Chapter 18
Inflammatory Mediators and Renal Fibrosis

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Abstract Renal inflammation is the initial, healthy response to renal injury. However, prolonged inflammation promotes the fibrosis process, which leads to chronic pathology and eventually end-stage kidney disease. There are two major sources of inflammatory cells: first, bone marrow-derived leukocytes that include neutrophils, macrophages, fibrocytes and mast cells, and second, locally activated kidney cells such as mesangial cells, podocytes, tubular epithelial cells, endothelial cells and fibroblasts. These activated cells produce many profibrotic cytokines and growth factors that cause accumulation and activation of myofibroblasts, and enhance the production of the extracellular matrix. In particular, activated macrophages are key mediators that drive acute inflammation into chronic kidney disease. They produce large amounts of profibrotic factors and modify the microenvironment via a paracrine effect, and they also transdifferentiate to myofibroblasts directly, although the origin of myofibroblasts in the fibrosing kidney remains controversial. Collectively, understanding inflammatory cell functions and mechanisms during renal fibrosis is paramount to improving diagnosis and treatment of chronic kidney disease.

Keywords Macrophage · Renal fibrosis · Myofibroblast · TGF-β

18.1 Introduction

Renal fibrosis is the consequence of a diverse range of kidney diseases and is characterized by excessive accumulation of fibroblasts and extracellular matrix (ECM) (Djudjaj and Boor 2018; Humphreys 2018; Liu 2006; Zeisberg and Neilson 2010). It is also the common pathological pathway leading to end-stage renal disease (ESRD) (Eddy and Neilson 2006; Meng et al. 2013). However, the mechanisms of renal fibrosis remain largely unclear. Indeed, current treatments are non-specific and ineffective. Thus, it is essential to better understand the inflammatory process from acute injury to chronic kidney disease (CKD).

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Renal inflammation serves as the initial response to kidney stress or injury, and it protects the kidney from further damage (Meng et al. 2014). However, unresolved inflammation destroys kidney structure and function, leading to CKD that is characterized by progressive renal fibrosis (Grande et al. 2010; Lee and Kalluri 2010). Several key steps are involved in this process: first, the renal injury itself, followed by recruitment of inflammatory cells and release of profibrotic mediators that trigger accumulation and activation of myofibroblasts, then production and deposition of extracellular matrix (ECM), followed finally by glomerulosclerosis and tubular atrophy that is accompanied by microvascular rarefaction (Lee and Kalluri 2010; Liu 2011).

Regardless of the initial trigger, renal inflammation is characterized by glomerular and tubulointerstitial infiltration of inflammatory cells like neutrophils, T cells, macrophages, fibrocytes and mast cells (Meng et al. 2014). Activated intrinsic kidney cells, such as mesangial cells (MCs), podocytes, tubular epithelial cells (TECs) and endothelial cells, function as inflammatory mediators that produce proinflammatory cytokines, chemokines and growth factors and also participate in the repair process (Boor et al. 2010). After prolonged inflammation, histological and functional dysfunction occurs from excessive fibroblast and myofibroblast accumulation and ECM production. In fact, accumulation of myofibroblasts is the predominant source for collagen production and the dominant event in renal fibrosis progression. However, the origin of myofibroblasts remains largely controversial. Some research shows epithelial–mesenchymal transition (EMT) and endothelial–mesenchymal transition (EndoMT) are sources of myofibroblasts (Allison 2013; LeBleu et al. 2013; Liu 2011). But, resident fibroblasts also contribute to renal fibrosis (Duffield and Humphreys 2011; Lin et al. 2008; Strutz and Zeisberg 2006). In addition, accumulating evidence suggests pericytes are a major source of myofibroblasts (Humphreys et al. 2010; Lin et al. 2008). And, bone marrow-derived cells like fibrocytes and macrophages also contribute to the local accumulation of myofibroblasts (Broekema et al. 2007; Meng et al. 2016b; Wang et al. 2016b, 2017b). Thus, understanding the origin of myofibroblasts may help to clarify the pathway from renal inflammation to fibrosis. The current chapter focuses on key inflammatory cell types and pathways linking renal inflammation with fibrosis.

18.2 Bone Marrow-Derived Inflammatory Cells in Renal Fibrosis

When renal injury occurs, circulating leukocytes are recruited to the kidney (Chung and Lan 2011). Lymphocytes, monocytes, macrophages, mast cells and fibrocytes produce tissue damage factors like reactive oxygen species, cytokines and growth factors (Boor et al. 2010; Grande et al. 2010; Lee and Kalluri 2010). These profibrotic mediators cause myofibroblast accumulation and ECM production. Collec-

tively, unresolved inflammation drives the profibrotic pathways that lead to fibrosis (Kanasaki et al. 2013; Lee and Kalluri 2010).

