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STATE OF THE ART REVIEW

Crosstalk between macrophages and adjacent cells in AKI to CKD transition

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ABSTRACT

Acute kidney injury (AKI), triggered by ischemia, sepsis, toxicity, or obstruction, is marked by a rapid impairment of renal function and could lead to the initiation and advancement of chronic kidney disease (CKD). The concept of AKI to CKD transition has gained much interest. Despite a series of studies highlighting the diverse roles of renal macrophages in the immune response following AKI, the intricate mechanisms of macrophage-driven cell–cell communication in AKI to CKD transition remains incompletely understood. In this review, we introduce the dynamic phenotype change of macrophages under the different stages of kidney injury. Importantly, we present novel perspectives on the extensive interaction of renal macrophages with adjacent cells, including tubular epithelial cells, vascular endothelial cells, fibroblasts, and other immune cells via soluble factors, extracellular vesicles, and direct contact, to facilitate the transition from AKI to CKD. Additionally, we summarize the potential therapeutic strategies based on the adverse macrophage-neighboring cell crosstalk.

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Introduction

Acute kidney injury (AKI) complicates approximately 10–15% of hospitalizations and is independently associated with an elevated risk of mortality [1]. According to the 2012 KDIGO guidelines, AKI can be diagnosed based on one of the following criteria: an increase in serum creatinine of ≥0.3 mg/dL (26.5 μmol/L) within 48 h, a 1.5-fold increase in serum creatinine from baseline, or less than 0.5 mL/kg/h urine output for 6 h [2]. Conversely, chronic kidney disease (CKD) is marked by abnormalities in kidney structure or function lasting for more than 3 months, with poor implications for health [2,3]. Growing evidence from clinical studies has revealed that patients with AKI significantly increase the risk of the progression of CKD [4,5]. Within a 3-year follow-up period, a cohort study found that 24.6% of patients with AKI developed CKD [6]. Notably, a large population study demonstrated that regardless of the severity of the AKI episode and proteinuria status, and even when post-episode kidney function is clearly recovered, an episode of AKI is associated with subsequent increased renal function decline lasting up to 10 years [7]. Although the process by which AKI contributes to the development of CKD in humans remains unclear, some mechanisms have been proposed in most animal studies, such as tubular dedifferentiation and atrophy, capillary rarefaction, persistent inflammation, and extracellular matrix (ECM) remodeling after AKI [8]. Recently, studies on macrophage-driven cell damage and persistent inflammation in the AKI to CKD transition have generated widespread interest [9,10].

Macrophages, as the major innate immune cells in the kidney, are involved in early inflammatory response and the balance of reparative and maladaptive kidney repair, due to their inherent heterogeneity and plasticity [11]. Several studies of single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics revealed that macrophage differentiation and its intercellular communication play a critical role in the transition of AKI to CKD [10,12–14]. Renal macrophages can release signals that promote immune cell recruitment, tubular injury or repair, fibroblast activation, and vascular remodeling through direct contact, soluble cytokines, and extracellular vesicles (EVs) [14–16]. In return, those adjacent cells could stimulate renal macrophages to proliferate and change phenotypes to adjust to the kidney-specific microenvironment [17]. Understanding the interactions between macrophages and their neighboring cells during kidney injury and tissue remodeling holds significant potential for identifying therapeutic targets capable of suppressing AKI to CKD transition.

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This review introduces the current research on renal macrophage phenotypes in AKI to CKD transition and focuses on the intercellular signaling between macrophages and adjacent cells involved in the transition from AKI to CKD. In addition, we highlight potential therapeutic strategies based on the adverse macrophage-adjacent cell crosstalk.

The phenotypes and functions of renal macrophages in AKI to CKD transition

Previous studies have suggested that macrophages can be divided into two subtypes based on stimulation *in vitro*: classic proinflammatory phenotype (M1 macrophages, defined by expression of iNOS and CD86) and alternative anti-inflammatory phenotype (M2 macrophages, defined by expression of arginase 1 (Arg1) and CD206). Additionally, M2 macrophages can be further subdivided into three subpopulations (M2a, M2b, M2c), depending on different in vitro stimuli and functions [11,18,19]. Notably, the complex microenvironment following kidney injury means that these single-stimulus-based macrophage subsets might not accurately reflect the pathological transition from AKI to CKD [20–22]. Current studies believe that renal macrophages can be broadly divided into kidney-resident macrophages (KRMs) and monocyte-derived macrophages (moMφs). A standard lineage tracing in mice found that KRMs, mainly derived from embryonic progenitors (yolk sac and fetal liver), expand and mature parallel with kidney growth after birth [22,23]. They demonstrate abilities in renal microenvironment homeostasis, immune surveillance, and tissue repair [24,25]. By contrast, circulating moMφs are primarily proinflammatory phenotypes with high levels of chemokines and cytokines and promote ECM remodeling [14,26]. Overall, both KRMs and moMφs have fluid spectrums of phenotypes.

Single-cell RNA sequencing and spatial transcriptomics provide new insight into characterizing KRMs. Cell surface markers (*Cd74* and *Cd81*) were defined as the characterization of KRMs in multiple species such as mouse, rat, pig, and human kidneys [27]. This lays the groundwork for subsequent research into the phenotypic changes of renal resident macrophages. After kidney injury, the KRMs exhibit significant proliferative characteristics and differentiate from a proliferative and immature state into repair-promoting macrophages, which facilitates angiogenesis and the proliferation of tubular epithelial cells (TECs) [14]. Further, the major histocompatibility complex class II (MHC-II) expression of KRMs is absent in the injury phase but reappears in the healing phase after AKI. This phenotype switch may influence the antigen presentation to $CD4^+$T cells and decrease subsequent chronic inflammation [28]. Even though tissue-resident macrophages can be replaced by bone marrow-derived progenitors in other organs, such as the skin and intestine, KRMs mainly self-renew *in situ* rather than receiving inputs from the bone marrow after AKI in mice [28]. Dick S.A. et al. used parabiotic and genetic fate mapping and developed a classification of three resident macrophage subpopulations in the kidney: TLF^{hi} (characterized by expressing *Timd4*, *Lyve1*, and *Folr2*), $Ccr2^+$, and MHC^{hi} populations [23]. Each subset presents a unique expression profile and life cycle. It was reported that $Ccr2^+$ macrophages were highly replaced by blood monocytes, whereas TLF^+ macrophages in particular received minimal monocyte input. Notably, as mice develop, the proportion of the TLF^+ population in the kidney gradually decreases to be absent, while the $Ccr2^+$ population gradually increases to become the main part. Although this study focused on the phenotype change in the murine developmental processes, it provided novel insight for studying the dynamic change of KRM populations after AKI. Yao et al. identified four distinct KRM subsets in the murine model of ischemia–reperfusion injury (IRI): MHC-II^{hi} KRMs, $Ccl4^{hi}$ KRMs, $Mrc1^{hi}$ KRMs, and $Slc40a1^{hi}$ KRMs. KRMs with high expression of *Ccl4* present the highest inflammation scores in the early stages of AKI, as they express the pro-inflammatory chemokines *Ccl3* and *Ccl4*, which recruit other immune cells to infiltrate the damaged kidneys [29]. Cheung et al. utilized spatial transcriptomics to classify seven unique KRM subsets corresponding to regions of the nephron and revealed that multiple subpopulations undergo significant changes in their spatial location and transcriptomic profiles from the acute phase to the chronic phase after kidney injury in mice, compared to the normal kidney [30]. This alteration did not recover even four weeks after injury, indicating a critical chronic immune dysfunction in the transition from AKI to CKD. The current understanding of phenotypes and functions of KRMs during the transition from AKI to CKD is limited and requires further research in the future.

When encountering various types of kidney injuries or stimuli by the kidney microenvironment, recruited moMφs experience significant changes in both numbers and phenotypes. In mice, differential expression of lymphocyte antigen 6C (Ly6C) present unique moMφ subpopulations after AKI: Ly6C high ($Ly6C^{hi}$), Ly6C intermediate ($Ly6C^{inter}$), and Ly6C low ($Ly\text{-}6C^{low}$) populations [21]. It has been reported that $S100a8/a9^{hi}$ $Ly6C^{hi}$ moMφs are the earliest monocyte-derived responders to kidney injury signals and interact with KRMs to initiate and amplify renal inflammation via the Toll-like receptor 4 (TLR4) pathway [29]. Evidence indicates that circulating $Ly6C^+$ monocytes are preferentially recruited into the glomerular capillaries by chemokines such as *Cxcl1*, *Ccl2*, and *Ccl3* released by renal tubule epithelial cells at 2 h post-injury [29]. This recruitment is also induced by TNF expressed by endothelial cells [31]. Conway et al. revealed that the $Ly6C^{hi}$ monocytes recruited early to the kidney subsequently transform toward Arg1-positive macrophages, which showed pro-inflammatory and pro-fibrotic behavior [20]. Similarly, bone marrow-derived ECM remodeling-associated macrophages, which express Arg1, appear in the early phase of kidney injury and adopt a proinflammatory phenotype persistently, which may be the critical issue for unsolved inflammation and progressive kidney fibrosis [14]. Notably, $Ly6C^{hi}$ macrophages were observed to differentiate into the $Ccr2^+$macrophage subset in late kidney injury. Despite consistent expression of Ccr2, their transcriptome is similar to that of KRMs [20]. It is unclear whether transitioned $Ccr2^+$

macrophages remain detrimental. In addition, Spp1^{+} macrophages were shown to originate from Ly6C^{hi} monocytes, which are mobilized by platelet-derived chemokine CXCL4 in the IR-induced AKI murine model [32]. This population is characterized by high expression of *Spp1*, *Arg1*, *Fn1*, and *Apoe*. Ouyang et al. integrated 15 single-cell RNA-sequencing datasets across multiple healthy and fibrotic organs in humans, including those in the kidney [33]. This study revealed that the proportion of Spp1^{+} macrophages is 17.3% in healthy control, 25.8% in AKI, and 23.7% in CKD and proposed that the conserved differentiation trajectory from monocytes to Spp1^{+} macrophages is driven by inflammatory signals in fibrotic kidneys.

