REVIEW

Macrophage polarization in kidney diseases

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Macrophage accumulation associates closely with the degree of renal structural injury and renal dysfunction in human kidney diseases. Depletion of macrophages reduces while adoptive transfer of macrophages worsens inflammation in animal models of the renal injury. However, emerging evidence support that macrophage polarization plays a critical role in the progression of a number of kidney diseases including obstructive nephropathy, ischemia-reperfusion injury, glomerulonephritis, diabetic nephropathy, and other kidney diseases. In this mini-review, we briefly summarize the macrophage infiltration and polarization in these inflammatory and fibrotic kidney diseases, discussing the results mostly from studies in animal models. In view of the critical role of macrophage in the progression of these diseases, manipulating macrophage phenotype may be a potential effective strategy to treat various kidney diseases.

Keywords: Macrophage; polarization, kidney diseases

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Introduction

Interferon (IFN)-γ, produced by lymphocytes, can transform resting macrophages into active ones that secrete pro-inflammatory cytokines and produce a large amount of toxic mediators [1]. Interleukin (IL)-4, another cytokine also produced by lymphocytes, converts the resting macrophages into an active state different from the IFN-γ-induced activation [2]. As the heterogeneity in the helper T-cell compartment is recognized, and the concept of Th1 and Th2 is subsequently proposed [3], the IFN-γ-activated macrophages become known as M1 (also known as classically activated) macrophages, and IL-4-activated macrophages are documented as M2 (also as known alternatively activated) macrophages. Since then, a great number of studies demonstrate that macrophages are capable of differentiating to the M1 or M2 phenotype when simulated by various environmental cues (e.g., microbial products, damaged cells, etc.) [4]. M1/M2 polarization may not depend on T cells because these polarizations are also observed in recombination-activating gene (Rag) knock-out and other immune deficient mice [5].

Subsequent studies have revealed that polarization diversity in macrophages gives rise to different functions and even opposite effects in the progression of many diseases. M1 macrophages express pro-inflammatory cytokines including tumor necrosis factor (TNF)-α, IL-1, IL-6, reactive nitrogen, and oxygen intermediates [6] while M2 phenotype expresses Arginase-1 (Arg1), chitinase 3-like 3, IL-10, and CD206. M1 macrophages have strong microbicidal and tumoricidal activity, but M2 macrophages are involved in tissue remodeling and tumor progression [7]. It seems that M1 and M2 macrophages can inter-switch their phenotype in particular microenvironment through the regulation of different transcription factors such as signal transducer and activator of transcription (STATs), interferon-regulatory factor (IRFs), peroxisome proliferator-activated receptor

(PPAR)-γ, nuclear factor (NF)-κB, and activator protein (AP). Among these factors, the balance between activation of STAT1 and STAT3/STAT6 tightly regulates the macrophage polarization [4]. However, it is important to note that M1 and M2 macrophages may be present at the same location simultaneously, and that the dominance of M1 or M2 may be the key factor influencing disease progression [8].

In this mini-review, we briefly summarize the macrophage accumulation in several inflammatory and fibrotic kidney diseases, discussing the results mostly from studies in animal models and focusing on the macrophage polarization and its role in kidney disease progression.

Macrophage polarization in kidney injury and repair

Macrophage polarization in obstructive nephropathy: Macrophage polarization occurs in different types of kidney injury and repair. Unilateral ureteral obstruction (UUO) causes acute renal injury leading to tubulointerstitial inflammation and fibrosis, replicating the common pathway of many chronic kidney diseases in human. Several early studies have demonstrated that the severity of the subsequent fibrosis is correlated with the infiltration of activated macrophages [9]. Systemic macrophage depletion one day prior to UUO reduces interstitial macrophage infiltration as well as subsequent fibrosis, indicating that the early phase of macrophage infiltration promotes the renal fibrosis [10]. However, recent studies show an inverse correlation between the number of interstitial macrophages and the fibrosis, suggesting an anti-fibrotic role of interstitial macrophages [11,12]. These studies demonstrate that interstitial macrophages display an anti-fibrotic effect at day 14, but not day 5, after UUO.

The pathogenic and protective macrophages in UUO kidney suggest that different macrophage polarizations may occur at different stages of UUO. Indeed, our recent studies show a dominance of F4/80+iNOS+ macrophages in kidney interstitium 5 day after UUO injury, indicating a M1 polarization at this stage [13]. Our results are backed by a recent study from a different group showing that the recruited macrophages are mainly M1 macrophages at early stage of UUO. However, these F4/80-positive and CD301-negative M1 macrophages are shortly polarized into CD301-positive M2 macrophages [14], indicating a macrophage polarization transition as UUO injury progresses.