18.2.1 Macrophages in Renal Inflammation and Fibrosis

In the injured kidney, monocytes transdifferentiate into macrophages in response to oxidative stress, toxins and hypoxia. This represents a critical component of the mononuclear phagocyte system (Anders and Ryu 2011; Vernon et al. 2010). Macrophages are divided into two subtypes, classically activated (M1) and alternatively activated (M2). Macrophages adopt the M1 phenotype when stimulated by interferon-γ (IFN-γ) and lipopolysaccharide (LPS). M2 phenotype is induced by interleukin (IL)-4 or IL-13. M2 macrophages are further categorized into three subsets according to their response to stimuli. M2a, wound healing macrophages, are induced by IL-4 and IL-13; M2b are induced by immune complexes; M2c, regulatory macrophages, are induced by IL-10, TGF-β or glucocorticoid. During the progression from kidney injury to repair processes, inflammatory M1 macrophages switch toward M2 phenotype and exert distinct functions supporting the pathological process (Anders and Ryu 2011). Accordingly, the proinflammatory M1 macrophages generate TNF-α, IL-1β and reactive oxygen species in response to renal injury. By contrast, the M2 macrophages secrete anti-inflammatory cytokines like IL-10 and insulin-like growth factor-1 that promote tissue healing and angiogenesis (Ricardo et al. 2008).

Macrophages are key inflammatory cells in proliferative glomerulonephritis (GN), particularly in crescentic GN (Han et al. 2011; Ma et al. 2009a, 2010). Macrophages are recruited from either circulation or local environment, which correlates with the severity of glomerular and tubulointerstitial damage, and renal function impairment, and is prognostic of disease progression (Eardley et al. 2008; Lan et al. 1995; Yang et al. 1998a). The findings that show co-localization of α-SMA + myofibroblasts and proliferative macrophages in areas of severe renal damage indicate a correlation between macrophages and renal fibrosis (Yang et al. 1998b). This is underscored by results from biopsies of patients with CKD and fibrotic kidney of animal models showing a similar relationship between macrophage recruitment and disease severity (Eardley et al. 2008; Nishida and Hamaoka 2008).

Inflammatory macrophages are a major source of proinflammatory cytokines, such as TNF-α and IL-1β, and chemokines like MCP-1(Ma et al. 2010). They also secrete macrophage migration inhibitory factor (MIF), a critical inflammatory mediator that promotes the progression of kidney diseases (Lan et al. 1997). Moreover, macrophages produce a number of growth factors like TGF-β and PDGF that play key roles linking renal inflammation with fibrosis.

To date, the profibrotic role of macrophages has been studied exclusively by various depletion techniques. They showed macrophage deficiency attenuated renal fibrosis in various disease models, including ischemic acute kidney injury (Ko et al. 2008), crescentic glomerulonephritis (Han et al. 2013), membranoproliferative glomeru-