Unlike proinflammatory Ly6C^{hi} moMφs, Ly6C^{low} moMφs appear to play a profibrotic role. A significant number of Ly6C^{low} moMφs are observed in both acute and chronic phases post-IRI in murine kidneys, where they contribute to the transdifferentiation of fibroblasts into myofibroblasts, thereby exacerbating AKI [34]. Ly6C^{low} macrophages have been shown to differentiate from Ly6C^{hi} moMφs and their transcriptional profile is characteristic of M2-like macrophages [35]. In conclusion, we have shed new insight into macrophage classification and described dynamic changes of KRM and moMφ phenotypes driven by complex signals in AKI and AKI to CKD transition (Figure 1).

Intercellular crosstalk of renal macrophages in AKI to CKD transition

Renal macrophages are scattered throughout the kidney, from the cortex to the medulla and papilla, which allows them to interact with parenchymal cells, mesenchymal cells, and other immune cells [30]. The growing evidence has gained consensus that macrophage-driving cell–cell communication plays a critical role in promoting AKI to CKD progression [12,36] (Figure 2).

The crosstalk between renal macrophages and tubular epithelial cells

Tubular epithelial cells are the predominant cell type in the kidney, especially the proximal tubules, which play crucial roles in nutrient absorption, barrier protection, and immune regulation [37]. The crosstalk between renal macrophages and TECs through complex intercellular mediators is one of the driving mechanisms for the progression of kidney fibrosis.

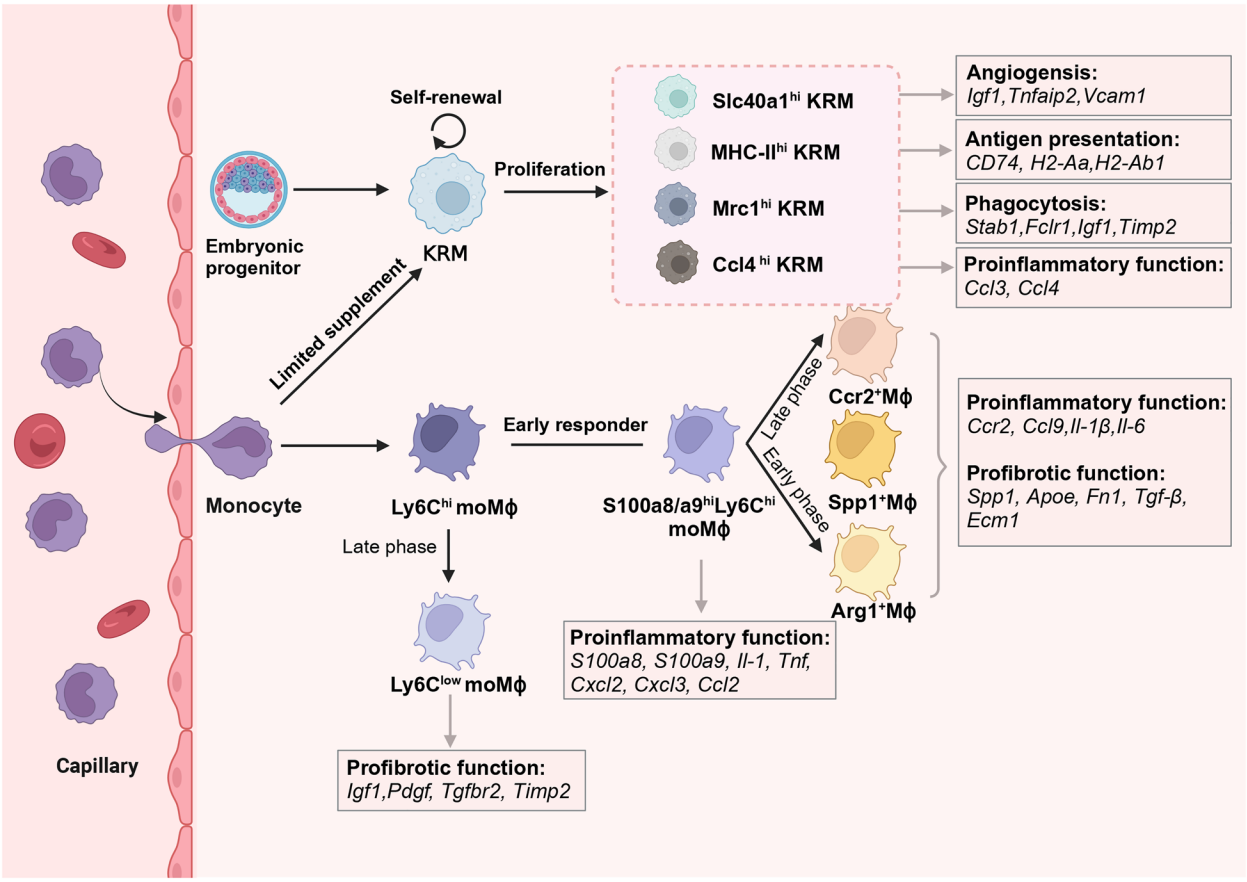

Figure 1. The current research of monocyte and resident macrophage differentiation in AKI to CKD transition. Following kidney injury, KRMs mainly undergo self-renewal and receive minimal contribution from circulating monocytes. Four selected KRM subsets present distinct functions. Additionally, a great number of Ly6C^{hi} monocytes infiltrate into the injured kidney and the S100a9^{hi}Ly6C^{hi} population represents the early blood-derived responder. Notably, Ly6C^{hi} moMφs primarily differentiate into several types of macrophages from the early to late phase of kidney injury, including the Arg1^{+}, Ccr2^{+}, Spp1^{+}, and Ly6C^{low} populations. Each subset's main functions and transcriptome signature are in the corresponding boxes. The black arrow means differentiation (created by biorender.com).

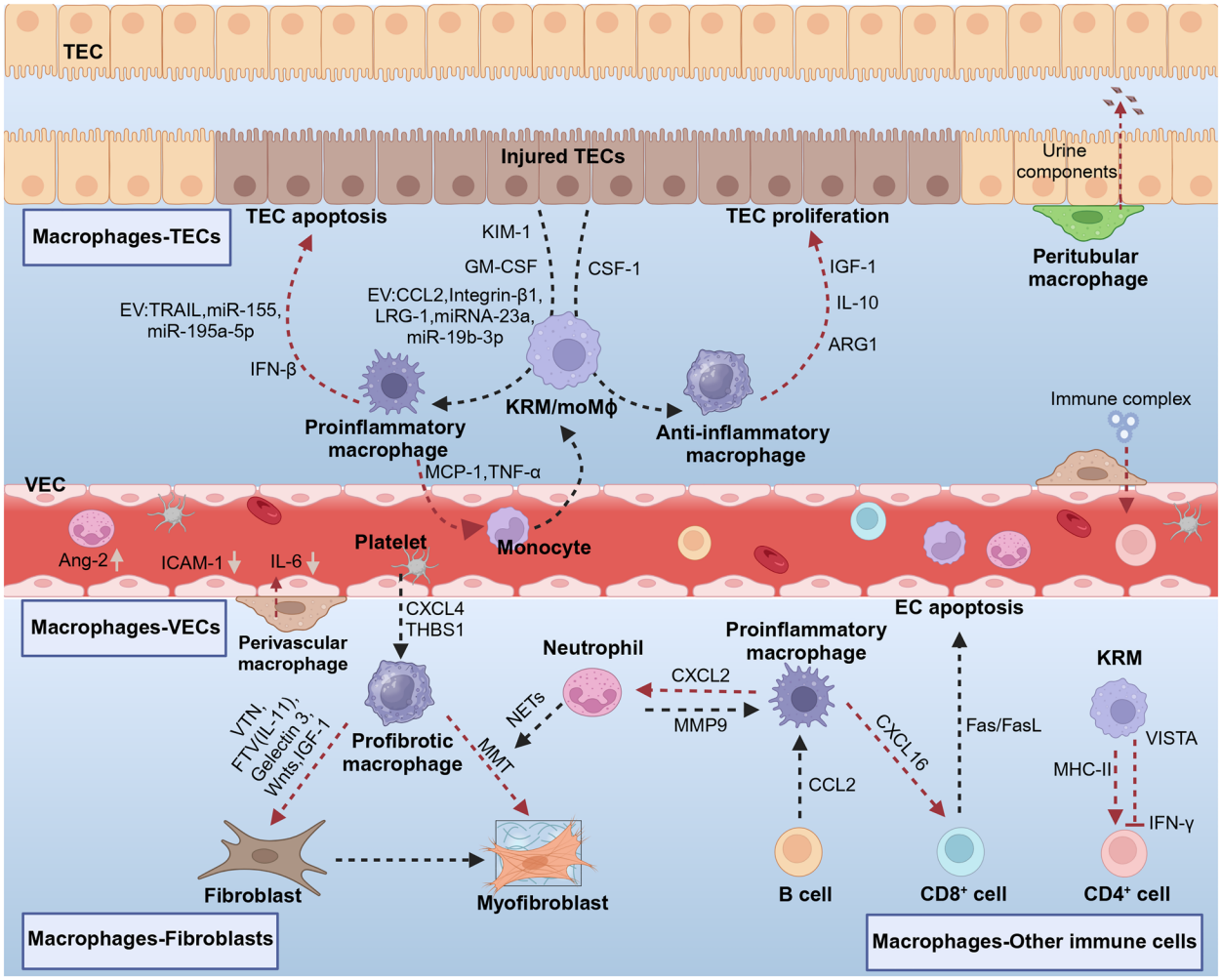

Figure 2. Crosstalk between renal macrophages and adjacent cells in the AKI to CKD transition. The illustration consists of four parts: macrophages-tubular epithelial cells (TECs); macrophages-vascular endothelial cells (VECs); macrophages-fibroblasts; macrophages-other immune cells. Additionally, macrophages are classified into KRMs/moMφs and proinflammatory/anti-inflammatory macrophages in this overview. KIM-1: kidney injury molecule-1; LRG-1: leucine-rich α-2-glycoprotein 1; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; Ang-2: angiopoietin-2; ICAM-1: intercellular adhesion molecule-1; VTN: vitronectin; FTV(IL-11): filopodial tip vesicles containing interleukin-11; THBS-1: thrombospondin1; MMT: macrophage-to-myofibroblast transition; NETs: neutrophil extracellular traps; MMP9: matrix metalloproteinase-9; VISTA: V-domain Ig suppressor of T-cell activation; EC: endothelial cell. The red dashed arrows represent signals emitted by macrophages, while the black dashed arrows represent signals from other crosstalk cells (created by biorender.com).

