyte or macrophage (37). After neutrophils, the early recruitment of monocytes to the kidney after ischemic or obstructive injury is primarily mediated by CCR2 (the chemokine receptor for CCL2) and CX3CR1 (the chemokine receptor for CX3CL1) (41). At the single-cell level, both *Ly6c2+* proinflammatory macrophages and reparative arginase-1+ (*Arg1+*) macrophages, which predominantly accumulate in the kidney 2 days after obstructive injury, express *Cx3cr1* and *Ccr2*, suggesting these macrophages are derived from recruited monocytes (7). Consistently, in the kidney 2 days after ischemic injury, proximal tubular epithelial cells of failed repair are projected to signal monocytes *via* a variety of chemokines and proinflammatory cytokines, including *Ccl2*, *Ccl5*, *Ccl7*, *Ccl8*, *Cxcl10*, *Csf1*, and *Tnf* (6). The immunostaining of kidney sections 1 day after ischemic injury confirms that monocyte chemoattractant protein-1 (also known as *Ccl2*) is predominantly expressed in the tubular epithelial cells (42), whereas CX3CL1 (also known as fractalkine) is highly expressed in the injured endothelial cells (43). In response to proinflammatory cytokines, tubular epithelial cells upregulate macrophage colony-stimulating factor 1, IL-34, and macrophage migration inhibitory factor (*Mif*), which signal macrophage proliferation and survival through CSF-1 receptor and CD74, respectively (44,52,53,55,56). Knocking out *Ccr2* or *Mif* or depleting macrophages protects mice against ischemic injury in the early phase (Table 2) (37,38,41–45), suggesting macrophages are detrimental in the early phase of AKI. Kidney-resident macrophages (KRMs) that are undifferentiated from the infiltrating macrophages present as a distinct cellular subpopulation after AKI (57). However, injury can result in KRMs reprogramming transcriptomes more closely to those found in kidney development (postnatal day 7), *i.e.*, enriched Wingless-type MMTV integration site

Table 1. The markers and origin(s) of myeloid cells in kidney

Myeloid Cell Type	Marker(s)	Origin	Reference
Neutrophil	CD45$^+$, CD16$^+$, CD66b$^+$ (homo), CD45$^+$, Ly-6G/Gr-1$^+$, CD11b$^+$ (mus)	HSCs	(14)
Eosinophil	CCR3$^+$, CD125$^+$, CD49d$^+$, Siglec-8$^+$ (homo), Siglec-F (mus)	HSCs	(15)
Basophil	FcεRIα^+, CD49b$^+$, CD203c$^+$, Thy1$^+$, c-Kit$^-$, FcγR$^+$, Siglec-2$^+$ (homo)	HSCs	(16)
Mast cell	CD11b$^-$, Lin$^-$, c-Kit^{high}, MITF$^+$, CD33$^+$ (homo), FcεRIα^+, IL-3Rα^+, CD203c$^+$	HSCs	(17)
Monocyte/macrophage	CD11b$^+$, CSF1R$^+$, Ly-6C$^+$, Ly-6G$^-$, F4/80$^+$ (mus), EMR1$^+$ (homo), CX3CR1$^+$, CCR2$^+$	HSCs	(18)
Resident macrophage	CD45$^+$, CD11b^{low}, F4/80^{high}, Ly-6C$^-$ (yolk sac EMP-derived resident macrophage)	Yolk sac EMPs, fetal liver EMPs, and HSCs	(19)
Dendritic cell	CD11c$^+$, MHC-II$^+$, CD103$^+$, CD11b^{low}, CX3CR1$^-$, F4/80$^-$, SIRP-α^- (CD103$^+$ renal DC), CD11b$^+$, CD103$^-$, CX3CR1$^+$, F4/80$^+$, SIRP-α^+ (CD11b$^+$ DC)	HSCs	(18,20)

homo, *Homo sapiens*; mus, *Mus musculus*; HSCs, hematopoietic stem cells; EMP, erythro-myeloid progenitor; DC, dendritic cell.

family (Wnt) signaling, indicating that mechanisms involved in kidney development may be functioning after injury in KRMs (57).