lonephritis (Guo et al. 2011), obstructive nephropathy (Kitamoto et al. 2009) and diabetic nephropathy(Lin et al. 2009; You et al. 2013). In contrast, reconstitution of macrophages significantly aggravates existing fibrotic lesions. Much research has focused on the regulatory mechanisms of macrophages during the profibrotic effect. For example, a recent study revealed that genetic ablation of galectin-3, a β-galactosidase-binding lectin, protected against renal fibrosis in a unilateral ureteral obstruction (UUO) model without affecting the number of infiltrated macrophages. And, adoptive transfer of macrophages from wild-type mice, instead of galectin-3 KO mice, restored renal fibrosis (Henderson et al. 2008). Another study demonstrated that CpG-oligodeoxynucleotides-induced activation of TLR9 on macrophages accelerated interstitial fibrogenesis (Anders et al. 2004). This indicates the toll-like receptor-mediated signals on macrophages play critical roles in the progression of renal fibrosis. In addition, pharmacological inhibition of c-fms, the monocyte/macrophage receptor for CSF1, reduced the number of renal macrophages and tubular apoptosis, but had marginal impact on renal fibrosis (Han et al. 2013; Ma et al. 2009b). A recent study showed that macrophage-specific cyclooxygenase (Cox)-2 polarized and maintained a macrophage tissue-reparative M2 phenotype that protected against diabetic nephropathy (Wang et al. 2017a). This evidence shows that macrophages are a key bridge linking renal inflammation and renal fibrosis through several mechanisms. First, M1 macrophages secrete chemokines, cytokines and matrix metalloproteinases (MMPs) to accelerate the excessive infiltration of leukocytes into the injured region, destroying the original architecture of the kidney and aggravating renal injury (Ricardo et al. 2008). Second, cytokines and growth factors released by macrophages facilitate the proliferation and activation of resident fibroblasts. Macrophages promote transdifferentiation of other cells into myofibroblast-like cells through paracrine signaling. Macrophages are a major source of TGF-β1 in pathological conditions, and increased release enhances the number of infiltrated myofibroblasts by triggering the transdifferentiation of epithelial cells, endothelial cells and activation of pericytes and resident fibroblasts. M2 macrophages release IGF-1 and PDGF that promote myofibroblast survival (Floege et al. 2008; Wynes et al. 2004). Macrophage-derived PDGF also targets local fibroblasts and pericytes where the receptors for PDGF are highly expressed (Lin et al. 2008). And, macrophage-secreted MMP-9 induces EMT. Third, macrophages support extracellular matrix framework containing fibrinogen and collagens (Gratchev et al. 2001; Schnoor et al. 2008). Fourth, inflammatory macrophages induce vascular injury and capillary rarefaction, leading to tissue hypoxia and progression of renal fibrosis (Fine and Norman 2008). Finally, macrophages directly transdifferentiate into myofibroblast-like cells. Indeed, cells co-expressing the markers for both macrophage (CD68 +) and myofibroblast (α-SMA+) have been detected in patients with progressive renal fibrosis and animal models of obstructive nephropathy and chronic renal allograft injury (Wang et al. 2016b, 2017b). Furthermore, myeloid macrophages labeled with red fluorescence using lineage-tracing techniques show that bone marrow-derived macrophages, particularly M2, directly transdifferentiate into the collagen-producing myofibroblast in obstructive renal fibrosis model. This indicates macrophages contribute to renal

fibrosis through direct mechanisms (Meng et al. 2016b). TGF-β/Smad3 signaling is a master regulator in this process (Wang et al. 2016b).

Several lines of evidence indicate that targeting the phenotypic alteration of macrophages has therapeutic potential in treating renal fibrosis. A recent study showed that transferring M2 macrophages significantly attenuated renal inflammation and fibrosis (Wang et al. 2007). Although M2a and M2c are both capable of attenuating renal injury by decreasing host macrophage and T cell infiltration, M2c is more effective at inducing Tregs and attenuating renal inflammation and fibrosis (Cao et al. 2013; Lu et al. 2013). Collectively, macrophages play a central role in linking renal inflammation and fibrosis (shown in Fig. 18.1). Inhibiting macrophage infiltration, modifying phenotype of macrophages by interfering with specific signaling molecules or transferring modified macrophages may represent a potential approach to treat renal fibrosis.

18.2.2 T Cells in Renal Fibrosis

T cells are found in kidneys of patients and experimental animals with chronic kidney disease (Harris and Neilson 2006; Robertson et al. 2004). In early stages of renal inflammation, T lymphocytes migrate to the injured region and are activated by antigen stimulation. Activated T cells produce a variety of cytokines and chemokines that recruit and activate macrophages, facilitating the inflammatory response (Lin et al. 2008). The functional role of T cells has been studied extensively in different renal disease models (Tipping and Holdsworth 2006; Zheng et al. 2005). For example, deletion of CD4+ T cells with a monoclonal antibody largely attenuated renal fibrosis. And, adoptive transfer of CD4+ T cells, but not CD8+ T cells, restored the severity of UUO-induced renal fibrosis without affecting the number of infiltrating macrophages (Tapmeier et al. 2010). This indicates CD4+ T cells directly contribute to renal fibrosis in a macrophage-independent manner. Additionally, T cells were shown to indirectly regulate fibrocyte differentiation (Niedermeier et al. 2009). In a study using chronic renal allograft, intratubular T cells triggered local epithelial cells to transition into proliferating fibroblast phenotype (Robertson et al. 2004). Among T cell subsets, Th2 cells play a more critical role in renal fibrosis. Reconstitution of Th2 cells in mice with CD4+ T cell deletion resulted in more severe renal fibrosis compared with adoptive transfer of Th1 cells (Liu et al. 2012). This indicates that targeting CD4+ T cells, particularly Th2 cells, may be a potential therapy for renal fibrosis. In another study, CD4+ Foxp3+ T cells mediated the repair of AKI and attenuated renal fibrosis via mTOR signaling (Chen et al. 2016). The function of Th17 cells and IL-17 in renal fibrosis is still under debate. IL-17 is mainly produced by Th17 and γδT cells (Kim et al. 2015). The Th17/IL-17 axis is profibrotic, and it induces the production of chemokine (C-X-C motif) ligand 5 (CXCL5) and recruits neutrophils that contribute to glomerular nephropathy (Disteldorf et al. 2015). Disruption of IL-17A reduces myofibroblast activation and extracellular matrix production in UUO nephropathy (Peng et al. 2015). Moreover, exposure to elevated dietary salt promotes

