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The varying roles of macrophages in kidney injury and repair

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Abstract

Purpose of review: Macrophages play an important role in regulating homeostasis, kidney injury, repair, and tissue fibrogenesis. This review will discuss recent advances that explore the novel subsets and functions of macrophage in the pathogenesis of kidney damage and hypertension.

Recent Findings: Macrophages differentiate into a variety of subsets in microenvironment-dependent manner. While the M1/M2 nomenclature is still applied in considering the pro- versus anti-inflammatory effects of macrophages in kidney injury, novel and accurate macrophage phenotypes are defined by flow cytometric markers and single-Cell RNA signatures. Studies exploring the crosstalk between macrophages and other cells are rapidly advancing with the additional recognition of exosome trafficking between cells. Using murine conditional mutants, actions of macrophage can be defined more precisely than in bone marrow transfer models. Some studies revealed the opposing effects of the same protein in renal parenchymal cells and macrophages, highlighting a need for the development of cell-specific immune therapies for translation.

Summary: Macrophage-targeted therapies hold potential for limiting kidney injury and hypertension. To realize this potential, future studies will be required to understand precise mechanisms in macrophage polarization, crosstalk, proliferation, and maturation in the setting of renal disease.

Keywords

Macrophage; acute kidney injury; chronic kidney disease; hypertension

Introduction

Macrophages are prototypical cells from the innate immune system, that were originally identified by their capacity for phagocytosis[1]. However, macrophages are multifunctional and perform diverse roles by integrating endocrine/paracrine signals or ligand-receptor signals in the local tissue environment[2–5]. In the kidney, the macrophages have been divided into infiltrating “bone marrow-derived macrophages” and long-lived “tissue-resident macrophages”[6–9]. The macrophages can either aggravate kidney injury by stimulating

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Conflicts of interest

None.

inflammation or perform a protective role by facilitating tissue repair[10–13]. Several groups have elucidated the role of macrophages in regulating the progression of kidney fibrosis, a final common pathway of chronic kidney disease (CKD) leading to end-stage renal disease (ESRD)[14–16]. Pro-inflammatory macrophages can exacerbate blood pressure elevation and target organ damage in hypertension[17–19], whereas VEGF-C-positive macrophages limit salt-sensitive hypertensive responses by preventing interstitial sodium accumulation [20]. In this review, we highlight advances in understanding in the roles of macrophages in acute kidney injury (AKI), CKD, and hypertension, focusing on the regulation of macrophage phenotype, surface marker expression, and the crosstalk between macrophages and kidney parenchymal cells or other immune cells.

Macrophage origin and polarization

Following the initial discovery of macrophages as a subset of bone marrow-derived phagocytic cells[1], lineage tracing techniques divided macrophages into two subsets based on their origin: embryonic-derived resident macrophages or bone marrow-derived infiltrating macrophages[21–23]. These two populations have diverse roles in maintaining homeostasis, responses to injury, and tissue repair. Embryonic macrophages are hematopoietic stem cell (HSC)-derived cells in the yolk sac, which contribute to the innate immune functions, red blood cell maturation, and development of fetal architecture[24]. Embryonic macrophages also migrate to various organs during development and mature into tissue-resident macrophages in the brain, heart, and liver. However, the kidney-resident macrophages are fetal monocyte-derived FLT3 negative macrophages but not yolk sac-derived[25]. In response to initial injury, resident macrophages sense damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs), leading to augmented phagocytosis, antigen processing and presentation, and secretion of pro-inflammatory cytokines[26]. Bone marrow-derived monocytes are then recruited into injured tissues and mature into monocyte-derived macrophages, resulting in augmented inflammatory responses.

Another classification of macrophages defines them as M1 (classically activated) or M2 (alternatively activated). *In vitro* experiments revealed that LPS and IFN-γ stimulation facilitates M1 polarization and pro-inflammatory cytokine secretion, whereas interleukin-4 (IL-4) and interleukin-13 (IL-13) administration leads to M2 polarization and anti-inflammatory cytokine production[27]. Although the definition of M1/M2 macrophage provided a simplified paradigm through which to study the phenotype and function of macrophages *in vitro*, the *in vivo* environment is more complex and dynamic, and clearly polarized M1 or M2 phenotypes are not uniformly observed in tissues during disease [28]. For example, a recent clinical study identified more than nine different types of macrophage polarization [29]. Thus, the M1/M2 paradigm has limitations in explaining the phenotype of a mixed subset of macrophages that show plasticity. Studies using single-cell RNA-Seq have highlighted macrophage phenotype changes that are inconsistent with the M1/M2 paradigm and revealed novel macrophage populations *in vivo* [30, 31]. While we employ the M1/M2 paradigm in some parts of this review for simplicity, we acknowledge that a more complex subset description may be necessary in certain disease settings.