Colony-stimulating factor (CSF)

The CSF family is a group of cytokines related to the differentiation and maturation of bone marrow cells in mammals. Injured proximal tubules are an important source of colony-stimulating factor 1 (CSF-1) which binds to colony-stimulating factor receptor 1 (CSF-1R) on macrophages and TECs, mediating kidney repair through both macrophage-dependent mechanisms and TEC autocrine/paracrine mechanisms [38]. Wang et al. utilized the IRI model combined with diphtheria toxin receptor (DTR)-mediated CSF-1 knockout transgenic mice to demonstrate that CSF-1 originating from proximal TECs plays a pivotal role in driving macrophage proliferation and M2 phenotypic polarization, thereby promoting kidney recovery and reducing tubulointerstitial fibrosis [39]. Injured tubular cells also produce granulocyte-macrophage colony-stimulating factor (GM-CSF) to induce macrophage chemoattractant protein-1 (MCP-1)-dependent monocytes or macrophage infiltration, resulting in sustained inflammation and tubular apoptosis [40]. Conversely, TECs exposed to dead cell debris improve the expression of GM-CSF to activate reparative macrophages, which can in turn secrete Arg1 to promote tubular cell proliferation directly *in vitro* [41]. Overall, the roles of CSF-1 and GM-CSF in TECs vary depending on the complex kidney microenvironment, and further research is needed to clarify their actual functions between macrophage and TEC interaction.

Soluble factors

Interleukin-10 (IL-10), a potent immunomodulator, is highly secreted by M2 macrophages and helps reduce TEC apoptosis by inhibiting the mTOR signal and stabilizing mitochondrial function [42]. Kidney injury molecule-1 (KIM-1), an epithelium-derived phosphatidylserine receptor, is upregulated following kidney injury and alleviates inflammatory responses during the early injury phase by augmenting autophagic activity in TECs [43]. However, sustained upregulation of KIM-1 by TECs leads to MCP-1 secretion and

MCP-1-dependent macrophage infiltration, contributing to the long-term progression of kidney fibrosis [44]. It was reported that TECs upregulate the expression of connexin 43 (Cx43) in both patients and mice with obstructive nephropathy. Mechanically, Cx43 induces injured TECs to release adenosine triphosphate (ATP), which binds to P2rx4 or P2rx7 positive macrophages, leading to macrophage pyroptosis and release of CXCL10 to activate intrarenal fibroblasts in murine unilateral ureter obstruction (UUO) model [45].

While polyploid tubular cells demonstrate functional preservation post-AKI, emerging evidence reveals a paradoxical effect: infiltrating F4/80^{low}CD11b^{hi} macrophages secrete interferon-β (IFN-β) that binds to IFN-α/β receptor 1 (IFNAR1) on TECs. This ligand-receptor interaction induces pathological polyploidization through the inorganic pyrophosphatase–YAP axis, upregulating p21 expression, thereby contributing to AKI-to-CKD transition [46]. By contrast, in a glyoxylate-induced kidney injury mouse model, Mrc1^{+} macrophages significantly upregulate insulin-like growth factor 1 (IGF-1), which can stimulate TEC proliferation through the AKT/Rb signaling pathway to alleviate kidney crystal injury [47]. However, other studies have suggested that the Mrc1 subset of M2 macrophages is strongly associated with murine renal fibrosis [48,49]. This raises the possibility that Mrc1^{+} macrophages may exhibit heterogeneity across different kidney diseases.

Extracellular vesicles

Recently, studies have demonstrated that EVs, which contain a variety of proteins, lipids, and nucleic acids (mRNA and noncoding RNA), are key mediators of macrophage–tubular cell communication [50]. The internalization of CC motif ligand 2 (CCL2)-containing EVs from albumin-treated TECs by macrophages initiates an inflammatory response and macrophage migration, representing a mechanism of EV-induced tubulointerstitial inflammation [51]. Ischemic-damaged proximal tubular cells can secrete EVs-containing integrin β1, which facilitates the adhesion and migration of Fn1^{+} macrophages. Conversely, infiltrated Fn1^{+} macrophages amplify the inflammatory response in surviving proximal tubules by secreting inflammatory factors TNF-α, MCP-1, and thrombospondin 1 (THBS-1) [52]. In a more complex scenario, EVs trigger multiple signaling pathways simultaneously. For instance, lipotoxicity-damaged TECs release leucine-rich α-2-glycoprotein 1 (LRG-1)-rich EVs that activate macrophages in a TGFβR1-dependent manner. In response, these macrophages secrete tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-rich EVs to bind death receptor 5 on TECs, inducing injured TEC apoptosis [17].

In recent years, an increasing number of studies have concentrated on non-coding RNA-rich EVs in the kidney owing to their significant impact on the metabolic reprogramming of cellular functions. For instance, miRNA-23a-rich EVs secreted by TECs promote the reprogramming of macrophages toward the M1 phenotype to develop tubulointerstitial inflammation in a hypoxia-inducible factor-alpha (HIF-1α) dependent manner [53]. Similarly, macrophages internalize miR-19b-3p-rich EVs from injured TECs, leading to M1 phenotype polarization via the NF-κB/SOCS-1 pathway, thus contributing to tubulointerstitial inflammation [54]. Macrophage-derived EVs have a great impact on TEC survival and function. In angiotensin II-induced murine kidney injury, macrophage-derived miR-155-rich exosomes induce telomere shortening and telomere dysfunction in proximal TECs by targeting telomere repeat-binding factor 1. The inhibition of miRNA-155 has been shown to attenuate kidney injury following Ang-II treatment [15]. In contrast, macrophage autophagy safeguards TECs from injury by clearing cellular debris and modulating inflammatory response during AKI. Deficiency in macrophage autophagy contributes to the increased secretion of miR-195a-5p-rich EVs, resulting in inflammatory response and mitochondrial dysfunction in TECs [55]. Overall, precise modulation of exosome-derived signaling pathways presents a promising therapeutic strategy for the treatment of AKI to CKD transition.

Direct contact

Macrophages also engage in immune surveillance through direct interaction with TECs. For example, peritubular macrophages in the renal medulla can extend long pseudopodia to detect urine components and assist in the removal of particles, thereby preventing tubular obstruction. This transepithelial activity of macrophages is dependent on integrin β1 expression of TECs [25]. Conversely, CX3CR1^{+} resident macrophages in the perivascular region of the kidney absorb urine-transported contrast agents through direct interactions with renal tubules, a process that can contribute to contrast-induced AKI [56].

Crosstalk between renal macrophages and vascular endothelial cells

During kidney development, the preponderance of renal macrophages situated around the interstitial vasculature secretes molecules that are indispensable for forming the blood vessel network and actively phagocytose mislocated vascular endothelial cells (VECs). Depletion of macrophages results in a significant reduction in the formation of endothelial cross-connections [57]. In facing injury and inflammation, endothelial cells play a key role in producing chemoattractants and adhesion molecules, thereby recruiting blood leukocytes to the injured kidney areas. A study found that the concentration of angiopoietin-2 in the plasma is significantly increased in patients with CKD. The inhibition of angiopoietin-2 attenuates renal inflammation, capillary rarefaction, and fibrosis in murine models of UUO. Mechanistically, angiopoietin-2 could induce endothelial cells to produce chemokine CCL2 mediating macrophage migration in an *in vitro* co-culture system [58]. Macrophages also modulate the immune response of VECs and maintain tissue homeostasis following injury. For instance, the vascular-resident CD169^{+} macrophages suppress the excessive activation of endothelial cells by downregulating the intercellular adhesion molecule-1 (ICAM-1) expression on VECs through direct interaction, therefore, reducing

excessive neutrophil accumulation and subsequent inflammatory cascades following IRI-AKI in mice [59]. Similarly, Il1rn expressed on macrophages could antagonize the IL-1 pathway in endothelial cells, and limit IL-6 generation and sepsis-induced kidney inflammation in mice [60]. It was reported that KRMs located between the capillary endothelium and the basement membranes of tubules are capable of monitoring and clearing immune complexes that are transported into the renal interstitium to reduce small immune complex-induced inflammatory response [61]. Furthermore, macrophages could collaborate with endothelial cells to amplify inflammation. For example, in a nephrotoxic mouse model, a subset of S100a9^{high} Ly6C^{high} moMφs is recruited into the glomerular capillary and S100a8/a9 (myeloid-related protein 8/14, also called calprotectin) complex augments kidney inflammation. *In vitro*, Mrp14-deficient bone marrow-derived macrophages cultured with renal microvascular endothelial cells result in significantly decreased cytokine levels of MCP-1, IL-8, and IL-6 [62].

Crosstalk between renal macrophages and fibroblasts

Fibroblasts are primarily responsible for maintaining the structure of tissues and organs by modulating ECM deposition and degradation. Notably, the crosstalk between macrophages and fibroblasts plays an essential role in coordinating responses in the fibrotic kidney. Multiple intercellular mediators induce their dynamic changes in phenotype and function. The concept of fibrogenic niche has improved our understanding of kidney fibrosis development. The fibrogenic niche is a unique ECM-remodeling microenvironment, including inflammatory immune cells, EVs, soluble factors, and metabolites [63,64].

ECM-related proteins

A recent study using a decellularized kidney tissue scaffold found that macrophage-assembled, vitronectin (VTN)-enriched extracellular microenvironment can activate fibroblasts by stimulating integrin αvβ5 and Src kinase signaling. Disrupting this fibrotic microenvironment can reduce kidney fibrosis [63]. Similarly, macrophages exposed to calcium oxalate monohydrate increase the secretion of inflammatory-related proteins to induce fibroblast activation, which is regarded as a novel mechanism in kidney stone-induced renal fibrogenesis [65].

EVs

Macrophage-derived EVs prove an efficient way to influence fibroblast function. Stimulated macrophages can extend a unique membrane structure to produce filopodial tip vesicles (FTVs), facilitating a novel form of intercellular communication through the transfer of multiple cargo-containing internal vesicles. High-glucose-exposed M1 macrophages generate numerous FTV enriched with interleukin-11 (IL-11) to promote the differentiation and migration of fibroblasts. The inhibition of FTVs or the targeting of IL-11 significantly mitigates renal interstitial fibrosis in mice [66].

