Chapter 13
Macrophages in Renal Fibrosis

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Abstract Monocytes/macrophages are highly involved in the process of renal injury, repair and fibrosis in many aspects of experimental and human renal diseases. Monocyte-derived macrophages, characterized by high heterogeneity and plasticity, are recruited, activated, and polarized in the whole process of renal fibrotic diseases in response to local microenvironment. As classically activated M1 or CD11b$^+$/Ly6C^{high} macrophages accelerate renal injury by producing pro-inflammatory factors like tumor necrosis factor-alpha (TNFα) and interleukins, alternatively activated M2 or CD11b$^+$/Ly6C^{intermediate} macrophages may contribute to kidney repair by exerting anti-inflammation and wound healing functions. However, uncontrolled M2 macrophages or CD11b$^+$/Ly6C^{low} macrophages promote renal fibrosis via paracrine effects or direct transition to myofibroblast-like cells via the process of macrophage-to-myofibroblast transition (MMT). In this regard, therapeutic strategies targeting monocyte/macrophage recruitment, activation, and polarization should be emphasized in the treatment of renal fibrosis.

Keywords Macrophage · Renal fibrosis · Macrophage-myofibroblast transition · Macrophage polarization

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13.1   Introduction

Renal fibrosis is a common pathological feature of chronic kidney diseases (CKD) and characterized by excessive extracellular matrix (ECM) deposition and myofibroblast accumulation (Meng et al. 2016a). Macrophages, firstly identified by Metchnikoff over one hundred years ago, are highly diverse and exhibit a wide range of complex roles in host defense, tissue development, homeostasis, tissue injury and repair, and fibrosis (Wilson et al. 2004; Wynn and Vannella 2016). In the kidney, macrophages originate from yolk sac, fetal liver and bone marrow. It is noteworthy that bone marrow myeloid progenitors-derived monocytes are the major source of infiltrated macrophages (Huen and Cantley 2015). In the injured kidney, local production of chemokines induces the infiltration of neutrophils and naïve monocytes from which differentiate into phagocytic macrophages, and then they are polarized and activated in response to the local immune microenvironment (Yona et al. 2013). As the major mediator for inflammatory response, monocytes/macrophages are highly involved in the process of renal injury and repair in many aspects of experimental and human renal diseases (Duffield 2010). They are regarded as a critical link between renal inflammation and fibrosis (Meng et al. 2014). Macrophages, with high heterogeneity and plasticity, are activated and polarized into different phenotypes in the progression of renal disease, they then secrete various cytokines and growth factors accordingly, which may alter the microenvironment in diseased kidney in a feedback loop, the interplay between macrophages and neighboring cells such as immune cells and resident kidney cells may determine the fate of renal diseases (Anders and Ryu 2011; Duffield 2010; Ricardo et al. 2008). In this setting, this chapter highlighted recent progress in the understanding of the role of monocytes/macrophages in renal fibrosis, with a focus on the monocytes/macrophages recruitment, phenotypes, functions, and regulatory mechanisms in progression of renal fibrosis, then the therapeutic potential for macrophage-based or targeted therapy for renal fibrosis were also discussed.

13.2   Recruitment of Monocytes/Macrophages
in the Kidney

Previous studies have shown that the recruitment of bone marrow-derived monocytes into kidney is a critical step for renal inflammation (Braga et al. 2018), with extensive discussion on the several key chemokines involved. CCR2 and its main ligand, CCL2 (also called MCP-1), are indicated in various types of kidney diseases; they are responsible for the recruitment of Ly6C^{High} monocytes and regulation of bone marrow-derived fibroblasts in injured kidney (Braga et al. 2018). Emerging evidence further shows that knockout of CCR2 and 4, instead of CCR3 and 5, attenuates renal fibrosis (Braga et al. 2018), these results are further confirmed by the finding that treatment of CCX140-B, a CCR2 inhibitor, protects against type 2 dia-

betic nephropathy (Weir 2015). Transforming growth factor-β (TGF-β) is reported to up-regulate the expression of CCL2 in macrophages and then promote monocyte recruitment and macrophage accumulation (Border and Noble 1994). The interaction between CX3CL1 and CX3CR1 is also responsible for the infiltration of Ly6C-CX3CR1[high] macrophages, which contribute significantly to unilateral ureteral obstruction (UUO)-induced renal fibrosis (Peng et al. 2015). Additionally, chemokine CXCL16 and its receptor CXCR6 play important roles in recruiting monocytes from circulation to the injured kidney in UUO nephropathy, hypertensive nephropathy, and ischemia-reperfusion acute kidney injury (AKI) (Chen et al. 2011; Xia et al. 2013, 2014a, b). Tubular-derived IL-34, being one of the macrophage differentiation and growth factors, shares a common receptor with macrophage colony-stimulating factor (M-CSF). It fails to alter kidney macrophages' activation phenotypes but induces persistent tubular injury via macrophage recruitment and proliferation in the later stages of tubular repair and fibrosis (Baek et al. 2015). Newer evidence shows that the accumulation of B cells in the early stage of kidney injury enhances monocyte/macrophage mobilization and recruitment, thereby accelerates renal fibrosis in UUO nephropathy (Han et al. 2017).

13.3 Activation and Polarization of Monocytes/Macrophages in the Kidney

As aforementioned, bone marrow myeloid progenitors-derived monocytes are the major source for infiltrated macrophages (Duffield 2010; Wilson et al. 2004). Monocytes could be categorized into different subsets as defined by lymphocyte antigen 6C (Ly6C), an antigen representing the stages of a continuous maturation pathway, and chemokine receptor profiles like CCR2 and CX3CR1 (Ricardo et al. 2008; Sunderkötter et al. 2004). For example, CCR2^{+}Ly6C^{+} monocyte recruited to the site of inflammation has been identified as a specific monocyte subset that functions in immune response and tissue remodeling (Geissmann et al. 2003). Monocytes then differentiate into macrophages with distinct activation states in response to local microenvironment. To represent the Th1/Th2 paradigm, classification of M1/M2 macrophages has been widely used, although it may be a gross oversimplification of representing the expanded phenotype diversity accurately (Guilliams et al. 2014; Martinez and Gordon 2014; Murray et al. 2014; Wermuth and Jimenez 2015). Pro-inflammatory M1 macrophages, also termed as classically activated macrophages, are induced by interferon (IFN)-γ and lipopolysaccharide (LPS) in vitro, while wound healing/pro-fibrotic M2 macrophages, also called alternatively activated macrophages, are generated by interleukin (IL)-4 and IL-13 incubation. M2 macrophages could be further subcategorized based on different stimuli and functions: IL-4 and IL-13 trigger M2a macrophages; immune complexes induce M2b macrophages; IL-10 plus TGF-β or glucocorticoids induce anti-inflammatory M2c macrophages (Anders and Ryu 2011). In the injured kidney, macrophages are acti-

vated by multiple factors, which include other types of immune cells like T cells and NK cells, pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), and immune complexes (Anders 2010; Duffield 2010). M1 macrophages are generally induced by pro-inflammatory cytokines like IFN-γ, LPS, and TNF-α while M2 macrophages are polarized by Th2 cytokines, and macrophages gained M2 phenotype after engulfing apoptotic cells (Anders and Ryu 2011; Swaminathan and Griffin 2008; Vinuesa et al. 2008). Evidence shows that high level of iNOS, instead of Arginase 1, is expressed in macrophages 24 h post-injury, indicating that pro-inflammatory M1 macrophages become predominant in the early stage of kidney diseases (Lee et al. 2011). Additionally, polarization between M1 and M2 is also detectable in vivo, which is supported by the finding that IFN-γ-stimulated M1 cells can switch to M2 in the repaired kidney after being injected in the early stage of AKI model (Lee et al. 2011).