Macrophages in acute kidney injury

Macrophages are involved in both the injury and repair phase of ischemic AKI, and the actions of macrophages are phenotype dependent[32, 33]. Lee *et al.*[34] found that the recruitment of iNOS-positive pro-inflammatory macrophages is dramatically increased within the first 48 hours after ischemic AKI, whereas renal macrophages in the later phases of AKI are mannose receptor and arginase 1 (Arg1) positive non-inflammatory macrophages. Within 24 hours after experimental AKI, circulating $Ly6C^{high}$ monocytes migrate to the inflamed site of kidney via the Chemokine Receptor (CCR2) and CX3C chemokine receptor 1 (CX3CR1)[35–37]. Mincle is a transmembrane pattern recognition receptor that is detected in $CD68^{+}iNOS^{+}$ M1 macrophages and is essential for the maintenance of M1 phenotype[38]. High-mobility group box 1 (HMGB1) as an extracellularly released nuclear factor can stimulate macrophage recruitment at day 5 after ischemic AKI[39]. During the maturation of these $Ly6C^{high}$ monocytes, the polarization towards a pro-inflammatory (M1) phenotype is strengthened and enforced by pro-inflammatory cytokines and DAMPs[40–42]. Suppressor of cytokine signaling 3 (SOCS3) in proximal tubular cells also exacerbates M1 polarization highlighting the reciprocal effects of renal parenchymal tissues on infiltrating macrophage phenotype during ischemic AKI. Exosomes deliver messages between cells via their packaged molecules. Tubular epithelial cell-derived exosomal RNA and microRNAs stimulate M1 macrophage responses and kidney injury during AKI[43–45]. Macrophage depletion prior to ischemic AKI protects against renal functional decline and tubular injury, whereas adoptive transfer of IFN-γ-induced M1 macrophages to macrophage deficient mice restores kidney injury after ischemic AKI[34, 46]. Interleukin-1β (IL-1β) as an M1 cytokine can stimulates kidney injury and inflammation through IL-1 receptor. Compared to the wide-type (WT) controls, the total numbers of $CD64^{+}$ macrophages were similar in the kidneys of IL-1 receptor knock out (IL1R KO) mice during cisplatin AKI, whereas the total numbers of $CD11b^{+}TNF^{+}$ macrophages in IL1R KO kidneys was reduced[47], indicating that IL-1R activation may exaggerate cisplatin nephrotoxicity by promoting TNF generation in myeloid cells. While pro-inflammatory (M1) macrophages can remove DAMPs and dead cells, the prolonged activation of pro-inflammatory (M1) macrophages leads to extensive inflammation and delayed tissue repair.

Anti-inflammatory (M2) macrophages are essential for the proliferation and regeneration of damaged epithelial cells and are increased at day 3 after ischemic AKI[34, 48, 49]. Baek *et al.*[50] found a phenotype conversion from $Ly6G^{-}F4/80^{+}NOS\text{-}2^{+}TNF\alpha^{+}$ (M1 like) to $Ly6G^{-}F4/80^{+}Arginase\text{-}1^{+}Dectin\text{-}1^{+}CD206^{+}$ (M2 like) macrophages at the later phase after ischemic AKI. M2-like macrophages exhibit beneficial effects after ischemic AKI, such as clearance of intraluminal debris, promotion of epithelial regeneration, activation of regulatory T cells, and attenuation of kidney inflammation[33, 51–53]. $Ly6C^{intermediate}$ macrophages facilitate kidney injury repair, whereas $Ly6C^{low}$ macrophages promote kidney fibrosis in the long term after ischemic AKI[37, 54]. Stimulating mineralocorticoid receptors on myeloid cells inhibits the polarization of macrophage toward M2 phenotype, thereby promoting the AKI to CKD transition[55]. $F4/80^{hi}Fcgr4^{hi}Fcgr1^{+}$ macrophages are newly defined kidney resident macrophages distinct from infiltrating monocytes[56]. These kidney

resident macrophages display a unique signature inconsistent with either M1 or M2 paradigm and promote tissue repair by activating the wingless-type MMTV integration site family (Wnt) pathway[56, 57].