Soluble factor

Recently, a new subset of moMφs characterized by high levels of IGF1 expression has been identified as a key player in ECM remodeling and the progression from AKI to CKD. Mechanistically, IGF1^{+} macrophages facilitate fibroblast activation and proliferation through the IGF-1/IGF-1R signaling pathway [14]. Galectin 3, a beta-galactoside-binding lectin, is upregulated in the murine model of UUO. In particular, the expression of galectin 3 on macrophages induces fibroblast activation with profibrotic characteristics [67]. In addition, macrophages facilitate the differentiation of fibroblasts into myofibroblasts which are characterized by an increased capacity for ECM secretion. A cohort study found that a proinflammatory fibroblast population (designated as CXCL-iFibro) accumulated in the early stages of CKD is associated with poor patient outcomes. Integrated analysis of single-cell transcriptomics and spatial transcriptomics data from CKD patients revealed that the CXCL-iFibro subset exhibits close cellular interactions with FOLR2^{+} macrophages. *In vitro* co-culture experiments validated that the CXCL-iFibro subset enables the transformation of CD14^{+} monocytes into FOLR2^{+} macrophages. In return, the FOLR2^{+} macrophages promote the transition of CXCL-iFibro into ECM-secreting myofibroblasts through activation of the WNT/β-catenin signaling [68]. Additionally, a study found that IL-1β from CX3CR1^{+} moMφs is essential for fibroblast activation in heart failure pathogenesis and this molecular mechanism can be a therapeutic approach to selectively inhibit inflammation [69]. This investigation also has important implications for understanding renal inflammation and maladaptive tissue remodeling.

Platelet-derived signals

Recent research has highlighted platelet activation and platelet-derived factors following renal injury, which mediate macrophage-fibroblast communication [70]. In the murine model of IRI-induced AKI, integrative scRNA-seq and spatial transcriptomics unveiled a novel subset of macrophages called 'cycling M2 macrophages', which present enhanced proliferative capacity. This subset modulated by platelet-derived thrombospondin-1 (THBS1) acquires profibrotic characteristics and frequently interacts with fibroblasts in the presence of platelets in the AKI to CKD transition. The administration of the platelet THBS1 antagonist (antibody R300) significantly diminishes the circulating M2 macrophages and reduces the expression of profibrotic genes associated with collagen synthesis and immune regulation in fibroblasts [71]. Additionally, the platelet-derived chemokine CXCL4 induces the activation of Spp1^{+} macrophages, which subsequently drive fibroblast activation through up-regulating the expression of profibrotic genes such as *Spp1*, *Fn1*, and *Sema3* in murine model of UUO [32]. The above evidence suggests that targeting platelet-derived signals may be an effective therapy for kidney inflammation and fibrosis.

Crosstalk between renal macrophages and other immune cells

Neutrophils

Following kidney injury, neutrophils and macrophages constitute the predominant populations in the early immune

response. Research has shown that S100a8^{hi} Ly6C^{hi} moMφs arrive earlier than neutrophils after AKI in mice and enhance neutrophil recruitment to amplify the inflammatory response [29]. Similarly, Shiga toxin-activated KRMs induce disease-promoting neutrophil recruitment via chemokine CXCL2, contributing to kidney injury in Shiga toxin-induced hemolytic uremic syndrome [16]. Notably, in contrast to conventional neutrophils, Siglec-F-expressing neutrophils possess enhanced capabilities to produce a substantial array of inflammatory and profibrotic cytokines [72]. Macrophages may induce neutrophils to express Siglec-F by generating inflammatory cytokines. In the murine model of UUO, infiltrated neutrophils can secrete matrix metalloproteinase-9 (MMP9) to promote macrophage recruitment, which plays a role in the pathogenesis of renal fibrosis. Early depletion of MMP9-positive neutrophils could reduce the production of inflammatory factors and suppress M2 macrophage accumulation [73]. This evidence suggests that neutrophils may work with macrophages to create a profibrotic microenvironment in the kidney. In addition, neutrophil-derived neutrophil extracellular traps (NETs) significantly influence the phenotype and functional attributes of renal macrophages. Gasdermin D (GSDMD), a pore-forming protein and a key executor of pyroptosis, can be cleaved by caspase-11 to form NETs [74]. In the murine model of UUO, GSDMD-dependent NETs promote the nuclear translocation of p65 in macrophages, subsequently initiating the expression of α-SMA by activating TGF-β1/Smad signaling [75].

T cells

Growing evidence has demonstrated that the accumulation and activation of T cells emerge in the recovery phase after AKI, with distinct T cell subpopulations mediating various effects [76,77]. Following IRI-induced AKI in mice, persistent macrophage infiltration overexpresses the pro-inflammatory cytokines *Cxcl16* to recruit *Cxcr6*$^{+}$T cells, contributing to secondary tubule injury [10]. In the nephrotoxic murine model, renal macrophages upregulate the expression of V-domain Ig suppressor of T-cell activation (VISTA), a sentinel protein, to mitigate tubulointerstitial fibrosis by suppressing infiltrating T cells to overproduce interferon-gamma (IFN-γ) [78]. In the settings of kidney injury, KRMs diminish antigen presentation to CD4^{+} T cells by downregulating MHC-II expression, which is a critical mechanism to inhibit CD4^{+}T cell-induced chronic kidney inflammation [28]. In the late stage of IRI-induced AKI in mice, some increased proportion of CD8^{+}T cells are recruited by macrophages through the CXCL16 and CXCR6 axis. Subsequently, these infiltrated CD8^{+}T cells promote endothelial cell apoptosis via Fas ligand-Fas signaling, leading to peritubular capillary rarefaction and renal fibrosis [79].

In addition to CD4^{+}T cells and CD8^{+}T cells, regulatory T cells (Tregs) have been shown to play a protective role in kidney regeneration and repair [80]. Tregs are observed in proximity to F4/80^{+} macrophages within regions of α-SMA deposition in fibrotic murine models, and similar distributions of Tregs are noted in human transplanted kidneys [80]. The transfusion of Tregs could shift M1 macrophages into M2 macrophages and promote the repair process in the UUO murine model [81]. Tregs contribute to the alleviation of adriamycin-induced glomerular and interstitial injury in a murine model by reducing macrophage activation and the production of pro-inflammatory cytokines in a TGF-β dependent manner [82]. Similarly, evidence shows that IL-10/TGF-β-modified macrophages reduce renal inflammation and augment the population of Tregs in lymph nodes via expressing regulatory co-stimulatory molecule B7-H4, offering protection against adriamycin-induced murine kidney injury [83]. Furthermore, M2c macrophages demonstrate greater efficacy compared to M2a macrophages in inducing Treg proliferation to protect against adriamycin-induced kidney injury [19]. Notably, the roles of Treg cells in AKI repair processes have not been fully elucidated [76] and further research is needed to clarify how macrophages affect Treg function.

B cells

B cells have been demonstrated to participate in the progression of tubular atrophy and tubulointerstitial fibrosis in multiple murine models. In the UUO mouse models, recruited B cells enhance macrophage mobilization and infiltration via the secretion of TNF-α and CCL2 to exacerbate tubulointerstitial fibrosis [84]. In contrast, resident B cells colocalizing with macrophages induce anti-inflammatory macrophage polarization and downregulate pro-inflammatory chemokines CCL2/CXCL2 through IL-10 secretion, thereby maintaining renal homeostasis in urinary tract infection models [85]. However, research on the precise roles of residents B cells in kidney injury and recovery is limited, and there is a need to investigate more potential roles of B cell subsets involved in the interaction with renal macrophages in AKI models.

New insight: cell chat between macrophages and adjacent cells by the integration of scRNA-seq with spatial transcriptomics

Histological tissue sections and co-culture *in vitro* are common experiments to screen cell–cell communication, but these assays can gain very limited information [86]. In the past decade, scRNA-seq has revolutionized our understanding of cell–cell communication through tremendous bioinformatic data and prediction of secreted signalings [87]. However, scRNA-seq does not capture spatial information of interacting cell types after tissue dissociation. Recently, spatial transcriptomics has become a promising tool for studying the spatial distribution of macrophage-mediated cell communications by localizing mRNA within tissues, using methods like *in situ* hybridization, *in situ* sequencing, and spatial barcoding [88]. However, according to Polonsky et al.'s spatial transcriptomics study, even when using a comprehensive gene panel that covers all major kidney cell types, the capture of macrophage subpopulations is more simplified compared to single-cell resolution [12]. This limitation makes it challenging to accurately identify distinct macrophage subpopulations and their interactions with other cells in the kidney. Recently, several studies have combined scRNA-seq and

spatial transcriptomics to gain a more comprehensive understanding of the complex interactions between macrophages and other cell types in the kidney. For instance, an ECM-remodeling macrophage subset with proinflammatory and profibrotic characteristics has a strong spatial dependency with proximal tubular cells and neutrophils at the early stages after AKI but a dependency with fibroblasts at the chronic stages. Additionally, the authors used ligand–receptor interaction pairs predicted by CellChat DB to reveal that the Igf1–Igf1r signaling axis mediates the interactions between ECM-remodeling macrophages and fibroblasts in kidney fibrosis [14]. Through integrated single-cell and spatial transcriptomics, macrophages were shown to be the central mediators governed by platelet-derived signaling following AKI in mice. Furthermore, an in-depth analysis of intercellular cell–cell communications with the CellChat tool revealed that platelet-derived THBS1 modulates cycling M2 macrophages and mediates the interaction between macrophages and fibroblasts in the AKI to CKD transition [71]. In addition, a study integrated single-nucleus RNA sequencing with spatial architecture analysis and revealed that F13a1^{+}CD163^{+} macrophages specifically interact with injured proximal tubular cells via the Gas6–Axl signaling axis in a rat model of crystal-induced kidney injury [89]. Notably, the inference of intercellular signaling was based on the RNA expression levels of ligands and receptors. Identified molecular interactions will have to be validated by additional experiments.

Current landscapes of preclinical macrophage-targeted therapeutic interventions in AKI to CKD transition

Even though about 25% of patients with AKI develop CKD within a 3-year follow-up period, there are limited drugs to suppress or reverse the transition from AKI to CKD [90]. The precise mechanisms of AKI to CKD transition remain incompletely understood. Renal macrophages, one of the most abundant immune cells, widely engage with parenchymal and other immune cells to influence inflammatory development and tissue repair. Here, we mainly introduce potential treatments regarding macrophage-related cell–cell communication (Table 1).