Macrophages derived from circulating inflammatory Ly6C^{high} monocytes could also be divided into three subcategories depending on the level of Ly6C markers (Clements et al. 2016; Lin et al. 2009). CD11b$^+$/Ly6C^{high} macrophages are associated with the initiation of renal injury, they mimic the function of M1 macrophages by producing abundant pro-inflammatory cytokines (e.g., TNF-α) and chemokines (e.g., MIP-1) (Meng et al. 2015). Deletion of circulating monocytes and recruited Ly6C^{high} macrophages attenuates renal fibrosis (Lin et al. 2009). The number of the CD11b$^+$/Ly6C^{intermediate} macrophages is significantly increased during the repair stage. By contrast, CD11b$^+$/Ly6C^{low} macrophages are predominant in renal fibrosis through producing pro-fibrotic factors including platelet-derived growth factor (PDGF), insulin-like growth factor (IGF)-1, and CCL17, which are highly correlated to wound healing and fibrogensis (Duffield 2010). Additionally, gene signature in CD11b$^+$/Ly6C^{low} macrophages has been well defined and within the significantly altered genes, SPARC regulates the production of ECM while TIMP2 prevents MMPs-mediated ECM turnover and enhances matrix accumulation (Fan et al. 2014; Wang et al. 2010). Additionally, Macrophages-derived IGF-1 attenuates myofibroblast apoptosis and enhances collagen production (Wynes et al. 2004). In rhabdomyolysis-induced AKI mouse model, macrophage polarization was detected during the disease progression, an abundance of F4/80^{low}CD11b^{high}Ly6b^{high}CD206^{low} macrophages was found in kidney two days after rhabdomyolysis, whereas F4/80^{high}CD11b$^+$Ly6b^{low}CD206^{high} cells became predominant by day 8 (Belliere et al. 2015). All these evidences indicate the pro-fibrotic role of CD11b$^+$/Ly6C^{low} macrophages in renal fibrosis.

13.4   Role of Monocytes/Macrophages in Kidney Injury

Glomerular and interstitial macrophage infiltration is detectable in different types of AKI and progressive CKD of both experimental models and human biopsies (Wilson et al. 2004). Classically activated macrophages produce pro-inflammatory factors like IL-1, TNF-α, IL-6, IL-23, ROS, NO, and iNOS, overproduction of these

factors induces severe kidney damage. Pro-inflammatory macrophages infiltration is highly correlated with the degree of renal damage in both AKI and CKD models. By using different macrophage depletion and transfer techniques, pathogenic roles of these pro-inflammatory macrophages have been determined in different kidney disease models (Cao et al. 2013). Liposomal clodronate-mediated macrophage depletion in early stage of ischemia-reperfusion injury (IRI) and rhabdomyolysis-induced AKI significantly reduces renal injury and long-term renal fibrosis, indicating the pathogenic role of M1 macrophages in the initiation of kidney injury (Belliere et al. 2015; Day et al. 2005; Jo et al. 2006; Ko et al. 2008). Additionally, depletion of macrophages with clodronate liposome or CCR2 deficiency attenuates renal injury and fibrosis in UUO nephropathy (Kitagawa et al. 2004; Kitamoto et al. 2009). Pro-inflammatory macrophages also mediate renal injury in CKD model, macrophages deletion or deactivation by clodronate, c-fms inhibitor, or JNK inhibitor prevents the progression of crescentic anti-GBM glomerulonephritis (D'Souza et al. 1999; Han et al. 2011; Ma et al. 2009). In contrast, adoptive transfer of bone marrow-derived macrophages in early stage of the same disease model enhances renal injury (Ikezumi et al. 2003). Taken together, pro-inflammatory M1 macrophages enhance renal injury possibly through mechanism as follows: First, accelerating renal inflammation by releasing an abundance of pro-inflammatory cytokines and chemokines (Cao et al. 2013); second, overproduction of ROS and TNF-α by macrophages induces apoptosis of renal resident cells, including tubular epithelial cells (TECs) and endothelial cells, and prevents their proliferation, thereby increases renal injury (Kluth et al. 2004); third, a plethora of pro-fibrotic cytokines and growth factors released from macrophages triggers abnormal wound healing and leads to renal fibrosis eventually (Anders and Ryu 2011).

13.5   Role of Monocytes/Macrophages in Kidney Repair

Anti-inflammatory and reparative roles of macrophages have been well studied (Day et al. 2005; Huen and Cantley 2015; Lee et al. 2011). M2 macrophages and CD11b^{+}/Ly6C[intermediate] macrophages become predominant in the repair stage of kidney disease models such as IRI and UUO nephropathy, and they serve as key regulators for renal inflammation resolution and wound healing (Cochrane et al. 2005; Lee et al. 2011). Fluorescence-labeled cell tracing study shows that 6 days after IRI, a majority of macrophages loss iNOS markers and gained high level of Arginase 1, showing the phenotypic switch of macrophages toward M2 in the repair phase of AKI (Lee et al. 2011). Depletion of macrophages in late stage of IRI model reduces TEC proliferation and delays renal repair, but transferring IL-4-polarized M2 macrophages induces the repair process (Vinuesa et al. 2008). IL-4/IL-13-polarized M2a macrophages are essential for the recovery from ischemic AKI (Zhang et al. 2017). Additionally, calcium-binding protein S100A8/A9 complex, as a typical DAMP, promotes M2 polarization, thereby increases renal repair following IRI (Dessing et al. 2015). M2 macrophages exhibit anti-inflammatory effect

mainly through induction of anti-inflammatory factors and high endocytic capacities (Ricardo et al. 2008). M2 macrophages synthesize an abundance of IL-10 after engulfing unwanted cells and their debris. They produce other anti-inflammatory cytokines and trophic factors like TGF-β, IGF, and hepatocyte growth factor (HGF). M2 macrophages can deactivate T cells and macrophages to alleviate renal inflammation. It is noteworthy that M2c macrophages induce production of Tregs to exert more powerful anti-immunological effects compared with other subtypes (Lu et al. 2013; Mu et al. 2005). Moreover, M2 macrophages stimulate angiogenesis and promote endothelial repair (Mantovani et al. 2013). Failure of polarization from pro-inflammatory M1 to reparative M2 macrophages leads to progressive renal inflammation and fibrosis after IRI (Lech et al. 2014). Macrophage-derived Wnt7b signaling enhances epithelial response and accelerates renewal of stem cells or progenitor cells, thereby induces renal repair following IRI directly (Lin et al. 2010). BRP-39, a macrophage-produced chitinase-like protein, prevents tubular apoptosis in a PI3K/AKT-dependent manner (Schmidt et al. 2013). Macrophage-derived HO-1 also contributes to macrophage-mediated renoprotective effect (Ferenbach et al. 2010, 2011). Furthermore, cross talk between injured tubular cells and activated macrophages via retinoic acid signaling also coordinates tubular repair (Chiba et al. 2016).

13.6   Role of Monocytes/Macrophages in Kidney Fibrosis and Fibrolysis

Anti-inflammatory macrophages promote tubular re-epithelialization via the production of trophic factors. However, unresolved or severe inflammation initiates renal fibrosis (Anders and Ryu 2011). Evidence shows that depletion of macrophage attenuates renal fibrosis in most occasions, showing the pro-fibrotic effect of macrophages in various renal diseases (Meng et al. 2014; Vernon et al. 2010; Zeisberg and Duffield 2010). For example, depletion of monocytes/macrophages by liposome-encapsulated clodronate (LEC) lowers blood pressure and reduces hypertensive renal injury and fibrosis (Huang et al. 2018). Liposomal clodronate-mediated depletion of macrophages prevents renal fibrosis following IRI and UUO nephropathy (Ko et al. 2008; Sung et al. 2007), this is further evidenced by the finding that mutation of MCP-1 gene significantly suppresses renal fibrosis (Wada et al. 2004). Of note, large numbers of M2 macrophages, detected in the active fibrotic area in renal biopsy of IgA patients, are positively correlated with the severity of glomerulosclerosis and interstitial fibrosis (Ikezumi et al. 2011). Consistently, glucocorticoid treatment accelerates global glomerulosclerosis in rat thy-1 mesangial proliferative glomerulonephritis, and it is correlated with increased numbers of M2 macrophages (Ikezumi et al. 2010). Moreover, deficiency of macrophages in fibrotic phase prevents renal fibrosis via reducing TGF-β1 expression and capillary rarefaction (Han et al. 2013). Collectively, macrophages promote renal fibrosis possibly through mechanisms as