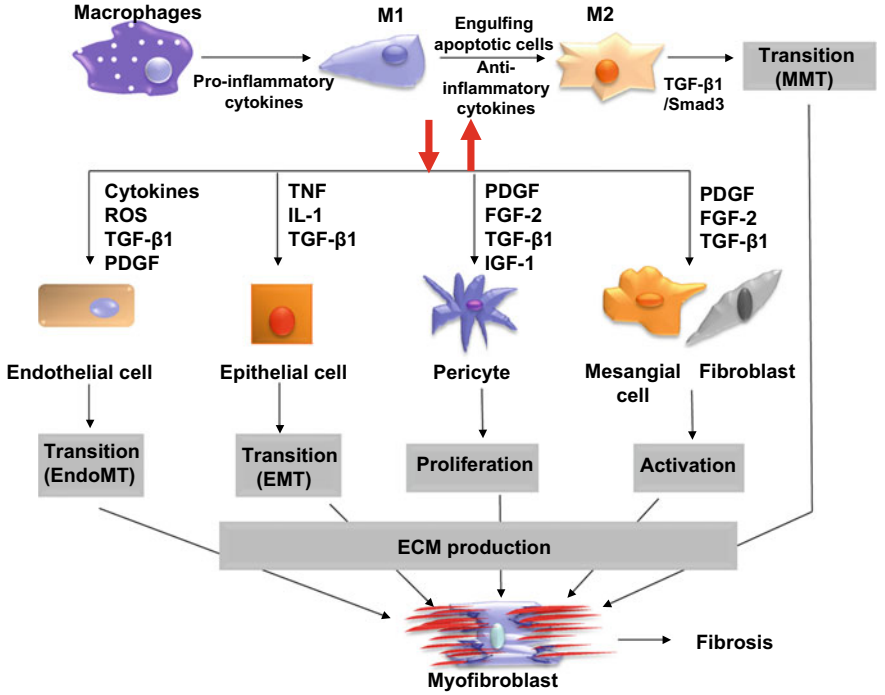

Fig. 18.1 Role of macrophages in linking renal inflammation and fibrosis. Monocyte/macrophages are recruited by chemokines released in response to microenvironment of injured kidney, and then they are activated by proinflammatory cytokines. These classically activated M1 macrophages activate intrinsic renal cells including tubular epithelial cells, endothelial cells and mesangial cells via producing factors such as cytokines (IL-1, TNF) and ROS. In the progression of renal disease, alternative activated M2 macrophages are induced by Th2 cytokines, and macrophages also gain M2 phenotype after engulfing apoptotic cells. These profibrotic macrophages promote renal fibrosis by producing an abundance of growth factors and ECM, and they may also undergo transition into myofibroblasts via TGF-β/Smad3-mediated MMT. In the fibrotic stage, the activated intrinsic renal cells proliferate, activate or directly transdifferentiate into myofibroblast-like cells directly via different mechanisms, and thereby participate in renal fibrosis. Abbreviations: ECM—extracellular matrix; EMT—epithelial–mesenchymal transition; EndoMT—endothelial–mesenchymal transition; MMT—macrophage–myofibroblast transition; FGF-2—fibroblast growth factor 2; IGF-1—insulin-like growth factor-1; PDGF—platelet-derived growth factor; ROS—reactive oxygen species; TGF-β—transforming growth factor β; and TNF—tumor necrosis factor

the progression from AKI to CKD through activation of Th17 cells (Mehrotra et al. 2015). This is consistent with the finding that disruption of IL-17 or IL-23 (a cytokine essential for the expansion and survival of Th17 cells) reduces albuminuria and glomerular crescent formation in experimental glomerulonephritis (Paust et al. 2009). In contrast, in a deoxycorticosterone acetate and angiotensin II-induced model of hypertensive nephropathy, loss of IL-17 accelerated hypertensive glomerular injury, which is correlated with reduced survival of TECs and more infiltration of γδT cells. Consistently, increased IL-17 suppressed renal inflammation and fibrosis in diabetic

nephropathy by protecting against TECs and podocytes (Mohamed et al. 2016). All of these findings underscore Th17/IL-17 acts in a disease type- and dosage-dependent way. It is important to note that CD11c+ CD8+ T cells likely induce fibroblast apoptosis, thereby limiting renal fibrosis (Wang et al. 2016a). This is in agreement with a previous study that showed loss of CD8+ T cells increased CD4+ T cell-mediated monocyte-to-fibroblast transition and renal fibrosis (Dong et al. 2016).