Interfering with recruiting signals of immune cells

Given that recruited moMφs are broadly influenced by microenvironmental factors from tubular cells and immune cells, modulating recruitment signals may affect macrophage-mediated intercellular communication. The crucial role of the CCL2–CCR2 axis in coordinating monocyte/macrophage recruitment makes it a promising target [102]. The administration of CCR2 inhibitor RS-102895 significantly reduces the number of CCR2-dependent macrophage accumulation and attenuates chronic renal damage in murine unilateral IRI [40]. Additionally, PC3-secreted microprotein (PSMP), a ligand of CCR2, emerges as a promising therapeutic target for macrophage modulation. PSMP-neutralizing antibody significantly reduces the population of CCR2^{+} Ly6C^{hi} or F4/80^{low} infiltrated macrophages and attenuates IRI-induced AKI models in mice [91]. The S100a9^{hi} Ly6C^{hi} moMφs subsets have shown frequent interaction with KRMs through S100a8/a9-TLR4 to amplify renal inflammation following the murine IRI-induced AKI. Two S100a9 inhibitors (tasquinimod and paquinimod) can bind the S100a8/a9 alarmin heterodimer and disrupt the interaction between S100a8/a9^{hi} Ly6C^{hi} moMφs and KRMs, thereby improving long-term outcomes with decreased kidney fibrosis [29].

Mesenchymal stem cells (MSCs), originating from the mesoderm, exhibit self-renewal potential and have a strong ability to differentiate into multiple cell lineages [103]. MSC-derived EVs proved more effective in promoting kidney repair compared with the direct administration of MSCs [104]. CCR2 high-expressed MSCs-derived exosomes tend to bind to their ligand CCL2 and reduce the recruitment of circulating macrophages in the murine IRI-induced AKI [92]. Additionally, human Wharton-Jelly MSCs-derived microvesicles (hWJMSC-MVs) ameliorate renal injury in both acute and chronic stages by downregulating CX3CL1 expression and decreasing the accumulation of CD68^{+} macrophages within the damaged kidney [93]. Following tissue injury, VECs can quickly up-regulate P-selectin, a cell adhesion molecule, which mediates monocyte slow rolling, arrest, and migration [105]. Zhang et al. found that P-selectin binding peptide-modified human placenta mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) specially target damaged endothelial cells, reduce moMφ adhesion and promote kidney reparative angiogenesis to assist kidney repair [94].

Inhibition of TGFβ1–Smad3 signaling in macrophage to myofibroblast transition

Current research has highlighted the mechanisms underlying the MMT process in CKD development [106]. The TGF-β1/Smad3 is one of the driving signaling pathways of the MMT process. A study demonstrated that moderate stimulation of TGF-β induces macrophage polarization toward the M2c phenotype, whereas excessive stimulation of TGF-β facilitates M2a-derived MMT, characterized by enhanced ECM production [18]. However, direct inhibition of excessive TGF-β signaling has not proven effective in slowing the progression of CKD in both humans and mice [107,108]. Furthermore, targeted deletion of TGF-β2 in the proximal tubule exacerbates mitochondrial damage and enhances the Th1 inflammatory response [109]. Thus, selective inhibition of specific TGF-β subtypes or targeted blockade of downstream effector molecules may offer a more effective approach to mitigating kidney fibrosis.

Macrophages undergoing MMT in sites of fibrosis in mouse and human CKD were identified with high expression of POU Class 4 Homeobox 1 (Pou4f1), a downstream regulator of the TGF-β1/Smad3. The pou4f1-silencing effectively mitigates MMT-induced fibrosis *in vitro* and *in vivo* [95]. To enhance the precision of drug delivery to fibrotic macrophages, one study designed a nanoemulsion that is composed of α-tocopherol succinate (α-TOS), egg yolk lecithin-80 (E80), and medium chain fatty acids (MCT). This nanomedicine co-loaded with endoplasmic reticulum stress inhibitors (Ceapin7) and conventional glucocorticoids (dexamethasone), named multistage

Table 1. Current status of preclinical intervention of macrophage-adjacent cell communication in AKI to CKD transition.

Study	Model	Therapeutic strategy	Therapeutic outcomes	Reference
Interfering with recruiting signals of immune cells				
Xu et al.	IRI	CCR2 inhibitor (RS102895)	RS-102895 reduces the number of CCR2-dependent macrophage accumulation and attenuates chronic renal damage.	[40]
Song et al.	IRI	PSMP-neutralizing antibody	PSMP-neutralizing antibody reduces the population of $CCR2^{+}$ $Ly6C^{hi}$ or $F4/80^{low}$ infiltrated macrophages and attenuates IRI-induced AKI.	[91]
Yao et al.	IRI	S100a8/a9 inhibitor	S100a9 inhibitor binds the S100a8/a9 alarmin heterodimer and disrupts the interaction between S100a8/$a9^{hi}Ly6C^{hi}$ moMφs and KRMs, thereby improving long-term outcomes with decreased kidney fibrosis.	[29]
Shen et al.	IRI	MSC-Exo	CCL2 high-expressed MSC-Exo bind to its ligand CCL2 and reduce the recruitment of circulating macrophages.	[92]
Zou et al.	IRI	HWJMSC-MVs	HWJMSC-MVs downregulate CX3CL1 expression in the kidney and decrease the accumulation of $CD68^{+}$ macrophages.	[93]
Zhang et al.	IRI	PBP-EVs	P-selectin binding peptide-engineered extracellular vesicles (PBP-EVs) target damaged endothelial cells, reduce monocyte-derived macrophage adhesion and promote kidney reparative angiogenesis to attenuate IRI-induced AKI.	[94]
Inhibition of TGFβ1-Smad3 signaling in macrophage to myofibroblast transition				
Tang et al.	UUO	Pou4f1 silence	The pou4f1-silencing effectively mitigates MMT-induced fibrosis *in vitro* and *in vivo* by downregulating the TGF-β1/Smad3 pathway.	[95]
Luo et al.	UUO	Nanoemulsions (T-NE (C + D))	Nanoemulsions (T-NE (C + D)) well suppress the MMT by regulating the ATF6/TGF-β/Smad3 signaling axis within macrophages and promote macrophage polarization toward the M2c phenotype.	[18]
Qiang et al.	UUO	MR inhibitor (Esaxerenone)	Esaxerenone suppresses aldosterone-induced MR activation and TGF-β production to halt the MMT process in fibrotic kidneys.	[96]
Chen et al.	UUO	P2Y12 inhibitor	P2Y12 inhibitor counters the upregulation of P2Y12 by TGF-β and suppresses the TGF-β/Smad3-induced MMT process.	[97]
Depletion of disease-associated macrophages				
Deng et al.	IRI	Kinase inhibitor (GW2580)	GW2580 reduces the population of $Ly6C^{+}$M2-like macrophage infiltration, mitigating ischemia-induced AKI and subsequent kidney fibrosis.	[98]
Sung et al.	CIN	Kinase inhibitor (PLX3397)	PLX3397 attenuates cisplatin-induced ototoxicity and nephrotoxicity by decreasing $CX3CR1^{+}$ macrophage-induced accumulation in the kidney.	[99]
Hu et al.	IRI	Clodronate	Clodronate-loaded liposomes alleviate renal fibrosis and tissue damage by reducing macrophage-derived inflammatory cytokines.	[100]
Ouyang et al.	IRI	BIVA-PK	Bioactivated *in vivo* assembly peptide conjugated LTX-315(BIVA-PK) induces the death of $Fn1^{+}Spp1^{+}Mrc^{+}$ macrophages and disrupts their mitochondrial homeostasis to reduce fibrotic cell communication.	[101]

IRI: ischemia–reperfusion injury; CIN: cisplatin-induced nephrotoxicity; UUO: unilateral ureteral obstruction; PSMP: PC3-secreted microprotein; MSC-Exo: mesenchymal stem cell-derived exosomes; HWJMSC-MVs: human Wharton-Jelly mesenchymal stem cell-derived microvesicles; PBP-EVs: P-selectin binding peptide-engineered extracellular vesicles; nanoemulsions (T-NE(C + D)): T (α-tocopherol succinate (α-TOS)), E (egg yolk lecithin-80 (E80)), C (Ceapin7), D (dexamethasone); BIVA-PK: bioactivated *in vivo* assembly peptide conjugated LTX-315 (PK).

targeted nanoemulsions (T-NE (C + D)), significantly suppresses the MMT by regulating ATF6/TGF-β/Smad3 signaling axis and promotes macrophage polarization toward M2c phenotype [18]. In addition, some applied clinical drugs exhibit effectiveness in inhibiting MMT. For instance, aldosterone mainly promotes M1 macrophage-to-myofibroblast transition by activating mineralocorticoid receptor (MR) and upregulating the expression of TGF-β1, while MR inhibitor eplerenone can counter these effects [96]. One study revealed that TGF-β can regulate the expression level of the P2Y12 receptor on macrophages in the fibrotic kidney. The administration of clopidogrel, a P2Y12 inhibitor, inhibits the TGF-β-induced upregulation of P2Y12 on macrophages and subsequently suppresses the TGF-β/Smad3-mediated MMT [97].

Depletion of disease-associated macrophages

Advancements in scRNA-seq and spatial transcriptomics have further identified disease-associated macrophage subpopulations and targeting these cells could interrupt adverse communication with adjacent cells during AKI to CKD transition. For instance, M2 macrophages are implicated in the progression of kidney fibrosis due to their elevated expression of profibrotic genes, including *Fn1*, *Spp1*, and *Tgf-β* [11]. The CSF-1/CSF-1R signaling pathway proves vital for the development, survival, and activation of macrophages [110]. Several studies have explored the efficacy of kinase inhibitors targeting CSF-1R. For example, GW2580 has been shown to significantly reduce profibrotic $Ly6C^{+}$M2-like macrophage infiltration, thereby mitigating ischemia-induced AKI and subsequent kidney fibrosis [98]. Interestingly, PLX3397, another kinase inhibitor, can attenuate cisplatin-induced ototoxicity and nephrotoxicity by decreasing $CX3CR1^{+}$ macrophage-induced accumulation of cisplatin in the kidney [99]. However, in CSF-1 deficient mice, there is a significant increase in renal calcium oxalate crystal deposition because of a large reduction of $CD11b^{+}F4/80^{+}CD163^{+}CD206^{high}$ macrophages compared to wild-type mice. The supplementation with human recombinant CSF-1 or the exogenous infusion of M2-like macrophages into CSF-1 deficient mice can mitigate kidney crystal formation [111]. Wang et al. also demonstrated that loss of CSF-1 in the proximal tubule delays renal repair following IRI for reduction of M2 macrophages, ultimately exacerbating tubulointerstitial fibrosis [39]. Therefore, extensive inhibition of CSF-1 signaling may impair macrophage functions to promote renal tissue repair and regeneration. Clodronate has been extensively utilized for the depletion of macrophages due to its ability to inhibit ATP-dependent enzymes and disrupt cellular energy metabolism, ultimately inducing

macrophage apoptosis. The application of clodronate-loaded liposomes has demonstrated efficacy in renal fibrosis and tissue damage by reducing macrophage-derived inflammatory cytokines [100]. However, in the context of IRI, liposomes were demonstrated to impede tubular cell proliferation and recovery during the recuperative phase [112]. Moreover, clodronate-loaded liposomes harm the abundance of osteoclasts in bone tissue and worsen osseous healing after systemic macrophage depletion [113]. The above indicates that systemic macrophage depletion easily increases the risk of immune-related adverse effects and selected treatment of pathogenic macrophage subpopulation is a future research direction.