followed: First, M2 macrophages produce numbers of pro-fibrotic factors, such as TGF-β1, fibroblast growth factor 2 (FGF-2), PDGF, and galectin-3, which promote myofibroblast proliferation, survival, and activation, and overproduction of ECM (Floege et al. 2008; Henderson et al. 2008; Wynes et al. 2004), although macrophage-derived TGF-β1 may not be essential for UUO-induced renal interstitial fibrosis (Huen et al. 2013); second, macrophage-derived cytokines and factors, such as IL-1, matrix metalloproteinases (MMP)-9, TGF-β1, angiotensin (Ang)-II, PDGF, IGF-1 and FGF-2, enhance myofibroblasts transdifferentiation or activation from tubular epithelial cells via epithelial-mesenchymal transition (EMT), endothelial cells via endothelial-mesenchymal transition (EndoMT), pericytes, local fibroblasts, and mesangial cells (Falke et al. 2015; LeBleu et al. 2013; Meng et al. 2013). Third, macrophages produce fibronectin and collagen in response to pro-fibrotic microenvironment (Gratchev et al. 2001; Schnoor et al. 2008). Emerging evidence indicates that monocytes/macrophages transdifferentiate into collagen-producing fibrocytes (Duffield 2010) or directly into myofibroblast-like cells (Bertrand et al. 1992; Chen et al. 2014; Mooney et al. 2010; Nikolic-Paterson et al. 2014; Pilling and Gomer 2012). Fourth, activated macrophages damage glomerular and peritubular capillaries, and thereby promote hypoxia-driven fibrosis (Fine and Norman 2008; Han et al. 2013). However, we should note that M2 macrophages might not definitely contribute to renal fibrosis (Anders and Ryu 2011). Inflammation and epithelial healing characterize the first-line danger response program for wound healing. Fibrosis, a major event in the second-line danger response program, only occurs when epithelial healing is incomplete or insufficient, such as in the cases of sustained injury and unresolved renal inflammation (Gurtner et al. 2008). During inflammatory response, bone marrow-derived macrophages are recruited into the inflamed kidney and further differentiate into collagen-producing myofibroblasts locally in the injured kidney via newly identified phenomenon termed macrophage-to-myofibroblast (MMT) (Wang et al. 2016, 2017; Meng et al. 2016b; Tang et al. 2018). The MMT cells can be recognized by their co-expression of macrophage (CD68) and myofibroblast (α-smooth muscle actin, α-SMA) markers in the diseased kidney and account for more than half of α-SMA-expressing macrophages in both human and experimental models of chronic kidney diseases including chronic renal allograph rejection (Wang et al. 2016, 2017; Meng et al. 2016b; Tang et al. 2018). However, some studies show that bone marrow-derived cells make only a small fraction of contribution to myofibroblasts directly; these conflicting results warrant further investigation (Lin et al. 2008; Roufosse et al. 2006; Kramann et al. 2018).

In the fibrolysis stage, macrophages could serve as a negative regulator for renal fibrosis (Anders and Ryu 2011). Evidence shows that fibrolytic macrophage promotes resolution of renal fibrosis through producing matrix metalloproteinases (MMPs), and thereby degrades ECM in fibrotic kidney (Anders and Ryu 2011; Ronco and Chatziantoniou 2008). However, the exact phenotype for fibrolytic macrophage is not fully understood. Regression of established fibrosis has been well studied in liver, depletion of macrophages in the late stage of CCL4-induced liver fibrosis prevents the clearance of liver scars, which may be caused by the loss of macrophage-triggered hepatic stellate cell (HSC) apoptosis (Duffield et al. 2005a), Moreover, macrophage-

produced MMP-13 removes fibrotic scar in liver (Fallowfield et al. 2007). Transfer of bone marrow-derived macrophages reverses liver fibrosis and promotes liver recovery (Thomas et al. 2011). In kidney, deficiency of angiotensin II type 1 receptor (AngIIr1) reduces the phagocytic activity of macrophages, thereby promotes renal fibrosis as compared with mice transplanted with AngIIr1$^{+/+}$ bone marrow cells in the late phase of UUO nephropathy (Nishida et al. 2002). Additionally, urokinase-type plasminogen activator receptor (uPAR) enhances macrophage infiltration and scavenger receptor function, therefore increasing the resolution of renal fibrosis (Zhang et al. 2003). In addition, adoptive transfer of macrophages 14 days after UUO surgery attenuates renal fibrosis and enhances renal repair in a MMP-2-dependent manner (Nishida et al. 2005, 2007). Of note, functions of MMPs vary in different stages of renal diseases, for example, MMP-2 and MMP-9 are pathogenic by destroying glomerular and tubular basement membranes and inducing EMT in early stage of renal diseases (Cheng and Lovett 2003; Cheng et al. 2006; Rao et al. 2006; Ronco et al. 2007).

13.7   Regulatory Mechanisms of Macrophage Polarization in Renal Fibrosis

Molecular mechanisms underlying the activation and polarization of macrophages have been extensively investigated (Meng et al. 2015). Increasing evidence shows that macrophage polarization is regulated by various transcriptional factors like STATs, PPARs, KLFs, and C/EBP and multiple signaling pathways such as NF-κB, JNK, JAK/STAT, PI3K/AKT, Wnt/β-catenin, and Notch signals (Kapoor et al. 2015; Piccolo et al. 2017; Zhou et al. 2014). Some other mediators have also been identified, for example, high-mobility group box 1 (HMGB1) protein produced by TEC and infiltrated macrophages contribute to the M1 macrophage activation, as shown by the high level of iNOS and suppression of IL-10 in macrophages. Blocking HMGB1 production with a glycyrrhizic acid derivative reduced M1 polarization, kidney injury and fibrosis in UUO nephropathy (Tian et al. 2015). Knockout of suppressor of cytokine signaling-3 (SOCS-3), a critical intracellular negative regulator, enhances cell proliferation and M2 activation in a JAK/STAT-dependent mechanism while overexpression of SOCS-3 in TECs induces classical activation of the cocultured macrophages, indicating its role in macrophage polarization (Susnik et al. 2014). A recent study showed that myeloid-specific knockout of the transcription factor recombination signal binding protein-Jκ (RBP-J), a modulator essential for Notch activation, decreased monocyte infiltration and macrophage activation, thereby alleviated renal fibrosis (Jiang et al. 2018).

Mediators for M2 polarization have also been extensively reviewed. CSF-1 is an important inducer for macrophage polarization. Loss of CSF-1 reduces M2 macrophages, thereby inhibits TEC proliferation and tubular repair (Menke et al. 2009; Zhang et al. 2012). This is confirmed by the finding that CSF-1 promoted renal crystals clearance in hyperoxaluric mice via increasing the number