Although accumulating evidence support that M1 to M2 macrophage shift takes place at the later stage of UUO, the role of M2 macrophage in interstitial fibrosis is still controversial. Earlier studies suggest that the number of macrophages is inversely correlated with interstitial fibrosis [15], and adoptive transfer of macrophages ameliorates renal fibrosis [12]. However, recent studies show that M2 macrophage depletion specifically inhibits epithelial-mesenchymal transition (EMT) and subsequently the renal fibrosis. Adoptive transplantation of M2 macrophages promotes renal fibrosis [14, 16]. This discrepancy warrants additional investigation into the macrophage polarization and its role in chronic fibrosis kidney disease because the phenotype and effect of macrophages in this disease model may be more complicated than we have anticipated.

Macrophage polarization in ischemia-reperfusion (I/R) injury: I/R injury is involved in many kidney diseases especially in the renal structure and function damage after kidney transplantation. Hypoxia occurs not only in I/R injury but also a number of chronic kidney diseases, in which the reduction of capillary density is characterized.

Macrophages infiltration due to I/R enhances the inflammatory cascade by producing pro-inflammatory cytokines. IL-6 production peaks at 4 hours after the reperfusion followed by the expression of TNF-α, IL-1β, and MCP-1 in the injured kidney [17]. Systemic monocyte-macrophage depletion significantly reduces the expression of these cytokine and chemokine genes, resulting in a less severe tubular necrosis and a reduction of inflammation and apoptosis of renal tubular epithelial cells. These findings suggest that M1 polarization plays a pathogenic role in the early stage of I/R injury. In a study with I/R injury for 8 weeks, Ko and his colleagues show that macrophage depletion attenuates inflammation and tubulointerstital fibrosis with a decrease in the expression of inflammatory and profibrotic cytokines [18], suggesting that macrophages are involved in both the early inflammation and later fibrogenesis. Moreover, when macrophage depletion is applied in reperfusion stage, tubular epithelial cell regeneration is blocked [19]. But when macrophage is re-injected, tubular epithelial cell regeneration is recovered [19], suggesting that macrophage is very important for tissue repair in the later stage of I/R injury.

An elegant study from Lee and his colleagues provide additional insights into the macrophage polarization shift in I/R injury. It appears that iNOS-positive M1 macrophages are recruited to the kidney in the first 48 hours after I/R injury, whereas arginase 1- and mannose receptor-positive M2 macrophages dominate at later stages [20]. Depletion of macrophages before I/R diminishes kidney injury, whereas depletion at 3 to 5 days after injury slows tubular cell proliferation and repair [20]. Likewise, infusion of INFγ-stimulated bone marrow-derived macrophages into macrophage-depleted mice at the time of reperfusion causes

the kidney injury/damage to a level similar to that observed in kidney with I/R without macrophage depletion, suggesting that M1 macrophages worsen the kidney damage. In contrast, the M2 phenotype correlates with the proliferative phase of kidney repair [20].

Intervention strategies via manipulating macrophage polarization appear to be effective in repairing I/R-caused injury. Human umbilical cord-derived stromal cells intravenous injection reduces M1 macrophage infiltration with an increased accumulation of anti-inflammatory M2 macrophages in renal interstitium 5 days post-reperfusion [21]. This treatment improves the renal function remarkably with a less tubular injury score and more proliferative but fewer apoptotic tubular cells in kidney tissue [21]. Consistently, adoptive transfer of netrin-1-induced M2 macrophages suppresses inflammation and kidney injury against I/R [22]. Conversely, administration of a neutralizing antibody against GM-CSF after renal I/R diminishes the macrophage alternative activation and suppresses the tubular repair [23]. Moreover, genetic or pharmacological inhibition of macrophage colony-stimulating factor (CSF-1) signaling blocks macrophage/dendritic cell proliferation, decreases M2 polarization, and inhibits I/R injury recovery [24]. These studies indicate that M2 macrophage polarization has a protective role in I/R injury, and that macrophage phenotype intervention may be a promising therapeutic strategy in reducing I/R-caused injury.