Mechanistically, in response to the local microenvironment with ROS and DAMPs released from neutrophils and injured/necrotic tubular cells, respectively, the recruited monocytes/macrophages and resident mononuclear phagocytes have been shown to differentiate into a proinflammatory state, partially mediated through Toll-like receptors (TLR2 and TLR4), and release proinflammatory cytokines, including IL-6, IL-12, and TNF-α and nitric oxide (NO) (11,24,37). NO can interact with ROS to generate cytotoxic peroxynitrites that leads to oxidative stress and apoptosis in tubular epithelial cells (11). However, similar to neutrophils, depleting macrophages or blocking macrophage infiltration is insufficient to protect mice against cisplatin-induced AKI (Table 2) (36), suggesting the role of myeloid cells in the pathogenicity of cisplatin-induced nephrotoxicity may differ from that of ischemic and obstructive injuries. Together, the current results suggest that macrophages are classically activated (M1) to promote kidney injury in the early phase of acute ischemic and obstructive injury.

In addition to macrophages, prolonged exposure of DCs to proinflammatory cytokines and/or DAMPs triggers DC maturation to activate T cells (58) and renal DCs to produce IFN-α, TNF-α, and IL-6 (59,60), suggesting DCs have a proinflammatory role in renal ischemic injury; however, some studies show that kidney DCs prevent ischemic tissue damage (61–63). For instance, blocking TNF-α *via* neutralizing binding protein or a pegylated form of soluble TNF receptor type 1 protects mice against renal ischemic and obstructive injury (64,65). Knocking out IL-6, IFN-γ/IL-12, or inducible NO synthase (iNOS; an enzyme to catalyze the production of NO) protects mice against renal ischemic injury (66–69). The data generated from the bulk RNA-seq analyses indicate that these oxidative stress- and hypoxia-initiated cascades of stress and immediate transcriptional responses in the early phase of AKI are largely conserved between mice and humans (70).

Myeloid Cell–Mediated Adaptive Kidney Repair

The inflammatory milieu is later reversed by the infiltrated/infiltrating cells that promote a reparative microenvironment by secreting anti-inflammatory cytokines. These cells include proreparative (also known as alternatively activated M2) macrophages that predominate between days 3 and 7 after ischemic injury (37). At the single-cell level, mannose receptor 1+ (Mrc1+) macrophages and Ccr2+ macrophages are predominantly found in the kidney 7 days after obstructive injury (7). Those Mrc1+ macrophages express multiple scavenger receptors, including *Mrc1*, *Fcrls*, *Stab1*, and *Igf1*, but downregulate MHC-II, suggesting the monocytes transition to a reparative state that can play a role in scavenging debris/excess ECM and kidney repair. Consistently, evidence shows that IFN-γ–primed proinflammatory macrophages switch to an anti-inflammatory (reparative) phenotype in the kidney 7 days after ischemic injury by upregulating *Arg1*, *Mrc1*, macrophage scavenger receptor 1, and *Igf1 via* STAT6 activation but downregulating *iNos* expression (37,71). Depleting macrophages during the repair phase diminishes kidney repair after ischemic injury (Table 2) (37,46,72), which can be recovered with reinjection of macrophages after depletion (73).

Mechanistically, tubular epithelial cells are involved in the activation of reparative macrophages through the production of macrophage growth factors, including macrophage colony-stimulating factor 1 and GM-CSF. Reparative macrophages are activated to express factors, including WNT7b, BRP-39 (also known as YKL-40, the orthologous human protein), and IL-22, that directly promote tubular repair after ischemic injury (46,74,75). For instance, depleting GM-CSF using neutralizing antibody during the repair phase attenuates the reparative macrophage activation and suppresses tubular proliferation after ischemic injury (71). DAMP released from injured and necrotic tubular epithelial cells induces proinflammatory macrophages *via* TLR4 to express IL-22, which promotes tubular epithelial cell proliferation and kidney