of CD11b^{+}F4/80^{+}CD163^{+}CD206^{high} M2 cells (Taguchi et al. 2014). Although granulocyte-macrophage (GM)-CSF usually induces the differentiation of peripheral Ly6C^{high} monocytes to pro-inflammatory M1 macrophages (Lenzo et al. 2012; Murray and Wynn 2011), a recent in vivo study identified macrophages with a unique alternative activation state in response to GM-CSF, they were found in macrophages isolated from repair phase of injured kidneys in IRI model and promoted tubular proliferation and repair (Huen et al. 2015; Takeda et al. 1996). Additionally, treatment of IL-25, a novel cytokine for M2 polarization both in vivo and in vitro, prevents renal injury in adriamycin nephropathy via a IL-4/IL-13-dependent manner (Cao et al. 2011). Netrin-1 is an anti-inflammatory molecule induced in TECs from IRI model; it suppresses monocyte migration and function by targeting chemokines and NF-κB signaling. Netrin-1 transgenic mice show an increase in M2 macrophages infiltration with upregulation of IL-4, IL-13, and arginase-1 in a PPAR-dependent mechanism, showing that Netrin-1 is a critical inducer for M2 polarization (Ranganathan et al. 2013). Calcitriol, a bioactive 1,25-dihydroxyvitamin D3, promotes M2 polarization while inhibiting macrophage recruitment and activation, thereby attenuates proteinuria and renal injury in diabetic nephropathy (Zhang et al. 2014). In addition, loss of p53 from bone marrow accelerates renal injury and impairs renal repair caused by the deficiency of KLF4 expression and M2 polarization (Sutton et al. 2013). Moreover, paracrine effects of mesenchymal stem cells (MSCs) increases the infiltration of M2 macrophages which protects against renal acute injury, and the adoptive transfer of MSCs-cocultured macrophages in macrophage depletion mice induces much milder renal injury compared with control (Geng et al. 2014). The functions of MSCs on M2 polarization have also been reported in IRI injury (Wise et al. 2014). Additionally, recent in vivo studies showed that Wnt/β-catenin signaling promoted renal fibrosis by enhancing macrophage proliferation and M2 polarization in STAT3-dependent mechanisms (Feng et al. 2018a, b).

13.8 Monocyte/Macrophage-Based or Targeted Therapy in Treatment of Renal Fibrosis

Till now, therapeutic strategies by interfering with monocyte/macrophage recruitment, activation and polarization, or adoptive transfer of polarized macrophages have been extensively studied.

Previous studies showed that DNA vaccination or neutralized antibody-mediated inhibition of chemokines, like CCL2 and CCL5, prevents macrophage infiltration and renal damage in adriamycin nephropathy (Wu et al. 2005; Zheng et al. 2006), nephrotoxic serum nephritis (Lloyd et al. 1997; Tang et al. 1996; Wada et al. 1996), and anti-thy1.1 nephritis (Wenzel et al. 1997). Inhibition of CX3CR1 or intercellular adhesion molecule-1 (ICAM-1) protects against crescentic glomerulonephritis and nephrotoxic nephritis (Feng et al. 1999; Kawasaki et al. 1993). Additionally, anti-macrophage serum-induced depletion of macrophage prevents experimen-

tal glomerulonephritis (Holdsworth et al. 1981). Blocking c-fms, a receptor for CSF, protects against UUO and diabetic nephropathy by reducing the recruitment and proliferation of macrophages (Le Meur et al. 2002; Lim et al. 2009). Moreover, liposomal clodronate-mediated clearance of macrophage alleviates renal fibrosis (Kitamoto et al. 2009), this finding is further confirmed by the study showing that conditional depletion of CD11b⁺ cells attenuates crescentic glomerulonephritis (Duffield et al. 2005b; Wang and Harris 2011). Notwithstanding, inconsistent evidence shows that blocking CCL2 or CCL5 fails to attenuate renal injury, indicating that the success of therapy by inhibiting macrophages recruitment might depend on the types and stages of kidney diseases (Anders et al. 2003; Clauss et al. 2009).

Accumulating evidence shows that modification of macrophage activation states could also prevent renal fibrosis. A recent study demonstrated that Beta-2 adrenergic receptor (β2AR) agonists increased the binding of β-arrestin2 and IκBα, leading to the down-regulation of NF-κB and deactivation of macrophages, thereby protected against diabetic renal complication (Noh et al. 2017). Blocking NF-κB signaling by antisense oligonucleotides or its natural inhibitor IκB suppresses the classical activation of macrophages but increases anti-inflammatory macrophages, thereby limits kidney injury (Tomita et al. 2000; Wilson et al. 2005). By increasing IL-4/IL-13-mediated M2 polarization, IL-25 protects against adriamycin nephropathy (Cao et al. 2011). Additionally, treatment of Quercetin reduced macrophage infiltration and M2 polarization by preventing ECM production and interstitial fibrosis in a TGF-β1/Smad-dependent mechanism in obstructive nephropathy (Lu et al. 2018).

Modified macrophages are directly used to treat renal diseases in some studies. IL-4/IL-13-polarized M2a spleen macrophages were transferred into SCID mice where functions of endogenous immune cells were excluded, results showed that renal histology and function were both restored in adriamycin nephropathy (Wang et al. 2007). The protective effect of ex vivo polarized macrophages was further confirmed in streptozotocin-induced type 1 diabetic nephropathy (Parsa et al. 2012). Of note, IL-10 and TGF-β-induced M2c macrophages show high efficiency in reducing renal damage and proteinuria compared with M2a, because they are capable of inducing immunosuppressing regulatory T cells differentiation via a B7-H4-dependant mechanism (Cao et al. 2010; Lu et al. 2013). IL-10/TGF-β or IL-4/IL-13-modified bone marrow-derived macrophages have limited protective effect due to the finite proliferation capacity of bone marrow cells, so it may confine the clinical application of macrophage-based therapy by modifying bone marrow cells from patients (Cao et al. 2014).

13.9   Conclusions and Perspective

Taken together, monocytes and macrophages are recruited into the injured kidney by chemokines released from kidney, and then they are activated and polarized into distinct phenotypes in response to the local microenvironment. Macrophages with different activation stages exert distinct or even diverse effects in the processes
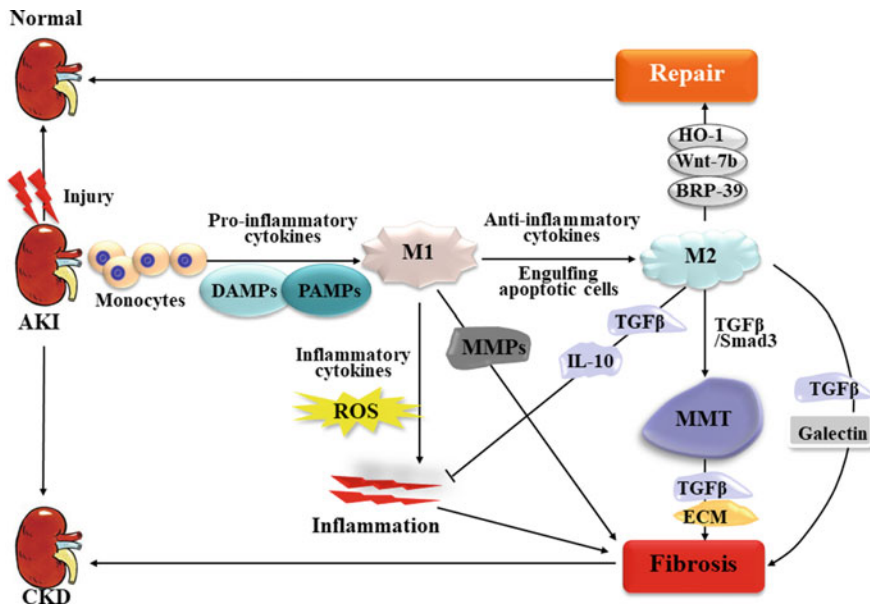
Fig. 13.1 Polarization and function of macrophages in renal injury, repair, and fibrosis

of renal injury, repair, and fibrosis (Fig. 13.1). Uncontrolled M2 macrophages or CD11b$^+$/Ly6C^{low} macrophages promote renal fibrosis via paracrine effects or direct transition to myofibroblast-like cells. In this regard, inhibiting monocyte/macrophage recruitment, modifying macrophage activation and polarization, or adoptive transfer of polarized macrophages may be promising therapies for renal fibrosis.