Macrophage polarization in chemical injury-induced nephropathy: Adriamycin nephropathy (AN) is an experimental model of chronic proteinuric kidney disease in which chemical injury is followed by immune and structural alterations that mimic human focal segmental glomerulosclerosis [25]. Early studies have shown that macrophage infiltration is involved in kidney injury in AN mice [26-28], but the M1 polarization is not confirmed until recently [29]. Several studies have explored the role of macrophage polarization in the development of nephropathy. Adoptive transfer of CpG DNA-activated M1 macrophages exacerbates kidney injury in AN mice [30]. On the other hand, both M2a and M2c subsets significantly reduce renal inflammation and renal injury although the M2c macrophages more effectively reduce glomerulosclerosis, tubular atrophy, interstitial expansion, proteinuria as well as renal fibrosis than the M2a macrophages in AN [31]. Moreover, macrophages modified ex vivo by IL-10/TGF-beta (M2c) significantly attenuate renal inflammation, structural injury, and functional decline by inducing regulatory T cells [32]. These data demonstrate that M2 macrophages play a protective role in AN.

Macrophage polarization in glomerulonephritis

Anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) is an animal model with prominent feature of human crescentic glomerulonephritis. Early studies indicate that macrophages infiltration and proliferation is a characteristic of anti-GBM GN [33-36]. Inhibition of macrophage accumulation by anti-macrophage serum markedly reduces the histologic lesion and profoundly decreases proteinuria, suggesting that macrophages mediate the glomerular injury and consequently proteinuria [37]. However, the macrophage polarization in this disease is not well studied due to the lack of a direct labeling approach.

Although no study has been designed to specifically differentiate macrophage phenotype in anti-GBM GN, several data provide important clues about the macrophage polarization in this disease. Macrophage depletion from the spleen, liver, kidney, and blood by clodronate markedly reduces the release of pro-inflammatory cytokines such as necrosis factor alpha and IL-1β [38], suggesting a M1 polarization in this model. In addition, it has been found that Th cells infiltrated into the kidney of anti-GBM GN mouse exhibit a Th1 phenotype [39]. Since the Th1 lymphokine IFNγ is a key contributor to macrophage M1 polarization, it is reasonable to assume that the glomerular and interstitial macrophages in anti-GBM GN are M1 phenotype.

Macrophages appear to play an important role in the development of anti-GBM GN. Pretreatment with cyclophosphamide to deplete macrophages prevents glomerular leukocyte accumulation and completely inhibits proteinuria, glomerular cell proliferation, and hypercellularity [40]. Adoptive transfer causing significant glomerular macrophage accumulation within 3 hours of injection induces more severe proteinuria, more prominent glomerular cell proliferation, and higher glomerular hypercellularity [40]. The degree of renal injury is associated with the number of transferred glomerular macrophages [40]. Likewise, exposure of macrophages to IFN-γ for 18 hours prior to the transfer causes a 2-fold increase in the degree of proteinuria and glomerular cell proliferation compared to the unstimulated cells [41], suggesting that M1 macrophage is a pathogenic factor in anti-GBM GN. On the contrary, systemic administration of adipose-derived stromal cells (ASCs) in a rat model of anti-GBM GN protects against renal injury, proteinuria, and crescent formation [42]. Importantly, ASCs polarize the macrophages into CD163+ M2 cells associated with the increased IL-10 production. Therefore, ASCs may exert their renoprotective effects in anti-GBM GN by promoting the phenotype switch from M1 to M2 macrophages.

Macrophage polarization in diabetic nephropathy

Streptozotocin-induced diabetic nephropathy (STZ DN) is a commonly used animal diabetic nephropathy model. A large amount of macrophages accumulates in glomerulus and interstitium of STZ DN kidney [43-45], which is a critical factor in the development of diabetic nephropathy. Reduction of macrophage accumulation using colchicin significantly decreases albuminuria, demonstrating that macrophages play a pathogenic role in the diabetic nephropathy [43]. However, whether or not macrophage polarization is involved in the progression of diabetic nephropathy has not been adequately explored until recently.

By examining the M1 (Ly6c, IL-6, and CCR2) and the M2 markers (CD206 and CD163), Devaraj *et al* have shown that peritoneal and kidney macrophages with STZ DN are predominantly M1 phenotype [46]. Consistently, increased infiltrating macrophages with M1 phenotype characterized by an elevated expression of inducible nitric oxide synthase and TNF-α are also evident in glomeruli and interstitium [47], suggesting a M1 dominance in STZ DN. Interestingly, macrophages in the kidneys of STZ DN rat with increased albuminuria levels are characterized by an elevated expression of galectin-3 and TGF-β [48], suggesting a M2 dominance. Although the species difference may contribute to the inconsistent findings, further investigation is necessary to determine the macrophage phenotypes in diabetic nephropathy.