Table 2. Specific depletion of myeloid cells and its outcomes in the rodent models of AKI and kidney repair

Rodent Model(s)	Phase of Injury	Targeting Cell(s)	Depletion Method(s)	Major Finding(s)	Reference
Cisplatin-induced AKI	Early phase	Neutrophil	Injection (i.p.) of neutralizing Ab (RB6-8C5) against Ly-6G on days −1, 0, +1, and +2 relative to the day of cisplatin injection	Neutrophil depletion insufficiently protects against cisplatin-induced ARF.	(35)
	Early phase	Macrophage	Injection (i.v.) of liposomal-encapsulated clodronate 2 days before and 1 day after cisplatin injection	Depletion of CD11b+ macrophages insufficiently protects against cisplatin-induced ARF.	(36)
	Early phase	Macrophage	Knocking out *Cx3cr1* or administration of neutralizing Ab against CX3CR1 either 1 hour or 1 day after cisplatin injection	Blockage of CX3CR1 is insufficient to prevent cisplatin-induced ARF.	(36)
IRI	Early phase	Myeloid phagocytes (circulating monocyte, tissue macrophage, CD11c+ dendritic cell, and neutrophil)	Injection (i.p.) of liposomal-encapsulated clodronate on two successive days before IRI	Depletion of myeloid phagocytes before IRI protects tubular epithelial cells from injury and ameliorates the loss of renal function induced by IRI.	(37,38, 39,40)
	Early phase	Macrophage	Knocking out *Ccr2*, *Ccl2*, or *Cx3cr1*	Deletion of *Ccr2* and *Cx3cr1*, but not *Ccl2*, suppresses macrophage infiltration and protects kidneys from IRI.	(41,42)
	Early phase	Macrophage	Injection (i.p.) of neutralizing Ab against CX3CR1 1 hour before IRI	Neutralizing Ab against CX3CR1 partially suppresses macrophage infiltration and protects kidneys from IRI.	(43)
	Early phase	Macrophage	Administration (orally) of CCR2 antagonist (RS-504393) every 12 hours from the day of IRI or propagermanium, which targets glycosylphosphatidylinositol-anchored proteins that are closely associated with CCR2, from 8 days before IRI	Both RS-504393 and propagermanium suppress macrophage infiltration and protects against tubular necrosis after IRI.	(42)
	Early phase	Macrophage	Knocking out *Mif*	Deletion of *Mif* reduces kidney macrophage accumulation in the area of damaged tubules and associated inflammation and protects kidneys from IRI.	(44)
	Early phase	Leukocyte	Injection (s.c.) of CXCR4 antagonists, plerixafor (AMD3100) or its monocyclam analogue (AMD3465)	CXCR4 antagonists suppress CD11b+ (neutrophils and monocytes) and CD4+ lymphocytes 24 hours after	(45)

Table 2. (Continued)