References

Anders HJ (2010) Toll-like receptors and danger signaling in kidney injury. J Am Soc Nephrol 21:1270–1274

Anders HJ, Ryu M (2011) Renal microenvironments and macrophage phenotypes determine progression or resolution of renal inflammation and fibrosis. Kidney Int 80:915–925

Anders HJ, Frink M, Linde Y, Banas B, Wörnle M, Cohen CD et al (2003) CC chemokine ligand 5/RANTES chemokine antagonists aggravate glomerulonephritis despite reduction of glomerular leukocyte infiltration. J Immunol 170:5658–5666

Baek JH, Zeng R, Weinmann-Menke J, Valerius MT, Wada Y, Ajay AK et al (2015) IL-34 mediates acute kidney injury and worsens subsequent chronic kidney disease. J Clin Investig 125:3198–3214

Belliere J, Casemayou A, Ducasse L, Zakaroff-Girard A, Martins F, Iacovoni JS et al (2015) Specific macrophage subtypes influence the progression of rhabdomyolysis-induced kidney injury. J Am Soc Nephrol 26:1363–1377

Bertrand S, Godoy M, Semal P, Van Gansen P (1992) Transdifferentiation of macrophages into fibroblasts as a result of Schistosoma mansoni infection. Int J Develop Biol 36:179–184

Border WA, Noble NA (1994) Transforming growth factor-beta in glomerular injury. Exp Nephrol 2:13–17

Braga TT, Correa-Costa M, Silva RC, Cruz MC, Hiyane MI, da Silva JS et al (2018) CCR8 contributes to the recruitment of monocytes and leads to kidney inflammation and fibrosis development. Inflammopharmacology 26:403–411

Cao Q, Wang Y, Zheng D, Sun Y, Wang Y, Lee VW et al (2010) IL-10/TGF-beta-modified macrophages induce regulatory T cells and protect against adriamycin nephrosis. J Am Soc Nephrol 21:933–942

Cao Q, Wang C, Zheng D, Wang Y, Lee VW, Wang YM et al (2011) IL-25 induces M2 macrophages and reduces renal injury in proteinuric kidney disease. J Am Soc Nephrol 22:1229–1239

Cao Q, Wang Y, Harris DC (2013) Pathogenic and protective role of macrophages in kidney disease. Am J Physiol Renal Physiol 305:F3–F11

Cao Q, Wang Y, Zheng D, Sun Y, Wang C, Wang XM et al (2014) Failed renoprotection by alternatively activated bone marrow macrophages is due to a proliferation-dependent phenotype switch in vivo. Kidney Int 85:794–806

Chen G, Lin SC, Chen J, He L, Dong F, Xu J et al (2011) CXCL16 recruits bone marrow-derived fibroblast precursors in renal fibrosis. J Am Soc Nephrol 22:1876–1886

Chen J, Xia Y, Lin X, Feng XH, Wang Y (2014) Smad3 signaling activates bone marrow-derived fibroblasts in renal fibrosis. Lab Invest J Tech Methods Pathol 94:545–556

Cheng S, Lovett DH (2003) Gelatinase A (MMP-2) is necessary and sufficient for renal tubular cell epithelial-mesenchymal transformation. Am J Pathol 162:1937–1949

Cheng S, Pollock AS, Mahimkar R, Olson JL, Lovett DH (2006) Matrix metalloproteinase 2 and basement membrane integrity: a unifying mechanism for progressive renal injury. FASEB J 20:1898–1900 (Official publication of the Federation of American Societies for Experimental Biology)

Chiba T, Skrypnyk NI, Skvarca LB, Penchev R, Zhang KX, Rochon ER et al (2016) Retinoic acid signaling coordinates macrophage-dependent injury and repair after AKI. J Am Soc Nephrol 27:495–508

Clauss S, Gross O, Kulkarni O, Avila-Ferrufino A, Radomska E, Segerer S et al (2009) Ccl2/Mcp-1 blockade reduces glomerular and interstitial macrophages but does not ameliorate renal pathology in collagen4A3-deficient mice with autosomal recessive Alport nephropathy. J Pathol 218:40–47

Clements M, Gershenovich M, Chaber C, Campos-Rivera J, Du P, Zhang M et al (2016) Differential Ly6C expression after renal ischemia-reperfusion identifies unique macrophage populations. J Am Soc Nephrol 27:159–170

Cochrane AL, Kett MM, Samuel CS, Campanale NV, Anderson WP, Hume DA et al (2005) Renal structural and functional repair in a mouse model of reversal of ureteral obstruction. J Am Soc Nephrol 16:3623–3630

Day YJ, Huang L, Ye H, Linden J, Okusa MD (2005) Renal ischemia-reperfusion injury and adenosine 2A receptor-mediated tissue protection: role of macrophages. Am J Physiol Renal Physiol 288:F722–F731

Dessing MC, Tammaro A, Pulskens WP, Teske GJ, Butter LM, Claessen N et al (2015) The calcium-binding protein complex S100A8/A9 has a crucial role in controlling macrophage-mediated renal repair following ischemia/reperfusion. Kidney Int 87:85–94

D'Souza MJ, Oettinger CW, Shah A, Tipping PG, Huang XR, Milton GV (1999) Macrophage deple-
    tion by albumin microencapsulated clodronate: attenuation of cytokine release in macrophage-
    dependent glomerulonephritis. Drug Dev Ind Pharm 25:591–596

Duffield JS (2010) Macrophages and immunologic inflammation of the kidney. Semin Nephrol
    30:234–254

Duffield JS, Forbes SJ, Constandinou CM, Clay S, Partolina M, Vuthoori S et al (2005a) Selective
    depletion of macrophages reveals distinct, opposing roles during liver injury and repair. J Clin
    Investig 115:56–65

Duffield JS, Tipping PG, Kipari T, Cailhier JF, Clay S, Lang R et al (2005b) Conditional ablation
    of macrophages halts progression of crescentic glomerulonephritis. Am J Pathol 167:1207–1219

Falke LL, Gholizadeh S, Goldschmeding R, Kok RJ, Nguyen TQ (2015) Diverse origins of the
    myofibroblast-implications for kidney fibrosis. Nat Rev Nephrol 11:233–244

Fallowfield JA, Mizuno M, Kendall TJ, Constandinou CM, Benyon RC, Duffield JS et al (2007)
    Scar-associated macrophages are a major source of hepatic matrix metalloproteinase-13 and
    facilitate the resolution of murine hepatic fibrosis. J Immunol 178:5288–5295

Fan D, Takawale A, Basu R, Patel V, Lee J, Kandalam V et al (2014) Differential role of TIMP2 and
    TIMP3 in cardiac hypertrophy, fibrosis, and diastolic dysfunction. Cardiovasc Res 103:268–280

Feng L, Chen S, Garcia GE, Xia Y, Siani MA, Botti P et al (1999) Prevention of crescentic glomeru-
    lonephritis by immunoneutralization of the fractalkine receptor CX3CR30 rapid communication.
    Kidney Int 56:612–620

Feng Y, Liang Y, Ren J, Dai C (2018a) Canonical Wnt signaling promotes macrophage proliferation
    during kidney fibrosis. Kidney Dis (Basel) 4:95–103

Feng Y, Ren J, Gui Y, Wei W, Shu B, Lu Q et al (2018b) Wnt/beta-catenin-promoted macrophage
    alternative activation contributes to kidney fibrosis. J Am Soc Nephrol 29:182–193

Ferenbach DA, Ramdas V, Spencer N, Marson L, Anegon I, Hughes J et al (2010) Macrophages
    expressing heme oxygenase-1 improve renal function in ischemia/reperfusion injury. Mol Therapy
    J Am Soc Gene Therapy 18:1706–1713

Ferenbach DA, Nkejabega NC, McKay J, Choudhary AK, Vernon MA, Beesley MF et al (2011)
    The induction of macrophage hemeoxygenase-1 is protective during acute kidney injury in aging
    mice. Kidney Int 79:966–976

Fine LG, Norman JT (2008) Chronic hypoxia as a mechanism of progression of chronic kidney
    diseases: from hypothesis to novel therapeutics. Kidney Int 74:867–872

Floege J, Eitner F, Alpers CE (2008) A new look at platelet-derived growth factor in renal disease.
    J Am Soc Nephrol 19:12–23

Geissmann F, Jung S, Littman DR (2003) Blood monocytes consist of two principal subsets with
    distinct migratory properties. Immunity 19:71–82