To address these concerns, targeted drug delivery systems using modifications of monoclonal antibodies, peptides, and small molecule compounds have been developed for macrophage-targeted therapy. For example, a bioactivated *in vivo* assembly (BIVA) peptide system consists of mannose targets, an *in situ* nanofiber-like assembly, and LTX-315 (PK). This drug-delivery system aims to reduce $Fn1^{+}Spp1^{+}Mrc1^{+}$ macrophages and disrupts their mitochondrial homeostasis to reduce fibrotic cell communication in the murine model of IRI [101].

Conclusions and future perspectives

Currently, emerging studies have emphasized the central roles of renal macrophages in inflammation, proliferation, and tissue repair after kidney injury. Macrophages can differentiate into different phenotypes to adapt to the local microenvironment. Furthermore, due to their strategic location in the kidney, renal macrophages widely engage in direct and paracrine interaction with neighboring cells to promote inflammatory and ECM remodeling microenvironment. Despite recent advances, our understanding of cell–cell communication networks based on specific macrophage subpopulations within the kidney remains shallow. To ultimately make renal macrophages more controllable, an in-depth understanding of the mechanisms of regulating intercellular communication is needed. Although significant progress has been made in targeting disease-associated macrophages to alleviate kidney injury and fibrosis, very few drugs have advanced to clinical applications because of limited safety. Thus, there is an urgent need to develop highly targeted therapeutics for disease-associated macrophage subsets. It is noted that the use of macrophage-derived EVs as drug carriers combined with membrane modification techniques has recently gained significant momentum due to their advantages of biocompatibility, targeting, and drug delivery diversity [114]. It is anticipated that more drugs designed to interrupt cell communication will soon enter clinical use.

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References

[1] Al-Jaghbeer M, Dealmeida D, Bilderback A, et al. Clinical decision support for in-hospital AKI. J Am Soc Nephrol. 2018;29(2):654–660. doi: 10.1681/ASN.2017070765.

[2] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179–c184. doi: 10.1159/000339789.

[3] Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet. 2019;394(10212):1949–1964. doi: 10.1016/S0140-6736(19)32563-2.

[4] He L, Wei Q, Liu J, et al. AKI on CKD: heightened injury, suppressed repair, and the underlying mechanisms. Kidney Int. 2017;92(5):1071–1083. doi: 10.1016/j.kint.2017.06.030.

[5] Lameire NH, Levin A, Kellum JA, et al. Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2021;100(3):516–526. doi: 10.1016/j.kint.2021.06.028.

[6] Horne KL, Packington R, Monaghan J, et al. Three-year outcomes after acute kidney injury: results of a Prospective Parallel Group Cohort Study. BMJ Open. 2017;7(3):e015316. doi: 10.1136/bmjopen-2016-015316.

[7] Hsu CY, Chinchilli VM, Coca S, et al. Post-acute kidney injury proteinuria and subsequent kidney disease progression: the Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) Study. JAMA Intern Med. 2020;180(3):402–410. doi: 10.1001/jamainternmed.2019.6390.

[8] Zhang T, Widdop RE, Ricardo SD. Transition from acute kidney injury to chronic kidney disease: mechanisms, models, and biomarkers. Am J Physiol Renal Physiol. 2024;327(5):F788–F805. doi: 10.1152/ajprenal.00184.2024.

[9] Yeh TH, Tu KC, Wang HY, et al. From acute to chronic: unraveling the pathophysiological mechanisms of the progression from acute kidney injury to acute kidney disease to chronic kidney disease. Int J Mol Sci. 2024;25(3):1755. doi: 10.3390/ijms25031755.

[10] Xu L, Guo J, Moledina DG, et al. Immune-mediated tubule atrophy promotes acute kidney injury to chronic kidney disease transition. Nat Commun. 2022;13(1):4892. doi: 10.1038/s41467-022-32634-0.

[11] Tang PM, Nikolic-Paterson DJ, Lan HY. Macrophages: versatile players in renal inflammation and fibrosis. Nat Rev Nephrol. 2019;15(3):144–158. doi: 10.1038/s41581-019-0110-2.

[12] Polonsky M, Gerhardt LMS, Yun J, et al. Spatial transcriptomics defines injury specific microenvironments and cellular interactions in kidney regeneration and disease. Nat Commun. 2024;15(1):7010. doi: 10.1038/s41467-024-51186-z.

[13] Polonsky M, Gerhardt LMS, Yun J, et al. Spatial transcriptomics defines injury-specific microenvironments in the adult mouse kidney and novel cellular interactions in regeneration and disease. bioRxiv. 2023. doi: 10.1101/2023.11.22.568217.

[14] Zhang YL, Tang TT, Wang B, et al. Identification of a novel ECM remodeling macrophage subset in AKI to CKD transition by integrative spatial and single-cell analysis. Adv Sci. 2024;11(38):e2309752. doi: 10.1002/advs.202309752.

[15] Yin Q, Tang TT, Lu XY, et al. Macrophage-derived exosomes promote telomere fragility and senescence in tubular epithelial cells by delivering miR-155. Cell Commun Signal. 2024;22(1):357. doi: 10.1186/s12964-024-01708-5.

[16] Lill JK, Thiebes S, Pohl JM, et al. Tissue-resident macrophages mediate neutrophil recruitment and kidney injury in shiga toxin-induced hemolytic uremic syndrome. Kidney Int. 2021;100(2):349–363. doi: 10.1016/j.kint.2021.03.039.

[17] Jiang WJ, Xu CT, Du CL, et al. Tubular epithelial cell-to-macrophage communication forms a negative feedback loop via extracellular vesicle transfer to promote renal inflammation and apoptosis in diabetic nephropathy. Theranostics. 2022;12(1):324–339. doi: 10.7150/thno.63735.

[18] Luo L, Wang S, Hu Y, et al. Precisely regulating M2 subtype macrophages for renal fibrosis resolution. ACS Nano. 2023;17(22):22508–22526. doi: 10.1021/acsnano.3c05998.

[19] Lu J, Cao Q, Zheng D, et al. Discrete functions of M2a and M2c macrophage subsets determine their relative efficacy in treating chronic kidney disease. Kidney Int. 2013;84(4):745–755. doi: 10.1038/ki.2013.135.

[20] Conway BR, O'Sullivan ED, Cairns C, et al. Kidney single-cell atlas reveals myeloid heterogeneity in progression and regression of kidney disease. J Am Soc Nephrol. 2020;31(12):2833–2854. doi: 10.1681/ASN.2020060806.

[21] Clements M, Gershenovich M, Chaber C, et al. Differential Ly6C expression after renal ischemia–reperfusion identifies unique macrophage populations. J Am Soc Nephrol. 2016;27(1):159–170. doi: 10.1681/ASN.2014111138.

[22] Liu F, Dai S, Feng D, et al. Distinct fate, dynamics and niches of renal macrophages of bone marrow or embryonic origins. Nat Commun. 2020;11(1):2280. doi: 10.1038/s41467-020-16158-z.

[23] Dick SA, Wong A, Hamidzada H, et al. Three tissue resident macrophage subsets coexist across organs with conserved origins and life cycles. Sci Immunol. 2022;7(67):eabf7777. doi: 10.1126/sciimmunol.abf7777.

[24] Zhu Q, Xiao L, Cheng G, et al. Self-maintaining macrophages within the kidney contribute to salt and water balance by modulating kidney sympathetic nerve activity. Kidney Int. 2023;104(2):324–333. doi: 10.1016/j.kint.2023.04.023.

[25] He J, Cao Y, Zhu Q, et al. Renal macrophages monitor and remove particles from urine to prevent tubule obstruction. Immunity. 2024;57(1):106–123.e7. doi: 10.1016/j.immuni.2023.12.003.

[26] Lefèvre L, Iacovoni JS, Martini H, et al. Kidney inflammaging is promoted by CCR2(+) macrophages and tissue-derived micro-environmental factors. Cell Mol Life Sci. 2021;78(7):3485–3501. doi: 10.1007/s00018-020-03719-0.

[27] Zimmerman KA, Bentley MR, Lever JM, et al. Single-cell RNA sequencing identifies candidate renal resident macrophage gene expression signatures across species. J Am Soc Nephrol. 2019;30(5):767–781. doi: 10.1681/ASN.2018090931.

[28] Lever JM, Hull TD, Boddu R, et al. Resident macrophages reprogram toward a developmental state after acute kidney injury. JCI Insight. 2019;4(2):e125503. doi: 10.1172/jci.insight.125503.

[29] Yao W, Chen Y, Li Z, et al. Single cell RNA sequencing identifies a unique inflammatory macrophage subset as a druggable target for alleviating acute kidney injury. Adv Sci. 2022;9(12):e2103675. doi: 10.1002/advs.202103675.

[30] Cheung MD, Erman EN, Moore KH, et al. Resident macrophage subpopulations occupy distinct microenvironments in the kidney. JCI Insight. 2022;7(20):e161078. doi: 10.1172/jci.insight.161078.

[31] Mysore V, Tahir S, Furuhashi K, et al. Monocytes transition to macrophages within the inflamed vasculature via monocyte CCR2 and endothelial TNFR2. J Exp Med. 2022;219(5):e20210562. doi: 10.1084/jem.20210562.

[32] Hoeft K, Schaefer GJL, Kim H, et al. Platelet-instructed SPP1(+) macrophages drive myofibroblast activation in fibrosis in a CXCL4-dependent manner. Cell Rep. 2023;42(2):112131. doi: 10.1016/j.celrep.2023.112131.

[33] Ouyang JF, Mishra K, Xie Y, et al. Systems level identification of a matrisome-associated macrophage polarisation state in multi-organ fibrosis. Elife. 2023;12:12. doi: 10.7554/eLife.85530.