Rodent Model(s)	Phase of Injury	Targeting Cell(s)	Depletion Method(s)	Major Finding(s)	Reference
			3.5 hours after IRI every 12 hours for 2 days	IRI, diminish epithelial and endothelial injury and interstitial inflammation, and ameliorate the loss of renal function induced by IRI.	
	Adaptive repair phase	Myeloid phagocytes (circulating monocyte, tissue macrophage, CD11c$^+$ dendritic cell, and neutrophil)	Injection (i.p.) of liposomal-encapsulated clodronate on two successive days 2 days after IRI	Depletion of myeloid phagocytes on day 3 after IRI diminishes tubular recovery from IRI, as shown in persistent luminal casts and decreased regenerating tubules.	(37)
	Adaptive repair phase	Macrophage	Injection (i.v.) diphtheria toxin to CD11b-DTR allele mice on day 3 and day 5 after IRI	Depletion of macrophages on day 3 and day 5 leads to a striking failure of normal regeneration of kidney tubule epithelium and normal functional recovery of the kidneys.	(46)
	Adaptive repair phase	Macrophage and dendritic cell	Injection (i.v.) diphtheria toxin to γ-GT Cre:CSF-1f/f:DTR mice	Proximal tubule–specific depletion of *Csf1* decreases reparative macrophage polarization, delays functional and structural recovery, and increases interstitial fibrosis.	(47)
	Adaptive repair phase	F4/80$^+$, CD11c$^+$ dendritic cell	Injection (i.v.) of liposomal-encapsulated clodronate on day 1 and day 3	Depletion of dendritic cells is associated with persistent kidney injury, apoptosis, inflammation, and impaired tubular cell proliferation.	(48)
	Maladaptive repair phase	Macrophage	Injection (i.v.) of liposomal-encapsulated clodronate on day 3 every 5 days thereafter until 8 weeks or every 7 days thereafter until 4 weeks after IRI	Depletion of macrophages attenuates interstitial fibrosis, inflammation, and the renal function impairment in the long-term (8 weeks) follow-up after IRI.	(49,50)
	Maladaptive repair phase	Macrophage	Knocking out Ccr2 or injection (i.p.) of CCR2 antagonist (RS102895) on day 7 after IRI and every 12 hours for 7 days	Blockage of MCP-1/CCR2 signaling markedly decreases macrophage infiltration and attenuates interstitial fibrosis and sustained inflammation during AKI-to-CKD transition.	(51)
	Maladaptive repair phase	Macrophage	Knocking out *Il34*	Deletion of *Il34* markedly suppresses macrophage proliferation and protects kidneys from AKI and subsequent CKD.	(52)

Table 2. (Continued)

Rodent Model(s)	Phase of Injury	Targeting Cell(s)	Depletion Method(s)	Major Finding(s)	Reference
Proximal tubule injury–mediated by diphtheria toxin in the Ggt1 DTR transgenic mice	Adaptive repair phase	Macrophage and dendritic cell	Injection (i.p.) of liposomal-encapsulated clodronate after DT injection every 3 days or injection of DT in the Ggt1/CD11c DTR double transgenic mice	Depletion of macrophages/dendritic cells induces a striking increase of tubular injury and kidney dysfunction and delays recovery after injury.	(53)
	Adaptive repair phase	Macrophage and dendritic cell	Knocking out *Csf1* or administration of CSF-1R inhibitor (GW2580, an inhibitor of c-fms, *via* gastric gavage) twice per day	Blocking CSF-1/CSF-1R signaling decreases macrophage/dendritic cell proliferation, markedly inhibits macrophage phenotype transition (from proinflammatory to reparative), and delays recovery from proximal tubule injury.	(53)
	Adaptive repair phase	Macrophage and dendritic cell	Injection (i.v.) diphtheria toxin to γ-GT Cre:CSF-1f/f:DTR mice	Proximal tubule–specific depletion of *Csf1* decreases reparative macrophage polarization, delays functional and structural recovery, and increases interstitial fibrosis.	(47)
Rhabdomyolysis (intramuscular injection of glycerol)-induced AKI	Early phase and maladaptive repair phase	Macrophage	Injection (i.p.) of liposomal-encapsulated clodronate 1 day before or after the glycerol injection	Depletion of macrophage before rhabdomyolysis improves animal survival and the eGFR at day 2 and subsequently attenuates interstitial fibrosis and inflammation 7 months after rhabdomyolysis.	(54)

i.p., intraperitoneal; Ab, antibody; ARF, acute renal failure; i.v., intravenous; IRI, ischemic-reperfusion injury; *Mif*, macrophage migration inhibitory factor; s.c., subcutaneous; DTR, diphtheria toxin receptor; MCP-1, monocyte chemoattractant protein-1; DT, diphtheria toxin.

repair (75). Of note, the downstream signaling of TLR4 is time dependent: early blockade of TLR4/IL-22 signaling prevents tubular necrosis, and late blockade of TLR4/IL-22 impairs tubular regeneration (75). In addition, macrophages can promote tubular repair indirectly. For instance, vascular-resident CD169+ macrophages prevent excessive inflammation in the kidney after ischemic injury by downregulating ICAM-1 expression on vascular endothelial cells (76). Depleting CD169+ cells enhances endothelial ICAM-1 expression, resulting in irreversible renal damage associated with infiltration of a large number of neutrophils (76).