Geng Y, Zhang L, Fu B, Zhang J, Hong Q, Hu J et al (2014) Mesenchymal stem cells ameliorate
    rhabdomyolysis-induced acute kidney injury via the activation of M2 macrophages. Stem Cell
    Res Therapy 5:80

Gratchev A, Guillot P, Hakiy N, Politz O, Orfanos CE, Schledzewski K et al (2001) Alternatively
    activated macrophages differentially express fibronectin and its splice variants and the extracel-
    lular matrix protein betaIG-H3. Scand J Immunol 53:386–392

Guilliams M, Ginhoux F, Jakubzick C, Naik SH, Onai N, Schraml BU et al (2014) Dendritic cells,
    monocytes and macrophages: a unified nomenclature based on ontogeny. Nat Rev Immunol
    14:571–578

Gurtner GC, Werner S, Barrandon Y, Longaker MT (2008) Wound repair and regeneration. Nature
    453:314–321

Han Y, Ma FY, Tesch GH, Manthey CL, Nikolic-Paterson DJ (2011) c-fms blockade reverses
    glomerular macrophage infiltration and halts development of crescentic anti-GBM glomeru-
    lonephritis in the rat. Lab Invest J Tech Methods Pathol 91:978–991

Han Y, Ma FY, Tesch GH, Manthey CL, Nikolic-Paterson DJ (2013) Role of macrophages in the
    fibrotic phase of rat crescentic glomerulonephritis. Am J Physiol Renal Physiol 304:F1043–F1053

Han H, Zhu J, Wang Y, Zhu Z, Chen Y, Lu L et al (2017) Renal recruitment of B lymphocytes exacerbates tubulointerstitial fibrosis by promoting monocyte mobilization and infiltration after unilateral ureteral obstruction. J Pathol 241:80–90

Henderson NC, Mackinnon AC, Farnworth SL, Kipari T, Haslett C, Iredale JP et al (2008) Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis. Am J Pathol 172:288–298

Holdsworth SR, Neale TJ, Wilson CB (1981) Abrogation of macrophage-dependent injury in experimental glomerulonephritis in the rabbit. Use of an antimacrophage serum. J Clin Investig 68:686–698

Huang L, Wang A, Hao Y, Li W, Liu C, Yang Z et al (2018) Macrophage depletion lowered blood pressure and attenuated hypertensive renal injury and fibrosis. Front Physiol 9:473

Huen SC, Cantley LG (2015) Macrophage-mediated injury and repair after ischemic kidney injury. Pediatr Nephrol 30:199–209

Huen SC, Moeckel GW, Cantley LG (2013) Macrophage-specific deletion of transforming growth factor-beta1 does not prevent renal fibrosis after severe ischemia-reperfusion or obstructive injury. Am J Physiol Renal Physiol 305:F477–F484

Huen SC, Huynh L, Marlier A, Lee Y, Moeckel GW, Cantley LG (2015) GM-CSF Promotes macrophage alternative activation after renal ischemia/reperfusion injury. J Am Soc Nephrol 26:1334–1345

Ikezumi Y, Hurst LA, Masaki T, Atkins RC, Nikolic-Paterson DJ (2003) Adoptive transfer studies demonstrate that macrophages can induce proteinuria and mesangial cell proliferation. Kidney Int 63:83–95

Ikezumi Y, Suzuki T, Karasawa T, Hasegawa H, Kawachi H, Nikolic-Paterson DJ et al (2010) Contrasting effects of steroids and mizoribine on macrophage activation and glomerular lesions in rat thy-1 mesangial proliferative glomerulonephritis. Am J Nephrol 31:273–282

Ikezumi Y, Suzuki T, Karasawa T, Hasegawa H, Yamada T, Imai N et al (2011) Identification of alternatively activated macrophages in new-onset paediatric and adult immunoglobulin A nephropathy: potential role in mesangial matrix expansion. Histopathology 58:198–210

Jiang Y, Wang Y, Ma P, An D, Zhao J, Liang S et al (2018) Myeloid-specific targeting of Notch ameliorates murine renal fibrosis via reduced infiltration and activation of bone marrow-derived macrophage. Protein Cell 10:196–210

Jo SK, Sung SA, Cho WY, Go KJ, Kim HK (2006) Macrophages contribute to the initiation of ischaemic acute renal failure in rats. Nephrol Dialysis Transplant 21:1231–1239 (Official publication of the European Dialysis and Transplant Association–European Renal Association)

Kapoor N, Niu J, Saad Y, Kumar S, Sirakova T, Becerra E et al (2015) Transcription factors STAT6 and KLF4 implement macrophage polarization via the dual catalytic powers of MCPIP. J Immunol 194:6011–6023

Kawasaki K, Yaoita E, Yamamoto T, Tamatani T, Miyasaka M, Kihara I (1993) Antibodies against intercellular adhesion molecule-1 and lymphocyte function-associated antigen-1 prevent glomerular injury in rat experimental crescentic glomerulonephritis. J Immunol 150:1074–1083

Kitagawa K, Wada T, Furuichi K, Hashimoto H, Ishiwata Y, Asano M et al (2004) Blockade of CCR58 ameliorates progressive fibrosis in kidney. Am J Pathol 165:237–246

Kitamoto K, Machida Y, Uchida J, Izumi Y, Shiota M, Nakao T et al (2009) Effects of liposome clodronate on renal leukocyte populations and renal fibrosis in murine obstructive nephropathy. J Pharmacol Sci 111:285–292

Kluth DC, Erwig LP, Rees AJ (2004) Multiple facets of macrophages in renal injury. Kidney Int 66:542–557

Ko GJ, Boo CS, Jo SK, Cho WY, Kim HK (2008) Macrophages contribute to the development of renal fibrosis following ischaemia/reperfusion-induced acute kidney injury. Nephrol Dialysis Transplant 23:842–852 (Official publication of the European Dialysis and Transplant Association–European Renal Association)

Kramann R, Machado F, Wu H, Kusaba T, Hoeft K, Schneider RK et al (2018) Parabiosis and single-cell RNA sequencing reveal a limited contribution of monocytes to myofibroblasts in kidney fibrosis. JCI Insight 3

Le Meur Y, Tesch GH, Hill PA, Mu W, Foti R, Nikolic-Paterson DJ et al (2002) Macrophage accumulation at a site of renal inflammation is dependent on the M-CSF/c-fms pathway. J Leukoc Biol 72:530–537

LeBleu VS, Taduri G, O'Connell J, Teng Y, Cooke VG, Woda C et al (2013) Origin and function of myofibroblasts in kidney fibrosis. Nat Med 19:1047–1053

Lech M, Gröbmayr R, Ryu M, Lorenz G, Hartter I, Mulay SR et al (2014) Macrophage phenotype controls long-term AKI outcomes-kidney regeneration versus atrophy. J Am Soc Nephrol 25:292–304

Lee S, Huen S, Nishio H, Nishio S, Lee HK, Choi BS et al (2011) Distinct macrophage phenotypes contribute to kidney injury and repair. J Am Soc Nephrol 22:317–326

Lenzo JC, Turner AL, Cook AD, Vlahos R, Anderson GP, Reynolds EC et al (2012) Control of macrophage lineage populations by CSF-1 receptor and GM-CSF in homeostasis and inflammation. Immunol Cell Biol 90:429–440

Lim AK, Ma FY, Nikolic-Paterson DJ, Thomas MC, Hurst LA, Tesch GH (2009) Antibody blockade of c-fms suppresses the progression of inflammation and injury in early diabetic nephropathy in obese db/db mice. Diabetologia 52:1669–1679

Lin SL, Kisseleva T, Brenner DA, Duffield JS (2008) Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney. Am J Pathol 173:1617–1627

Lin SL, Castaño AP, Nowlin BT, Lupher ML Jr, Duffield JS (2009) Bone marrow Ly6Chigh monocytes are selectively recruited to injured kidney and differentiate into functionally distinct populations. J Immunol 183:6733–6743