Macrophage phenotype switch appears to affect the progression of STZ DN. Hemin, a heme-oxygenase inducer suppressing renal M1 macrophage, blocks the expression of macrophage inflammatory protein 1α (MIP-1α), macrophage chemoattractant protein-1 (MCP-1), IL-1β, IL-6, and TNF-α while attenuating glomerulosclerosis, tubular necrosis, tubular vacuolization, and interstitial macrophage infiltration [49]. Therefore, hemin may ameliorate diabetic nephropathy by selectively enhancing the M2 macrophages. Additionally, Toll-like receptor-2 knock-out promotes kidney macrophage M1 to M2 polarization shift, decreases albuminuria while restoring podocyte number and effacement [46]. However, enalapril treatment causing a re-polarization of the macrophages towards a M1-like phenotype appears to inhibit the progression of kidney damage in the same DN model [48]. These controversial findings about the role of macrophage phenotypes in DN may only be clarified with more careful studies.

Macrophage polarization in other kidney diseases

Lupus nephritis (LN): Lupus nephritis induced in NZB/WF1 or MRL/1pr mouse mimics the pathophysiology of human lupus nephritis. Progression of lupus nephritis is closely related to the macrophage accumulation [50,51]. Activated macrophages expressing inflammatory cytokines are considered as a marker of the disease onset while the presence of type 2-activated macrophages M2b is a sign of disease remission [52]. Therefore, macrophage polarization shift may be a characteristic of the lupus nephritis progression. However, controversies exist. Triantafyllopoulou *et al* have reported that the crescent formation and renal matrix metalloproteinase (MMP) expression requires the renal macrophages to express IL-10, MMPs, osteopontin, and growth factors such as platelet-derived growth factor C and heparin-binding EGF-like growth factor [53], suggesting that M2 macrophages may be a pathogenic factor in lupus nephritis progression. Chen *et al* have also reported recently that overexpression of granulin enhances macrophage polarization to M2b, and markedly exacerbates LN [54]. These data indicate that although both M1 and M2 polarized macrophage are involved in LN progression, their specific roles in the disease progression remain to be clearly defined.

Cisplatin nephrotoxicity: Cisplatin is a nephrotoxic agent that is widely used in blocking cancer progression. Acute kidney injury due to cisplatin nephrotoxicity (CN) is characterized by acute tubular necrosis. Early studies show that macrophage accumulation is correlated with kidney injury in CN. Blockade of macrophage infiltration promotes a functional and histological renal protection, indicating a pathogenic role of macrophages [55-57]. Although no study has been conducted to identify the macrophage polarization in CN, several studies have indicated that macrophage infiltration is closely related to the pro-inflammatory cytokine release in the CN [58,59]. Therefore, it is presumable that these macrophages are M1 phenotype.

Conclusion and perspective

A phase-dependent macrophage polarization is involved in various kidney diseases. M1 polarization appears to play a predominant role in the inflammatory stage and correlate with inflammation initiation and early tissue injury. M2 polarization is closely related to disease remission and tissue repair. However, it is very important to note that the enhanced M2 polarization may be a culprit in many abnormal repair processes such as interstitial fibrosis and crescent formation.

Several challenges hinder the progress in macrophage polarization studies in animal models. Firstly, macrophage populations are highly heterogeneous and cannot be simply divided into M1 and M2. M2 macrophages exhibit different subsets that may play different roles as diseases progress [60].

Secondly, phenotype markers co-regulated in cultured macrophages are likely expressed independent of each other in vivo. M1 or M2-associated markers may also be expressed simultaneously by the tissue macrophages [61]. Thirdly, accumulated macrophages may be derived from both blood monocytes and resident macrophage proliferation. The relative importance of blood monocyte versus resident macrophage to disease pathophysiology is likely to depend on the model type or the severity of injuries [62]. Lastly, both M1 and M2 macrophages are not stabilized phenotypes. Adoptive transferred macrophages may undergo polarization switch in vivo. Therefore, it is critically important to identify the local environmental factors that influence the macrophage polarization, as recent studies have implied [63,64].

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Conflict-of-Interest: None

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