Similarly to macrophages, DCs may contribute to the recovery process by a dynamic phenotype change from a proinflammatory to anti-inflammatory (expressing high levels of IL-10) state with modulation of immune response (48). After ischemic injury, oxidative stress can also activate DCs to express IFN regulatory factor 4, which attenuates secretion of proinflammatory cytokines from resident antigen-presenting cells and prevents excess ischemic damage (77). Depleting DCs during the repair phase leads to persistence of the inflammatory milieu, tubular injury, and apoptosis in both ischemic and nephrotoxic nephritis models (Table 2) (48,78).

Myeloid-derived suppressor cells are a heterogeneous population of cells, generally composed of progenitors and precursors of DCs, macrophages, and granulocytes at various stages of differentiation. Myeloid-derived suppressor cells can also be recruited into the injured kidneys after the interaction of CXCL1 and CXCL2 with their receptor CXCR2 (79,80) to protect the kidney from ischemic injury by suppressing effector T-cell activation and subsequently downregulating production of proinflammatory cytokines (IFN-γ, IL-1β, and IL-6) (80).

Myeloid Cell–Mediated Maladaptive Kidney Repair

In the event of optimal repair, deactivation or egress of macrophages is required for resolution of inflammation after ischemic injury. However, persistent parenchymal inflammation or more severe injury leads to macrophage persistence, which is strongly associated with renal fibrosis, tubular atrophy, and progressive CKD (81,82). For instance, knocking out IRAK-M, a cell-intrinsic pathway that suppresses TLR/IL-1R signaling, leads to persistence of proinflammatory macrophages and late tubular atrophy (83). Sustained tubular injury after ischemic injury leads to tubular expression of GM-CSF and BRP-39, which, in turn, activate interstitial macrophages to express monocyte chemoattractant protein-1 to recruit monocytes/macrophages and transition to a profibrotic phenotype, respectively (51,84). These profibrotic macrophages, a MRC1+ (CD206+) subset of reparative macrophages, persist in the kidney interstitium adjacent to nonrepaired tubules and promote kidney fibrosis directly or indirectly through myofibroblast activation in both human and mouse models (50,51,84–88). Long-term depletion of macrophages or blockade of certain macrophage homing signaling pathways attenuates late renal fibrosis after ischemic injury (Table 2) (49–51), which is also shown in the obstructive injury model (unilateral ureter obstruction) (89–91).

Macrophages isolated from kidney at the late stage of ischemic injury reveal high-level expression of *Lgals3* (also known as galectin-3), *Pdgfb*, *Tgfb1*, *Tgfb2*, and *Egf* (profibrotic growth factors), but low-level expression of *Nos2* and *Arg1* (proinflammatory and reparative phenotype markers) (84). Myeloid cell–specific knockout of *Lgals3* reduces late fibrosis severity but does not alter macrophage recruitment in the kidney after obstructive injury, suggesting galectin-3 promotes interstitial fibrosis through fibroblast/myofibroblast activation. Macrophages are also a major source for matrix metalloproteinases (MMPs) (6,7), which play a complex role in the development of kidney fibrosis by promoting fibrosis and degrading ECM. For instance, whole-body knockout of *Mmp2* and *Mmp9*, but not *Mmp12*, promotes macrophage accumulation and kidney fibrosis after obstructive injury (40,92,93), suggesting MMP2 and MMP9, but not MMP12, are required for macrophage migration within the tubulointerstitium. Macrophage-specific knockout of twist-related protein 1, a transcription factor that regulates the expression of several MMPs, such as MMP13, to facilitate ECM degradation, promotes kidney fibrosis after obstructive injury (94,95). In addition, macrophages may potentially promote renal fibrosis directly *via* macrophage-myofibroblast transition (MMT), which is driven by TGF-β1/SMAD3 signaling *via* an Src-centric regulatory network (96). These MMT cells are recognized by coexpressing macrophage marker CD68 and myofibroblast marker α-smooth muscle actin in the diseased kidneys in both mouse obstructive model and human biopsy specimen (96–98). The MMTs may serve as a key checkpoint in the progression of chronic inflammation to renal fibrosis (99). In contrast, evidence shows that DCs do not directly promote kidney fibrosis after obstructive injury (100), suggesting fibrosis is mainly driven by profibrotic macrophages. However, DCs adopt a proinflammatory phenotype and become more effective antigen-presenting cells to activate T cells after ischemic and obstructive injury (62,100,101).