18.2.3 Fibrocytes in Renal Fibrosis

Fibrocytes are bone marrow-derived circulating cells that originate from CD14+ monocytic lineage and share markers with leukocytes like CD45 and mesenchymal cells like type I collagen (Bucala et al. 1994; Chesney et al. 1998). In the injured kidney, fibrocytes are recruited via their highly expressed chemokine receptors CCR2, CCR7 and CXCR4 (Chen et al. 2011a; Reich et al. 2013; Sakai et al. 2006). The regulation of fibrocyte differentiation has been studied extensively. It is clear that profibrotic Th2 cytokines, like IL-4 and IL-13, induce the differentiation of fibrocytes into myofibroblasts in vitro. However, Th1 cytokines like IFN-γ exert inhibitory effects on this process (Shao et al. 2008). Further, inhibiting CCL21/CCR7 signaling with anti-CCL21 antibodies or genetic deletion inhibits fibrocyte recruitment and renal fibrosis (Wada et al. 2007). CCR2 is also a key mediator for migration of fibrocytes to the injured kidney (Reich et al. 2013). As monocyte-derived precursor cells, fibrocytes not only participate in renal inflammation but also contribute to renal fibrosis through several mechanisms. First, they produce a large amount of collagen and profibrotic growth factors such as TGF-β in response to stimuli (Buchtler et al., 2018). Second, they secrete a number of cytokines, such as TNF-α and MCP-1, that contribute to renal inflammation (Chesney et al. 1998; Reilkoff et al. 2011). Third, they directly convert into myofibroblast phenotype. Although this remains controversial, some studies report that a considerable ratio of collagen-producing fibroblasts in obstructive kidney diseases originates from fibrocytes or bone marrow (Broekema et al. 2007; Niedermeier et al. 2009).

18.2.4 Mast Cells in Renal Fibrosis

Mast cells are tissue-specific multifunctional cells found in low numbers in healthy kidneys, but are significantly increased in tubulointerstitial injury, regardless of the initiating disease (Holdsworth and Summers 2008). As granulated cells, mast cells produce an array of inflammatory cytokines, chemokines, growth factors and cell-specific neutral proteases that facilitate leukocyte recruitment and microbial destruction. Interestingly, infiltration of mast cells is positively correlated with disease severity (Kondo et al. 2001). However, the functional role of mast cells in fibrosis is still not clear (Mack and Rosenkranz 2009). It is possible that mast cells promote fibro-

sis by releasing profibrotic mediators, such as TGF-β and MMP, or by activating the AngII pathway through chymase-dependent mechanisms (Margulis et al. 2009; Wasse et al. 2012). Direct evidence of a role for mast cells in renal inflammation and fibrosis comes from a number of studies using mast cell-deficient mice. In one study, deletion of a key differentiation factor c-kit in $Kit^{W-sh/W-sh}$ mice inhibited renal CD4+ T cells, macrophages and renal fibrosis. These were restored by adoptive transfer of bone marrow-derived mast cells from wild-type mice (Summers et al. 2012). In another, depletion of mast cells in the early phase of renal ischemia–reperfusion injury prevented CKD progression (Danelli et al. 2017). Consistent results were also found by deleting mouse mast cell protease 4 (mMCP4), the functional counterpart of human chymase, in mouse models of experimental anti-glomerular basement glomerulonephritis and UUO nephropathy. Results showed that mMCP4-deficient mice had significantly less renal inflammation and fibrosis; they were protected from progressive renal injury (Pons et al. 2017; Scandiuzzi et al. 2010). In contrast, results from other studies do not support the pathogenic role of mast cells in renal inflammation and fibrosis. For example, deletion of mMCP4 in UUO nephropathy increased kidney-infiltrating macrophages, T cells and local profibrotic TGF-β1 and CCL2 (Miyazawa et al. 2004). Similarly, in mast cell-deficient (Ws/Ws) rats, renal fibrosis in puromycin aminonucleoside nephrosis was measurably worse (Beghdadi et al. 2013; Miyazawa et al. 2004). This finding is further evidenced by a well-designed study that showed deficiency of mast cells in Kit(W)/Kit(W-v) mice enhanced renal fibrosis by increasing the infiltration of inflammatory cells (T cells and macrophages) and TGF-β production in obstructive kidney. The study also showed adoptive transfer of mast cells effectively suppressed renal fibrogenesis (Kim et al. 2009). Although the role of mast cells in renal inflammation and fibrosis remains unclear, there is no doubt that mast cells contribute to the pathological process from renal inflammation to fibrosis. The convincing and conflicting results from different animal models warrant further investigation.