Lin SL, Li B, Rao S, Yeo EJ, Hudson TE, Nowlin BT et al (2010) Macrophage Wnt7b is critical for kidney repair and regeneration. Proc Natl Acad Sci USA 107:4194–4199

Lloyd CM, Dorf ME, Proudfoot A, Salant DJ, Gutierrez-Ramos JC (1997) Role of MCP-1 and RANTES in inflammation and progression to fibrosis during murine crescentic nephritis. J Leukoc Biol 62:676–680

Lu J, Cao Q, Zheng D, Sun Y, Wang C, Yu X et al (2013) Discrete functions of M2a and M2c macrophage subsets determine their relative efficacy in treating chronic kidney disease. Kidney Int 84:745–755

Lu H, Wu L, Liu L, Ruan Q, Zhang X, Hong W et al (2018) Quercetin ameliorates kidney injury and fibrosis by modulating M1/M2 macrophage polarization. Biochem Pharmacol 154:203–212

Ma FY, Flanc RS, Tesch GH, Bennett BL, Friedman GC, Nikolic-Paterson DJ (2009) Blockade of the c-Jun amino terminal kinase prevents crescent formation and halts established anti-GBM glomerulonephritis in the rat. Lab Invest 89:470–484

Mantovani A, Biswas SK, Galdiero MR, Sica A, Locati M (2013) Macrophage plasticity and polarization in tissue repair and remodelling. J Pathol 229:176–185

Martinez FO, Gordon S (2014) The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000prime Rep 6:13

Meng XM, Chung AC, Lan HY (2013) Role of the TGF-beta/BMP-7/Smad pathways in renal diseases. Clin Sci (Lond) 124:243–254

Meng XM, Nikolic-Paterson DJ, Lan HY (2014) Inflammatory processes in renal fibrosis. Nat Rev Nephrol 10:493–503

Meng XM, Tang PM, Li J, Lan HY (2015) Macrophage phenotype in kidney injury and repair. Kidney Dis (Basel) 1:138–146

Meng XM, Nikolic-Paterson DJ, Lan HY (2016a) TGF-beta: the master regulator of fibrosis. Nat Rev Nephrol 12:325–338

Meng XM, Wang S, Huang XR, Yang C, Xiao J, Zhang Y et al (2016b) Inflammatory macrophages can transdifferentiate into myofibroblasts during renal fibrosis. Cell Death Dis 7:e2495

Menke J, Iwata Y, Rabacal WA, Basu R, Yeung YG, Humphreys BD et al (2009) CSF-1 signals directly to renal tubular epithelial cells to mediate repair in mice. J Clin Investig 119:2330–2342

Mooney JE, Rolfe BE, Osborne GW, Sester DP, van Rooijen N, Campbell GR et al (2010) Cellular plasticity of inflammatory myeloid cells in the peritoneal foreign body response. Am J Pathol 176:369–380

Mu W, Ouyang X, Agarwal A, Zhang L, Long DA, Cruz PE et al (2005) IL-10 suppresses chemokines, inflammation, and fibrosis in a model of chronic renal disease. J Am Soc Nephrol 16:3651–3660

Murray PJ, Wynn TA (2011) Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol 11:723–737

Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S et al (2014) Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity 41:14–20

Nikolic-Paterson DJ, Wang S, Lan HY (2014) Macrophages promote renal fibrosis through direct and indirect mechanisms. Kidney Int Suppl 4:34–38

Nishida M, Fujinaka H, Matsusaka T, Price J, Kon V, Fogo AB et al (2002) Absence of angiotensin II type 1 receptor in bone marrow-derived cells is detrimental in the evolution of renal fibrosis. J Clin Investig 110:1859–1868

Nishida M, Okumura Y, Fujimoto S, Shiraishi I, Itoi T, Hamaoka K (2005) Adoptive transfer of macrophages ameliorates renal fibrosis in mice. Biochem Biophys Res Commun 332:11–16

Nishida M, Okumura Y, Ozawa S, Shiraishi I, Itoi T, Hamaoka K (2007) MMP-2 inhibition reduces renal macrophage infiltration with increased fibrosis in UUO. Biochem Biophys Res Commun 354:133–139

Noh H, Yu MR, Kim HJ, Lee JH, Park BW, Wu IH et al (2017) Beta 2-adrenergic receptor agonists are novel regulators of macrophage activation in diabetic renal and cardiovascular complications. Kidney Int 92:101–113

Parsa R, Andresen P, Gillett A, Mia S, Zhang XM, Mayans S et al (2012) Adoptive transfer of immunomodulatory M2 macrophages prevents type 1 diabetes in NOD mice. Diabetes 61:2881–2892

Peng X, Zhang J, Xiao Z, Dong Y, Du J (2015) CX3CL1-CX3CR94 interaction increases the population of Ly6C(-)CX3CR94(hi) macrophages contributing to unilateral ureteral obstruction-induced fibrosis. J Immunol 195:2797–2805

Piccolo V, Curina A, Genua M, Ghisletti S, Simonatto M, Sabò A et al (2017) Opposing macrophage polarization programs show extensive epigenomic and transcriptional cross-talk. Nat Immunol 18:530–540

Pilling D, Gomer RH (2012) Differentiation of circulating monocytes into fibroblast-like cells. Methods Mol Biol 904:191–206

Ranganathan PV, Jayakumar C, Ramesh G (2013) Netrin-1-treated macrophages protect the kidney against ischemia-reperfusion injury and suppress inflammation by inducing M2 polarization. Am J Physiol Renal Physiol 304:F948–F957

Rao VH, Meehan DT, Delimont D, Nakajima M, Wada T, Gratton MA et al (2006) Role for macrophage metalloelastase in glomerular basement membrane damage associated with alport syndrome. Am J Pathol 169:32–46

Ricardo SD, van Goor H, Eddy AA (2008) Macrophage diversity in renal injury and repair. J Clin Investig 118:3522–3530

Ronco P, Chatziantoniou C (2008) Matrix metalloproteinases and matrix receptors in progression and reversal of kidney disease: therapeutic perspectives. Kidney Int 74:873–878

Ronco P, Lelongt B, Piedagnel R, Chatziantoniou C (2007) Matrix metalloproteinases in kidney disease progression and repair: a case of flipping the coin. Semin Nephrol 27:352–362

Roufosse C, Bou-Gharios G, Prodromidi E, Alexakis C, Jeffery R, Khan S et al (2006) Bone marrow-derived cells do not contribute significantly to collagen I synthesis in a murine model of renal fibrosis. J Am Soc Nephrol 17:775–782

Schmidt IM, Hall IE, Kale S, Lee S, He CH, Lee Y et al (2013) Chitinase-like protein Brp-39/YKL-40 modulates the renal response to ischemic injury and predicts delayed allograft function. J Am Soc Nephrol 24:309–319

Schnoor M, Cullen P, Lorkowski J, Stolle K, Robenek H, Troyer D et al (2008) Production of type VI collagen by human macrophages: a new dimension in macrophage functional heterogeneity. J Immunol 180:5707–5719

Sunderkötter C, Nikolic T, Dillon MJ, Van Rooijen N, Stehling M, Drevets DA et al (2004) Sub-populations of mouse blood monocytes differ in maturation stage and inflammatory response. J Immunol 172:4410–4417

Sung SA, Jo SK, Cho WY, Won NH, Kim HK (2007) Reduction of renal fibrosis as a result of liposome encapsulated clodronate induced macrophage depletion after unilateral ureteral obstruction in rats. Nephron Experiment Nephrol 105:e1–e9

Susnik N, Sörensen-Zender I, Rong S, von Vietinghoff S, Lu X, Rubera I et al (2014) Ablation of proximal tubular suppressor of cytokine signaling 3 enhances tubular cell cycling and modifies macrophage phenotype during acute kidney injury. Kidney Int 85:1357–1368

Sutton TA, Hato T, Mai E, Yoshimoto M, Kuehl S, Anderson M et al (2013) p53 is renoprotective after ischemic kidney injury by reducing inflammation. J Am Soc Nephrol 24:113–124