Macrophages in chronic kidney disease

Bone marrow-derived monocytes are precursors to the macrophages that accumulate in the injured kidney and proliferate locally during chronic kidney injury[58–60]. Accordingly, blockade of colony-stimulating factor 1 receptor (CSF1R) significantly inhibits monocyte proliferation in the bone marrow, which limits renal macrophage accumulation and attenuates kidney injury during nephrotoxic nephritis (NTN) and kidney allograft rejection[10, 61]. CCL2 mediates the migration of bone marrow-derived monocyte to the injured kidney, such that CCL2 blockade attenuates glomerular and interstitial infiltration of pro-inflammatory macrophages[62–64]. Other chemokines such as CX3CL1, CXCL16, and macrophage migration inhibitory factor (MIF) also contribute to renal macrophage recruitment in kidney disease[65–68]. Complements and deposited immunoglobulin can stimulate macrophage recruitment and activation through a fragment receptor (FcR)-dependent manner[69, 70], but may not be required for vascular monocyte-driven autoimmune damage to the kidney[71]. By contrast, we found that the mononuclear cell chemokine C-C motif chemokine 5 (CCL5) constrains CCL2 expression, macrophage infiltration, and kidney damage and fibrosis in hypertension via blood pressure-independent mechanisms, emphasizing a complex network of overlapping chemokines[19].

Recruited macrophages then produce a range of cytokines including tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), which in turn exacerbate M1 polarization and CKD[16, 72, 73]. Renal parenchyma-derived DAMPs such as DNA, high mobility group protein B1 (HMGB1), and C-reactive protein also augment the renal accumulation of pro-inflammatory macrophages and aggravate kidney injury in several CKD models [74–78]. As direct evidence of M1 macrophage contributions to CKD pathogenesis, the adoptive transfer of M1 polarized macrophages exacerbates glomerular and interstitial injury in CKD[73, 79]. Inversely, blockade M1 macrophage signaling pathways attenuates kidney injury[80–82]. In some renal diseases, the macrophage is not a major source of TNF-α that injures the kidney[83]. However, in an autoimmune nephritis model, we found that $CD11b^{+}Ly6C^{hi}$ macrophage-derived TNF-α stimulates kidney injury and interstitial fibrosis by inducing epithelial necroptosis[16]. The renin-angiotensin system (RAS) activation generally stimulates tissue injury and inflammation. For example, activating the type 1 angiotensin receptor (AT1R) in renal parenchymal cells drives kidney injury, blood pressure elevation, and cardiac hypertrophy[84, 85]. By contrast, in our hands, AT1R activation on T lymphocytes blunts Th1 responses and reduces pro-inflammatory macrophage differentiation[86]. Similarly, stimulating the AT1R on myeloid cells attenuates M1 pro-inflammatory cytokine production, leading to reduced kidney injury and fibrosis in rodent models of kidney injury induced by hypertension, obstruction, and obesity[87–89].

Anti-inflammatory (M2) macrophages are recruited in the chronic phase of the disease, leading to kidney repair and/or fibrosis. Clinical studies have revealed a correlation between renal accumulation of $CD163^{+}$ (M2) macrophages and the severity of kidney fibrosis in

patients with immunoglobulin A (IgA) nephropathy, type 2 diabetes, or chronic kidney allograft injury[90–93]. Similarly, M2 macrophages promote glomerulosclerosis and interstitial fibrosis in rodent models of NTN[94, 95]. Adoptive transfer of splenic macrophages pre-conditioned with IL-10/TGF-β protect against kidney injury in adriamycin nephrosis[96, 97]. Macrophage-derived matrix metallopeptidases also regulate matrix deposition and degradation in renal disease[98, 99]. For example, our studies revealed that Twist1 in $CD11b^{+}Ly6C^{low}$ macrophages decreases matrix accumulation in in obstructed kidneys by promoting MMP13 production[15]. By contrast, Twist1 in the distal nephron but not infiltrating macrophages stimulates kidney inflammation and fibrosis during aristolochic acid nephropathy, showing that the actions of macrophage Twist1 in CKD pathogenesis is context-dependent[100]. Wnt / b-catenin signaling plays a key role in renal fibrogenesis, and we previously reported that blocking Wnt secretion by disrupting the catalytic activity of the Wnt-acyl transferase Porcupine ameliorates fibrosis in the obstructed kidney[101]. However, deleting Porcupine selectively from myeloid cells exaggerates kidney scar formation and renal inflammation[102]. Thus, in selected injury models, macrophage-derived Twist1 and Porcupine both play renoprotective roles in contrast to their pathogenic actions within injured kidney tubular cells.