18.3 Intrinsic Kidney Cells in Renal Inflammation and Fibrosis

Intrinsic kidney cells include tubular epithelial cells, podocytes, mesangial cells and endothelial cells. They actively participate in the disease process from inflammation to fibrosis after kidney injury. When activated, they produce a number of inflammatory cytokines, chemokines and growth factors, leading to progression of kidney diseases from acute inflammation to chronic fibrosing stage, resulting in ESRD (Gewin et al. 2017). In this regard, intrinsic kidney cells also function as inflammatory cells, like infiltrating leukocytes, and play critical roles in mediating fibrosis in CKD.

18.3.1 Tubular Epithelial Cells in Renal Inflammation and Fibrosis

Tubular epithelial cells (TECs) are the primary target of a variety of metabolic, immunologic, ischemic and toxic insults. TECs exhibit a wide range of responses including growth arrest, proliferation, apoptosis, autophagy and transdifferentiation that lead to tubular atrophy and renal fibrosis (Gewin 2018; Liu 2011). Several lines of evidence indicate TECs are not only common targets, but also major initiators of renal injury as producers of cytokines and chemokines (Hato et al. 2013; Liu et al. 2018; Nielsen et al. 2013). For instance, in a kidney transplantation model, activated TECs attracted all subsets of leukocytes and promoted their migration into the graft at early inflammatory stage of allograft rejection by releasing TEC-generated chemokines CCL2, CCL5, macrophage chemotactic osteopontin (OPN) and macrophage migration inhibitory factor (MIF) (Demmers et al. 2013; Nguan and Du 2009). Indeed, TEC itself is capable of producing abundant cytokines, including TNF-α, IL-1β, IL-15 and IL-6 to enhance local inflammation (Nguan and Du 2009). This proinflammatory property of TECs is highlighted by a study showing that deficiency of renal collecting duct epithelial cell-specific Klf5 largely attenuated renal inflammation by decreasing chemokine secretion (Fujiu et al. 2011). In addition, constitutive activation of TGF-β receptor type 1 (TβR1) kinase in tubular epithelial cells was sufficient to induce AKI, characterized by tubular cell apoptosis and necrosis, oxidative stress, interstitial accumulation of inflammatory cells and loss of renal function (Gentle et al. 2013). Consistently, blocking TGF-β signaling in tubular epithelial cells has significant impacts on renal inflammation, apoptosis and fibrogenesis in animal models of toxic nephropathy (Gewin et al. 2012) and obstructive nephropathy (Gewin et al. 2010; Meng et al. 2012a, b). Overactivation of TGF-β/Smad signaling in TEC promotes renal fibrosis in vivo and in vitro. In response to TGF-β1, TECs release a number of profibrotic factors like TGF-β1, which stimulate TECs to produce collagen extracellular matrix (Meng et al. 2010). Direct evidence comes from a number of studies that showed activated TEC transitions from epithelial into mesenchymal phenotype, the EMT process, which is mainly found in vitro in response to TGF-β, IL-1β and angiotensin II (AngII), in a number of animal models (Fan et al. 1999, 2001; Liu 2004, 2010; Yang et al. 2002). However, the EMT concept has been challenged by cell lineage-tracing studies showing myofibroblasts originate from TECs; it is rare to find EMT cells in renal biopsy samples from patients with chronic kidney disease (Allison 2013; LeBleu et al. 2013). It is worth noting that TECs undergo partial EMT, instead of completely transdifferentiating to myofibroblasts, and this is sufficient to drive renal interstitial fibrosis (Grande et al. 2015; Lovisa et al. 2015).