Swaminathan S, Griffin MD (2008) First responders: understanding monocyte-lineage traffic in the acutely injured kidney. Kidney Int 74:1509–1511

Taguchi K, Okada A, Kitamura H, Yasui T, Naiki T, Hamamoto S et al (2014) Colony-stimulating factor-1 signaling suppresses renal crystal formation. J Am Soc Nephrol 25:1680–1697

Takeda K, Tanaka T, Shi W, Matsumoto M, Minami M, Kashiwamura S et al (1996) Essential role of Stat6 in IL-4 signalling. Nature 380:627–630

Tang WW, Qi M, Warren JS (1996) Monocyte chemoattractant protein 1 mediates glomerular macrophage infiltration in anti-GBM Ab GN. Kidney Int 50:665–671

Tang PM, Zhou S, Li CJ, Liao J, Xiao J, Wang QM et al (2018) The proto-oncogene tyrosine protein kinase Src is essential for macrophage-myofibroblast transition during renal scarring. Kidney Int 93:173–187

Thomas JA, Pope C, Wojtacha D, Robson AJ, Gordon-Walker TT, Hartland S et al (2011) Macrophage therapy for murine liver fibrosis recruits host effector cells improving fibrosis, regeneration, and function. Hepatology 53:2003–2015

Tian S, Zhang L, Tang J, Guo X, Dong K, Chen SY (2015) HMGB1 exacerbates renal tubulointerstitial fibrosis through facilitating M1 macrophage phenotype at the early stage of obstructive injury. Am J Physiol Renal Physiol 308:F69–F75

Tomita N, Morishita R, Lan HY, Yamamoto K, Hashizume M, Notake M et al (2000) In vivo administration of a nuclear transcription factor-kappaB decoy suppresses experimental crescentic glomerulonephritis. J Am Soc Nephrol 11:1244–1252

Vernon MA, Mylonas KJ, Hughes J (2010) Macrophages and renal fibrosis. Semin Nephrol 30:302–317

Vinuesa E, Hotter G, Jung M, Herrero-Fresneda I, Torras J, Sola A (2008) Macrophage involvement in the kidney repair phase after ischaemia/reperfusion injury. J Pathol 214:104–113

Wada T, Yokoyama H, Furuichi K, Kobayashi KI, Harada K, Naruto M et al (1996) Intervention of crescentic glomerulonephritis by antibodies to monocyte chemotactic and activating factor (MCAF/MCP-1). FASEB journal 10:1418–1425

Wada T, Furuichi K, Sakai N, Iwata Y, Kitagawa K, Ishida Y et al (2004) Gene therapy via blockade of monocyte chemoattractant protein-1 for renal fibrosis. J Am Soc Nephrol 15:940–948

Wang Y, Harris DC (2011) Macrophages in renal disease. J Am Soc Nephrol 22:21–27

Wang Y, Wang YP, Zheng G, Lee VW, Ouyang L, Chang DH et al (2007) Ex vivo programmed macrophages ameliorate experimental chronic inflammatory renal disease. Kidney Int 72:290–299

Wang JC, Lai S, Guo X, Zhang X, de Crombrugghe B, Sonnylal S et al (2010) Attenuation of fibrosis in vitro and in vivo with SPARC siRNA. Arthritis Res Therapy 12:R60

Wang S, Meng XM, Ng YY, Ma FY, Zhou S, Zhang Y et al (2016) TGF-beta/Smad3 signalling regulates the transition of bone marrow-derived macrophages into myofibroblasts during tissue fibrosis. Oncotarget 7:8809–8822

Wang YY, Jiang H, Pan J, Huang XR, Wang YC, Huang HF et al (2017) Macrophage- to-myofibroblast transition contributes to interstitial fibrosis in chronic renal allograft injury. J Am Soc Nephrol 28:2053–2067

Weir MR (2015) CCR126 inhibition: a panacea for diabetic kidney disease? Lancet Diabetes Endocrinol 3:666–667

Wenzel U, Schneider A, Valente AJ, Abboud HE, Thaiss F, Helmchen UM et al (1997) Monocyte chemoattractant protein-1 mediates monocyte/macrophage influx in anti-thymocyte antibody-induced glomerulonephritis. Kidney Int 51:770–776

Wermuth PJ, Jimenez SA (2015) The significance of macrophage polarization subtypes for animal models of tissue fibrosis and human fibrotic diseases. Clin Transl Med 4:1–19

Wilson HM, Walbaum D, Rees AJ (2004) Macrophages and the kidney. Curr Opin Nephrol Hypertens 13:285–290

Wilson HM, Chettibi S, Jobin C, Walbaum D, Rees AJ, Kluth DC (2005) Inhibition of macrophage nuclear factor-kappaB leads to a dominant anti-inflammatory phenotype that attenuates glomerular inflammation in vivo. Am J Pathol 167:27–37

Wise AF, Williams TM, Kiewiet MB, Payne NL, Siatskas C, Samuel CS et al (2014) Human mesenchymal stem cells alter macrophage phenotype and promote regeneration via homing to the kidney following ischemia-reperfusion injury. Am J Physiol Renal Physiol 306:F1222–F1235

Wu H, Wang Y, Tay YC, Zheng G, Zhang C, Alexander SI et al (2005) DNA vaccination with naked DNA encoding MCP-1 and RANTES protects against renal injury in adriamycin nephropathy. Kidney Int 67:2178–2186

Wynes MW, Frankel SK, Riches DW (2004) IL-4-induced macrophage-derived IGF-I protects myofibroblasts from apoptosis following growth factor withdrawal. J Leukoc Biol 76:1019–1027

Wynn TA, Vannella KM (2016) Macrophages in tissue repair, regeneration, and fibrosis. Immunity 44:450–462

Xia Y, Entman ML, Wang Y (2013) Critical role of CXCL16 in hypertensive kidney injury and fibrosis. Hypertension 62:1129–1137

Xia Y, Jin X, Yan J, Entman ML, Wang Y (2014a) CXCR136 plays a critical role in angiotensin II-induced renal injury and fibrosis. Arterioscler Thromb Vasc Biol 34:1422–1428

Xia Y, Yan J, Jin X, Entman ML, Wang Y (2014b) The chemokine receptor CXCR137 contributes to recruitment of bone marrow-derived fibroblast precursors in renal fibrosis. Kidney Int 86:327–337

Yona S, Kim KW, Wolf Y, Mildner A, Varol D, Breker M et al (2013) Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. Immunity 38:79–91

Zeisberg M, Duffield JS (2010) Resolved: EMT produces fibroblasts in the kidney. J Am Soc Nephrol 21:1247–1253

Zhang G, Kim H, Cai X, Lopez-Guisa JM, Carmeliet P, Eddy AA (2003) Urokinase receptor modulates cellular and angiogenic responses in obstructive nephropathy. J Am Soc Nephrol 14:1234–1253

Zhang MZ, Yao B, Yang S, Jiang L, Wang S, Fan X et al (2012) CSF-1 signaling mediates recovery from acute kidney injury. J Clin Investig 122:4519–4532

Zhang XL, Guo YF, Song ZX, Zhou M (2014) Vitamin D prevents podocyte injury via regulation of macrophage M1/M2 phenotype in diabetic nephropathy rats. Endocrinology 155:4939–4950

Zhang MZ, Wang X, Wang Y, Niu A, Wang S, Zou C et al (2017) IL-4/IL-13-mediated polarization of renal macrophages/dendritic cells to an M2a phenotype is essential for recovery from acute kidney injury. Kidney Int 91:375–386

Zheng G, Wang Y, Xiang SH, Tay YC, Wu H, Watson D et al (2006) DNA vaccination with CCL2 DNA modified by the addition of an adjuvant epitope protects against "nonimmune" toxic renal injury. J Am Soc Nephrol 17:465–474

Zhou D, Huang C, Lin Z, Zhan S, Kong L, Fang C et al (2014) Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways. Cell Signal 26:192–197