Discussion and Outlook

To date, the roles of myeloid cells in AKI and kidney repair remain heavily studied in rodent models of kidney injury using ischemia/reperfusion, ureteral obstruction, or nephrotoxin administration. By manipulating models and controlling time, researchers can reveal the biologic responses that lead to inflammation, cell death/proliferation, kidney repair, and long-term fibrosis after the injury. Among the myeloid cells (Table 1), the roles of eosinophils and basophils in AKI have been reported in a small number of case reports and observational studies (102,103). In contrast, mast cells have been shown to not necessarily be involved in the development of kidney pathology, but could have a beneficial role in restoration of normal kidney homeostasis (104). Neutrophils, macrophages, and DCs become the major players in response to AKI and kidney repair (Table 2). Consistently, an increase in the number of neutrophils and macrophages has also been observed in the biopsy specimens from patients with sepsis-induced AKI, acute tubular necrosis and acute tubular injury, and DCs in the biopsy specimens from patients with GN

(105–108). However, the substantial increase of understanding rodent AKI has not led to effective therapies to treat patients with AKI. The disconnection between rodent models and human AKI may be due to many causes, including, but not limited to, distinct pathogenic pathways that are activated by different initial stressors and distinct biologic and immune responses that are not identical between rodent models and human diseases. For instance, in the rodent models of AKI, myeloid cells, such as macrophages and DCs, generally promote kidney injury in the early phase, kidney repair afterwards, and kidney fibrosis in the maladaptive kidney repair after IRI; however, depletion of macrophages or DCs does not protect kidneys from cisplatin-induced AKI, suggesting the involvement of myeloid cells is likely different not only depending on the time but also the types of injury.

Recently, kidney tissues obtained from patients with diabetes undergoing partial or radical nephrectomy, kidney transplant biopsy, normal kidney tissues obtained at least 2 cm away from tumor tissue, and fetal kidneys from gestational weeks 7–25 have been subjected to the scRNA-seq or single-nucleus RNA-seq to understand the pathogenesis of diabetic nephropathy, chronic transplant rejection, and kidney development in humans (4,109–113). The application of single-cell technologies on human AKI biopsy specimens holds the potential to fill the gap for understanding the pathogenesis of human AKI, especially the roles of myeloid cells in AKI, and how it may differ from those in the rodent models of AKI. Such technology, however, relies on tissue dissociation and does not offer spatial context, *e.g.*, what specific type(s) of myeloid cells are adjacent to the tubular epithelial/endothelial cells at the point of injury, apoptosis, necrosis, repair, proliferation, or fibrosis (to the interstitial fibroblast/myofibroblasts). Recent advanced mass cytometry technology, *i.e.*, imaging mass cytometry supports simultaneous detection of >40 protein markers on a single section of formalin-fixed, paraffin-embedded kidney biopsy specimen, termed Kidney-MAPPS (multiplexed antibody-based profiling with preservation of spatial context) (114). In addition to single-cell technologies, the application of Kidney-MAPPS holds the potential to greatly expand our understanding of the role of myeloid cells in human AKI.

Disclosures

The author has nothing to disclose.

Funding

This work was supported by National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases grant K01 DK120783.

Author Contributions

L. Xu conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

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Received: February 1, 2021 **Accepted:** September 17, 2021