Macrophages in hypertension

Angiotensin (Ang) II regulates blood pressure levels and natriuresis via the AT1R activation on renal parenchymal cells[84]. Ang II also regulates the differentiation and infiltration of pro-inflammatory monocyte/macrophages in the hypertensive kidney[87, 103, 104]. Bone marrow-derived monocytes accumulate in the vascular wall and kidney to exacerbate n RAS-induced hypertension[17, 105]. Hypertensive patients have increased numbers of pro-inflammatory monocytes and elevated levels of cytokines in the circulation[106, 107]. Inversely, deleting monocytes and macrophages in mice limits blood pressure elevation and vascular damages during chronic Ang II infusion, whereas adoptive transfer of wild type monocytes restores the Ang II-induced hypertensive response and target organ damage[17, 108]. In contrast to the protective effects of global AT1 receptor (AT1R) blockade, we have found previously that AT1R deletion on myeloid populations can aggravate target organ damage during hypertension, highlighting a protective effect of AT1R activation on immune cells[85, 109, 110]. In salt-sensitive hypertension, high salt concentrations facilitate macrophages polarization toward a pro-inflammatory (M1) phenotype and blunts IL-4/IL-13-induced anti-inflammatory (M2) differentiation[111–113]. In the spontaneously hypertensive rat, $CD161a^{+}CD68^{+}$ pro-inflammatory macrophages infiltrate the renal medulla and exacerbate hypertensive responses[114]. However, the phenotype of macrophages is not static during the evolution of hypertension. Moore *et al.*[115] found that a shift from M1 to the M2 phenotype occurs at the 7–14 days after Ang II infusion with consequent increases in tissue fibrosis.

Infiltrating pro-inflammatory macrophages can regulate blood pressure by producing a variety of pro-inflammatory cytokines such as TNF-α and IL-1β. Renal parenchyma-derived TNF-α exacerbates blood pressure levels and causes targets organ damage by impairing nitric oxide production[116, 117]. Similarly, IL-1β stimulates hypertensive responses and kidney damage through IL-1 receptor activation [87, 118]. In our hands, IL-1 receptor

activation suppressed the maturation of NO-expressing $Ly6C^{+}Ly6G^{-}$ macrophages with consequent inhibition of the NKCC2 sodium cotransporter[119]. Macrophages can also regulate hypertensive end-organ damage via blood pressure-independent mechanisms. Accordingly, deficiency in CCR2 or colony-stimulating factor 1 (CSF-1) reduces renal macrophage recruitment and both kidney and vascular damage in Ang II-induced hypertension[120–122].

Nevertheless, the role of macrophages in hypertension is also tissue-dependent, as dermal macrophages attenuate sodium retention and salt-sensitive hypertension by stimulating lymphangiogenesis[20]. The transcription factor tonicity-responsive enhancer-binding protein (TONEBP) in kidney macrophages also facilitates NOS2-dependent NO production leading to increased vasodilation and sodium excretion[111, 119]. Similarly, cyclooxygenase-2 (COX2) in skin macrophages stimulates M2 polarization and inhibits salt-sensitive hypertension via vascular endothelial growth factor C (VEGF-C)- dependent lymphangiogenesis[123]. Finally, endothelin-1 (ET-1) mediates vasoconstriction via receptors on vascular smooth muscle cells, but, endothelin-B receptor (ETBR) deficiency on myeloid cells also attenuates blood pressure elevation and endothelial dysfunction without impacting macrophage polarization in Ang II-induced hypertension[124].

Conclusions

Monocytes/macrophages are recruited and activated by diverse chemokines and play a critical role in renal injury, repair, and fibrosis. Although the simplified pro-inflammatory (M1) and anti-inflammatory (M2) macrophage paradigm has been widely used, macrophages also regulate the process of wound repair, pro-/anti-fibrogenesis, and tissue regeneration through complex phenotypes than the simple, dichotomous paradigm. Moreover, differentiation of macrophages shows plasticity during renal disease pathogenesis, leading researchers to explore new combinations of surface markers to distinguish macrophage subpopulation. Several proteins including AT1R, Twist1, and Porcupine on renal parenchymal and myeloid cells serve opposing functions during CKD and hypertension. Thus, targeting macrophages to limit kidney injury and blood pressure elevation will require incisive and cell-directed strategies.

Thus, therapies targeting the macrophage in renal disease will require a clearer understanding of macrophage functions at each stage of injury or repair. Several questions linger: How does the microenvironment in injured kidneys impact macrophage phenotype? What are the key mechanisms regulating macrophage phenotype switching? How can a stable, therapeutic macrophage phenotype be established following renal injury? What are the mechanisms controlling the self-renewal of kidney resident macrophage? What is the nature of the crosstalk between resident and infiltrating macrophages following a kidney insult? Finally, how can new tools such as single-Cell RNA sequencing be harnessed to identify and promote healthful macrophage subpopulations in the injured kidney? Future studies will address these and other key questions to shape innate immune responses that can and limit renal damage and fibrosis and drive kidney repair.

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Key points

Macrophages are critical in maintaining kidney health and in instigating both kidney damage and repair.

The macrophage phenotype depends on the renal microenvironment and changes in different phases of kidney disease.

Macrophages have a wide range of phenotypes beyond M1 and M2.

Signaling pathways in macrophages and renal parenchymal cells may exhibit opposite effects during the pathogenesis of kidney disease.