[34] Yang Q, Wang Y, Pei G, et al. Bone marrow-derived Ly6C(−) macrophages promote ischemia-induced chronic kidney disease. Cell Death Dis. 2019;10(4):291. doi: 10.1038/s41419-019-1531-3.

[35] Lin SL, Castaño AP, Nowlin BT, et al. Bone marrow Ly6Chigh monocytes are selectively recruited to injured kidney and differentiate into functionally distinct populations. J Immunol. 2009;183(10):6733–6743. doi: 10.4049/jimmunol.0901473.

[36] He M, Liu Z, Li L, et al. Cell–cell communication in kidney fibrosis. Nephrol Dial Transplant. 2024;39(5):761–769. doi: 10.1093/ndt/gfad257.

[37] Guo JK, Cantley LG. Cellular maintenance and repair of the kidney. Annu Rev Physiol. 2010;72(1):357–376. doi: 10.1146/annurev.physiol.010908.163245.

[38] Menke J, Iwata Y, Rabacal WA, et al. CSF-1 signals directly to renal tubular epithelial cells to mediate repair in mice. J Clin Invest. 2009;119(8):2330–2342. doi: 10.1172/jci39087.

[39] Wang Y, Chang J, Yao B, et al. Proximal tubule-derived colony stimulating factor-1 mediates polarization of renal macrophages and dendritic cells, and recovery in acute kidney injury. Kidney Int. 2015;88(6):1274–1282. doi: 10.1038/ki.2015.295.

[40] Xu L, Sharkey D, Cantley LG. Tubular GM-CSF promotes late MCP-1/CCR2-mediated fibrosis and inflammation after ischemia/reperfusion injury. J Am Soc Nephrol. 2019;30(10):1825–1840. doi: 10.1681/ASN.2019010068.

[41] Shin NS, Marlier A, Xu L, et al. Arginase-1 is required for macrophage-mediated renal tubule regeneration. J Am Soc Nephrol. 2022;33(6):1077–1086. doi: 10.1681/ASN.2021121548.

[42] Tang TT, Wang B, Wu M, et al. Extracellular vesicle-encapsulated IL-10 as novel nanotherapeutics against ischemic AKI. Sci Adv. 2020;6(33):eaaz0748. doi: 10.1126/sciadv.aaz0748.

[43] Yang L, Brooks CR, Xiao S, et al. KIM-1-mediated phagocytosis reduces acute injury to the kidney. J Clin Invest. 2015;125(4):1620–1636. doi: 10.1172/JCI75417.

[44] Humphreys BD, Xu F, Sabbisetti V, et al. Chronic epithelial kidney injury molecule-1 expression causes murine kidney fibrosis. J Clin Invest. 2013;123(9):4023–4035. doi: 10.1172/JCI45361.

[45] Xu H, Wang M, Li Y, et al. Blocking connexin 43 and its promotion of ATP release from renal tubular epithelial cells ameliorates renal fibrosis. Cell Death Dis. 2022;13(5):511. doi: 10.1038/s41419-022-04910-w.

[46] Wang Y, Lan Q, Li F, et al. Macrophage-derived type 1 IFN, renal tubular epithelial cell polyploidization, and AKI-to-CKD transition. J Am Soc Nephrol. 2024. doi: 10.1681/ASN.0000000577.

[47] Huang L, Chen W, Tan Z, et al. Mrc1(+) macrophage-derived IGF1 mitigates crystal nephropathy by promoting renal tubule cell proliferation via the AKT/Rb signaling pathway. Theranostics. 2024;14(4):1764–1780. doi: 10.7150/thno.89174.

[48] Toki D, Zhang W, Hor KL, et al. The role of macrophages in the development of human renal allograft fibrosis in the first year after transplantation. Am J Transplant. 2014;14(9):2126–2136. doi: 10.1111/ajt.12803.

[49] Wang YY, Jiang H, Pan J, et al. Macrophage-to-myofibroblast transition contributes to interstitial fibrosis in chronic renal allograft injury. J Am Soc Nephrol. 2017;28(7):2053–2067. doi: 10.1681/ASN.2016050573.

[50] Maas SLN, Breakefield XO, Weaver AM. Extracellular vesicles: unique intercellular delivery vehicles. Trends Cell Biol. 2017;27(3):172–188. doi: 10.1016/j.tcb.2016.11.003.

[51] Lv LL, Feng Y, Wen Y, et al. Exosomal CCL2 from tubular epithelial cells is critical for albumin-induced tubulointerstitial inflammation. J Am Soc Nephrol. 2018;29(3):919–935. doi: 10.1681/asn.2017050523.

[52] Wang W, Ren X, Chen X, et al. Integrin beta1-rich extracellular vesicles of kidney recruit Fn1+ macrophages to aggravate ischemia–reperfusion-induced inflammation. JCI Insight. 2024;9(2):e169885. doi: 10.1172/jci.insight.169885.

[53] Li ZL, Lv LL, Tang TT, et al. HIF-1α inducing exosomal microRNA-23a expression mediates the cross-talk between tubular epithelial cells and macrophages in tubulointerstitial inflammation. Kidney Int. 2019;95(2):388–404. doi: 10.1016/j.kint.2018.09.013.

[54] Lv LL, Feng Y, Wu M, et al. Exosomal miRNA-19b-3p of tubular epithelial cells promotes M1 macrophage activation in kidney injury. Cell Death Differ. 2020;27(1):210–226. doi: 10.1038/s41418-019-0349-y.

[55] Yuan Y, Yuan L, Yang J, et al. Autophagy-deficient macrophages exacerbate cisplatin-induced mitochondrial dysfunction and kidney injury via miR-195a-5p–SIRT3 axis. Nat Commun. 2024;15(1):4383. doi: 10.1038/s41467-024-47842-z.

[56] Lau A, Chung H, Komada T, et al. Renal immune surveillance and dipeptidase-1 contribute to contrast-induced acute kidney injury. J Clin Invest. 2018;128(7):2894–2913. doi: 10.1172/JCI96640.

[57] Munro DAD, Wineberg Y, Tarnick J, et al. Macrophages restrict the nephrogenic field and promote endothelial connections during kidney development. Elife. 2019;8:8. doi: 10.7554/eLife.43271.

[58] Chang FC, Liu CH, Luo AJ, et al. Angiopoietin-2 inhibition attenuates kidney fibrosis by hindering chemokine C-C motif ligand 2 expression and apoptosis of endothelial cells. Kidney Int. 2022;102(4):780–797. doi: 10.1016/j.kint.2022.06.026.

[59] Karasawa K, Asano K, Moriyama S, et al. Vascular-resident CD169-positive monocytes and macrophages control neutrophil accumulation in the kidney with ischemia–reperfusion injury. J Am Soc Nephrol. 2015;26(4):896–906. doi: 10.1681/ASN.2014020195.

[60] Privratsky JR, Ide S, Chen Y, et al. A macrophage–endothelial immunoregulatory axis ameliorates septic acute kidney injury. Kidney Int. 2023;103(3):514–528. doi: 10.1016/j.kint.2022.10.008.

[61] Stamatiades EG, Tremblay ME, Bohm M, et al. Immune monitoring of trans-endothelial transport by kidney-resident macrophages. Cell. 2016;166(4):991–1003. doi: 10.1016/j.cell.2016.06.058.

[62] Pepper RJ, Wang HH, Rajakaruna GK, et al. S100A8/A9 (calprotectin) is critical for development of glomerulonephritis and promotes inflammatory leukocyte–renal cell interactions. Am J Pathol. 2015;185(5):1264–1274. doi: 10.1016/j.ajpath.2015.01.015.

[63] Peng Y, Li L, Shang J, et al. Macrophage promotes fibroblast activation and kidney fibrosis by assembling a vitronectin-enriched microenvironment. Theranostics. 2023;13(11):3897–3913. doi: 10.7150/thno.85250.

[64] Li L, Lu M, Peng Y, et al. Oxidatively stressed extracellular microenvironment drives fibroblast activation and kidney fibrosis. Redox Biol. 2023;67:102868. doi: 10.1016/j.redox.2023.102868.

[65] Yoodee S, Noonin C, Sueksakit K, et al. Effects of secretome derived from macrophages exposed to calcium oxalate crystals on renal fibroblast activation. Commun Biol. 2021;4(1):959. doi: 10.1038/s42003-021-02479-2.

[66] Zhu X, Zhao Y, Liu Y, et al. Macrophages release IL11-containing filopodial tip vesicles and contribute to renal interstitial inflammation. Cell Commun Signal. 2023;21(1):293. doi: 10.1186/s12964-023-01327-6.