During inflammatory responses, several signaling pathways, including β-catenin (He et al. 2009), ILK (Li et al. 2003), Notch1 (Bielesz et al. 2010; Sharma et al. 2011; Ueno et al. 2013) and hypoxia-inducible factor 1 (HIF1) (Higgins et al. 2007), are activated in TECs and contribute to the progression of renal fibrosis. TEC-specific toll-like receptors, like TLR4, are key mediators in renal inflammation (Cheng et al. 2013; Correa-Costa et al. 2011; Lin et al. 2012; Zhang et al. 2008) and promote

renal fibrosis (Campbell et al. 2011; Lin and Tang 2013). TLR4 suppressed BAMBI, the membrane-bound competitive inhibitor of the TGF-β type 1 receptor, increased the susceptibility of renal cells to TGF-β signaling and enhanced renal fibrogenesis (Pulskens et al. 2010). TLR4-mediated signaling promotes inflammatory cytokine IL-18-induced α-SMA and collagen production, and also decreases E-cadherin levels through AP-1 activation (Meldrum et al. 2012). Interestingly, the inflammatory phase of TECs also affects the repair process after AKI. It is now clear that the c-reactive protein (CRP) pathway is induced in TECs and plays an active role in promoting renal inflammation and fibrosis in diabetic kidney injury (Liu et al. 2011). Activation of the CRP pathway in TECs also delays the recovery from acute ischemic renal injury by impairing the G1/S cell cycle (Liu et al. 2011). Moreover, a previous study highlighted a link between TECs and renal fibrosis by demonstrating that G2/M-arrested proximal tubular cells activated c-jun NH(2)-terminal kinase (JNK) signaling, thereby inducing profibrotic cytokine production (Yang et al. 2010).

18.3.2 Mesangial Cells in Renal Inflammation and Fibrosis

Glomerulosclerosis pathogenesis is correlated with activation and proliferation of MCs, abnormalities of podocytes and endothelial cell dysfunction (Abboud 2012; Schnaper et al. 2003). As the key cell type for glomerulosclerosis, MCs are the primary target of immune-mediated glomerular diseases like IgA nephropathy or metabolic diseases like diabetic nephropathy (Gomez-Guerrero et al. 2005). When challenged by stimuli, MCs produce inflammatory mediators, including chemokines (e.g., CCL2), cytokines (e.g., TNF-α and IL-6) and various oxygen species (Schlondorff and Banas 2009). Results of transcriptomic and proteomic profiling reveal that multiple inflammatory pathways, such as LXR/RXR, FXR/RXR, and acute-phase response signaling were activated in MCs from IgA nephropathy (Liu et al. 2017). Evidence from a recent study showed that parathyroid hormone-related protein (PTHrP) served as a critical modulator of inflammatory cytokine production in MCs (Hochane et al. 2018). Proinflammatory mediators released by MCs damage the endothelial barrier, exposing the mesangium to macromolecules that trigger a positive feedback loop of inflammatory cascades (Schlondorff and Banas 2009). Leukocyte migration and infiltration into the glomerulus cause initiation and amplification of glomerular injury and are mediated by adhesion molecules and chemokines, which can be locally synthesized by MCs (Lu et al. 2018). Thus, MCs function to amplify inflammatory processes in the inflamed glomerulus. Growing evidence shows that MC-derived cytokines induce podocyte injury, resulting in proteinuria (Lai et al. 2008, 2009). It is also worth noting that inflammatory mediators released by MCs promote activation and proliferation of MC themselves via an autocrine mechanism. Furthermore, activated MCs produce growth factors, including TGF-β, PDGF, FGF, HGF, EGF and CTGF (Crean et al. 2004; Floege et al. 1998, 2008; Laping et al. 2000; Schnaper et al. 2003). These induce MC proliferation, α-SMA + phenotype transformation and ECM production, leading to glomerulosclerosis (Taniguchi et al.

2013). The findings that ECM accumulation often appears to begin in the mesangium of glomerulosclerosis suggest a critical role for mesangial cells in glomerulosclerosis (Schnaper et al. 2003).

18.3.3 Podocytes in Renal Inflammation and Fibrosis

Podocytes are terminally differentiated epithelial cells with limited proliferative capacity. They play an important role in renal inflammation and fibrosis, especially in glomerular diseases (Fogo 2011; Grahammer et al. 2013). Functionally, one study showed podocyte-specific ablation of NEMO, an NF-κB essential modulator, decreased secretion of proinflammatory chemokines and increased remission of proteinuria, restoring podocyte morphology in a mouse model of nephrotoxic nephritis (Brahler et al. 2012). Consistently, conditional knockout of signal transducer and activator of transcription 3 (STAT3) from podocytes attenuated inflammatory response and development of crescentic glomerulonephritis (Dai et al. 2013). Further, a recent study showed that podocyte-specific chemokine receptor (CCR) 2 overexpression enhanced inflammatory response in diabetic nephropathy (You et al. 2017).