[67] Henderson NC, Mackinnon AC, Farnworth SL, et al. Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis. Am J Pathol. 2008;172(2):288–298. doi: 10.2353/ajpath.2008.070726.
[68] Cohen C, Mhaidly R, Croizer H, et al. WNT-dependent interaction between inflammatory fibroblasts and FOLR2+ macrophages promotes fibrosis in chronic kidney disease. Nat Commun. 2024;15(1):743. doi: 10.1038/s41467-024-44886-z.
[69] Alexanian M, Padmanabhan A, Nishino T, et al. Chromatin remodelling drives immune cell-fibroblast communication in heart failure. Nature. 2024;635(8038):434–443. doi: 10.1038/s41586-024-08085-6.
[70] Jansen MPB, Florquin S, Roelofs J. The role of platelets in acute kidney injury. Nat Rev Nephrol. 2018;14(7):457–471. doi: 10.1038/s41581-018-0015-5.
[71] Liu J, Zheng B, Cui Q, et al. Single-cell spatial transcriptomics unveils platelet-fueled cycling macrophages for kidney fibrosis. Adv Sci. 2024;11(29):e2308505. doi: 10.1002/advs.202308505.
[72] Ryu S, Shin JW, Kwon S, et al. Siglec-F-expressing neutrophils are essential for creating a profibrotic microenvironment in renal fibrosis. J Clin Invest. 2022;132(12):e156876. doi: 10.1172/JCI156876.
[73] Wang H, Gao M, Li J, et al. MMP-9-positive neutrophils are essential for establishing profibrotic microenvironment in the obstructed kidney of UUO mice. Acta Physiol. 2019;227(2):e13317. doi: 10.1111/apha.13317.
[74] Sollberger G, Choidas A, Burn GL, et al. Gasdermin D plays a vital role in the generation of neutrophil extracellular traps. Sci Immunol. 2018;3(26):eaar6689. doi: 10.1126/sciimmunol.aar6689.
[75] Wang Y, Li Y, Chen Z, et al. GSDMD-dependent neutrophil extracellular traps promote macrophage-to-myofibroblast transition and renal fibrosis in obstructive nephropathy. Cell Death Dis. 2022;13(8):693. doi: 10.1038/s41419-022-05138-4.
[76] Lee K, Jang HR, Rabb H. Lymphocytes and innate immune cells in acute kidney injury and repair. Nat Rev Nephrol. 2024;20(12):789–805. doi: 10.1038/s41581-024-00875-5.
[77] D'Alessio FR, Kurzhagen JT, Rabb H. Reparative T lymphocytes in organ injury. J Clin Invest. 2019;129(7):2608–2618. doi: 10.1172/JCI124614.
[78] Kim MG, Yun D, Kang CL, et al. Kidney VISTA prevents IFN-gamma/IL-9 axis-mediated tubulointerstitial fibrosis after acute glomerular injury. J Clin Invest. 2022;132(1):e151189. doi: 10.1172/JCI151189.
[79] Jiang W, Tang TT, Zhang YL, et al. CD8 T cells induce the peritubular capillary rarefaction during AKI to CKD transition. Int J Biol Sci. 2024;20(8):2980–2993. doi: 10.7150/ijbs.96812.
[80] do Valle Duraes F, Lafont A, Beibel M, et al. Immune cell landscaping reveals a protective role for regulatory T cells during kidney injury and fibrosis. JCI Insight. 2020;5(3):e130651. doi: 10.1172/jci.insight.130651.
[81] Song J, Gong YH, Yan X, et al. Regulatory T cells accelerate the repair process of renal fibrosis by regulating mononuclear macrophages. Am J Med Sci. 2021;361(6):776–785. doi: 10.1016/j.amjms.2021.01.022.
[82] Mahajan D, Wang Y, Qin X, et al. CD4+CD25+ regulatory T cells protect against injury in an innate murine model of chronic kidney disease. J Am Soc Nephrol. 2006;17(10):2731–2741. doi: 10.1681/ASN.2005080842.
[83] Cao Q, Wang Y, Zheng D, et al. IL-10/TGF-beta-modified macrophages induce regulatory T cells and protect against adriamycin nephrosis. J Am Soc Nephrol. 2010;21(6):933–942. doi: 10.1681/ASN.2009060592.
[84] Han H, Zhu J, Wang Y, et al. Renal recruitment of B lymphocytes exacerbates tubulointerstitial fibrosis by promoting monocyte mobilization and infiltration after unilateral ureteral obstruction. J Pathol. 2017;241(1):80–90. doi: 10.1002/path.4831.
[85] Suchanek O, Ferdinand JR, Tuong ZK, et al. Tissue-resident B cells orchestrate macrophage polarisation and function. Nat Commun. 2023;14(1):7081. doi: 10.1038/s41467-023-42625-4.
[86] Armingol E, Officer A, Harismendy O, et al. Deciphering cell–cell interactions and communication from gene expression. Nat Rev Genet. 2021;22(2):71–88. doi: 10.1038/s41576-020-00292-x.
[87] Shao X, Lu X, Liao J, et al. New avenues for systematically inferring cell–cell communication: through single-cell transcriptomics data. Protein Cell. 2020;11(12):866–880. doi: 10.1007/s13238-020-00727-5.
[88] Longo SK, Guo MG, Ji AL, et al. Integrating single-cell and spatial transcriptomics to elucidate intercellular tissue dynamics. Nat Rev Genet. 2021;22(10):627–644. doi: 10.1038/s41576-021-00370-8.
[89] Wang Z, Deng Q, Gu Y, et al. Integrated single-nucleus sequencing and spatial architecture analysis identified distinct injured-proximal tubular types in calculi rats. Cell Biosci. 2023;13(1):92. doi: 10.1186/s13578-023-01041-3.
[90] Sato Y, Yanagita M. Immune cells and inflammation in AKI to CKD progression. Am J Physiol Renal Physiol. 2018;315(6):F1501–F1512. doi: 10.1152/ajprenal.00195.2018.
[91] Song Z, Yao W, Wang X, et al. The novel potential therapeutic target PSMP/MSMP promotes acute kidney injury via CCR2. Mol Ther. 2024;32(7):2248–2263. doi: 10.1016/j.ymthe.2024.05.028.
[92] Shen B, Liu J, Zhang F, et al. CCR2 positive exosome released by mesenchymal stem cells suppresses macrophage functions and alleviates ischemia/reperfusion-induced renal injury. Stem Cells Int. 2016;2016(1):1240301. doi: 10.1155/2016/1240301.
[93] Zou X, Zhang G, Cheng Z, et al. Microvesicles derived from human Wharton's Jelly mesenchymal stromal cells ameliorate renal ischemia–reperfusion injury in rats by suppressing CX3CL1. Stem Cell Res Ther. 2014;5(2):40. doi: 10.1186/scrt428.
[94] Zhang K, Li R, Chen X, et al. Renal endothelial cell-targeted extracellular vesicles protect the kidney from ischemic injury. Adv Sci. 2023;10(3):e2204626. doi: 10.1002/advs.202204626.
[95] Tang PM, Zhang YY, Xiao J, et al. Neural transcription factor Pou4f1 promotes renal fibrosis via macrophage–myofibroblast transition. Proc Natl Acad Sci U S A. 2020;117(34):20741–20752. doi: 10.1073/pnas.1917663117.
[96] Qiang P, Hao J, Yang F, et al. Esaxerenone inhibits the macrophage-to-myofibroblast transition through mineralocorticoid receptor/TGF-beta1 pathway in mice induced with aldosterone. Front Immunol. 2022;13:948658. doi: 10.3389/fimmu.2022.948658.

[97] Chen J, Tang Y, Zhong Y, et al. P2Y12 inhibitor clopidogrel inhibits renal fibrosis by blocking macrophage-to-myofibroblast transition. Mol Ther. 2022;30(9):3017–3033. doi: 10.1016/j.ymthe.2022.06.019.

[98] Deng X, Yang Q, Wang Y, et al. CSF-1R inhibition attenuates ischemia-induced renal injury and fibrosis by reducing Ly6C(+) M2-like macrophage infiltration. Int Immunopharmacol. 2020;88:106854. doi: 10.1016/j.intimp.2020.106854.

[99] Sung CYW, Hayase N, Yuen PST, et al. Macrophage depletion protects against cisplatin-induced ototoxicity and nephrotoxicity. Sci Adv. 2024;10(30):eadk9878. doi: 10.1126/sciadv.adk9878.

[100] Hu Z, Zhan J, Pei G, et al. Depletion of macrophages with clodronate liposomes partially attenuates renal fibrosis on AKI-CKD transition. Ren Fail. 2023;45(1):2149412. doi: 10.1080/0886022X.2022.2149412.

[101] Ouyang Q, Wang C, Sang T, et al. Depleting profibrotic macrophages using bioactivated in vivo assembly peptides ameliorates kidney fibrosis. Cell Mol Immunol. 2024;21(8):826–841. doi: 10.1038/s41423-024-01190-6.

[102] Furuichi K, Wada T, Iwata Y, et al. CCR2 signaling contributes to ischemia–reperfusion injury in kidney. J Am Soc Nephrol. 2003;14(10):2503–2515. doi: 10.1097/01.asn.0000089563.63641.a8.

[103] Westenfelder C, Togel FE. Protective actions of administered mesenchymal stem cells in acute kidney injury: relevance to clinical trials. Kidney Int Suppl (2011). 2011;1(3):103–106. doi: 10.1038/kisup.2011.24.

[104] Zhao M, Liu S, Wang C, et al. Mesenchymal stem cell-derived extracellular vesicles attenuate mitochondrial damage and inflammation by stabilizing mitochondrial DNA. ACS Nano. 2021;15(1):1519–1538. doi: 10.1021/acsnano.0c08947.

[105] Kral-Pointner JB, Haider P, Szabo PL, et al. Reduced monocyte and neutrophil infiltration and activation by P-selectin/CD62P inhibition enhances thrombus resolution in mice. Arterioscler Thromb Vasc Biol. 2024;44(4):954–968. doi: 10.1161/ATVBAHA.123.320016.

[106] Wei J, Xu Z, Yan X. The role of the macrophage-to-myofibroblast transition in renal fibrosis. Front Immunol. 2022;13:934377. doi: 10.3389/fimmu.2022.934377.

[107] Voelker J, Berg PH, Sheetz M, et al. Anti-TGF-beta1 antibody therapy in patients with diabetic nephropathy. J Am Soc Nephrol. 2017;28(3):953–962. doi: 10.1681/ASN.2015111230.

[108] Neelisetty S, Alford C, Reynolds K, et al. Renal fibrosis is not reduced by blocking transforming growth factor-beta signaling in matrix-producing interstitial cells. Kidney Int. 2015;88(3):503–514. doi: 10.1038/ki.2015.51.

[109] Kayhan M, Vouillamoz J, Rodriguez DG, et al. Intrinsic TGF-beta signaling attenuates proximal tubule mitochondrial injury and inflammation in chronic kidney disease. Nat Commun. 2023;14(1):3236. doi: 10.1038/s41467-023-39050-y.

[110] Sehgal A, Irvine KM, Hume DA. Functions of macrophage colony-stimulating factor (CSF1) in development, homeostasis, and tissue repair. Semin Immunol. 2021;54:101509. doi: 10.1016/j.smim.2021.101509.

[111] Taguchi K, Okada A, Kitamura H, et al. Colony-stimulating factor-1 signaling suppresses renal crystal formation. J Am Soc Nephrol. 2014;25(8):1680–1697. doi: 10.1681/ASN.2013060675.

[112] Kim MG, Boo CS, Ko YS, et al. Depletion of kidney CD11c+F4/80+ cells impairs the recovery process in ischaemia/reperfusion-induced acute kidney injury. Nephrol Dial Transplant. 2010;25(9):2908–2921. doi: 10.1093/ndt/gfq183.

[113] Kozutsumi R, Kuroshima S, Al-Omari FA, et al. Depletion of macrophages deteriorates bisphosphonate-related osteonecrosis of the jaw-like lesions in mice. Bone. 2023;177:116899. doi: 10.1016/j.bone.2023.116899.

[114] Tang TT, Wang B, Lv LL, et al. Extracellular vesicles for renal therapeutics: state of the art and future perspective. J Control Release. 2022;349:32–50. doi: 10.1016/j.jconrel.2022.06.049.