Podocytes also play pivotal roles in the development of glomerulosclerosis and tubulointerstitial fibrosis, which lead to progressive proteinuric kidney disease (Deelman and Sharma 2009; Shih et al. 1999). A previous study demonstrated that deficiency of Akt2 in podocytes exacerbated glomerulosclerosis and albuminuria (Canaud et al. 2013). In another, increased caspase-8-mediated apoptosis in podocytes significantly increased kidney damage, foot process effacement, mesangial expansion and glomerulosclerosis (Rutkowski et al. 2013). In addition, conditional knockout of yes-associated protein (YAP) from podocytes accelerated FSGS and progressive renal failure (Schwartzman et al. 2016).

Podocyte-related mechanisms in glomerular diseases, especially diabetic nephropathy (DN), are a hot topic. In diabetic models, Notch signaling plays a critical role in podocyte injury; overexpression of the intracellular domain of Notch (ICN) in podocytes induces proteinuria and glomerulosclerosis. This demonstrates a prominent role in podocyte dysfunction as a key step in glomerulosclerosis and renal fibrosis (Niranjan et al. 2008). Evidence also shows that vitamin D/vitamin D receptor (VDR) signaling in podocytes protects against podocyte loss and glomerular fibrosis in diabetic kidneys (Wang et al. 2012). The role of podocyte-specific mTOR is also important, as it is highly expressed in human DN samples. Indeed, increased activation of mTORC1 enhances proteinuria and progressive glomerulosclerosis in DN, but genetic reduction of mTORC1 decreases symptoms (Inoki et al. 2011). Interestingly, another study demonstrated that knockout of mTOR accelerated glomerular damage. However, inhibiting mTORC1 signaling by genetically reducing mTORC1 copy number prevented glomerulosclerosis and progression of glomerular disease in DN. This highlights the importance of a critical balance in mTOR activity as a regulator of the pathology of diabetic kidney diseases (Fogo 2011; Godel et al. 2011).

Podocyte-secreted growth factors also induce renal fibrosis by building new microenvironments in glomeruli. Vascular endothelial growth factor (VEGF) regulates endothelial functions, including endothelial cell migration, differentiation and survival. Podocytes are a major source of VEGF in the kidney (Mathieson 2009). Selective knockdown of VEGF in podocytes caused endothelial and mesangial cell dysfunction and progressive glomerulosclerosis (Eremina et al. 2006; Siddiqi and Advani 2013). In contrast, overexpression of VEGF in a mouse model of diabetes led to advanced diabetic glomerulopathy, characterized by proteinuria, glomerulomegaly, glomerular basement membrane thickening and excessive mesangial expansion (Veron et al. 2010, 2011). This is consistent with previous findings that showed doxycycline-induced overexpression of soluble VEGF receptor-1 (sFlt-1) in podocytes ameliorated glomerulopathy in diabetic mice (Ku et al. 2008). In addition, podocyte-specific PDGF overexpression induced mesangial cell proliferation and led to mesangioproliferative disease, glomerulosclerosis and crescentic glomerulonephritis (van Roeyen et al. 2011). CTGF, a matricellular protein, is also a critical pathogenic factor in podocytes. One study showed CTGF overexpression induced expansion of the mesangial matrix and exacerbated albuminuria in a mouse model of DN (Yokoi et al. 2008).

Renin–angiotensin system (RAS) is an important target in renal fibrosis (Mezzano et al. 2001). Several studies have shown that RAS components are highly expressed in podocytes (Durvasula and Shankland 2006, 2008), indicating a potential role in podocyte-mediated renal fibrosis. Moreover, podocyte-specific deletion of the mammalian homologue of yeast vacuolar protein sorting defective 34 (mVps34), a critical regulator in autophagy, led to glomerulosclerosis and interstitial fibrosis accompanied by podocyte vacuolization and proteinaceous casts (Chen et al. 2013).

A final note, EMT is found in podocytes in animal models (Li et al. 2008; Sam et al. 2006) and human biopsy samples of diabetic nephropathy, IgA nephropathy and lupus nephritis (Yamaguchi et al. 2009). Clearly, podocytes participate in disease states and regulate pathology when environmental conditions are primed.

18.3.4 Endothelial Cells in Renal Inflammation and Fibrosis

Endothelial cells play critical roles in the pathophysiological processes of regional blood flow regulation and leukocyte recruitment (Pober and Sessa 2007). When the kidney is injured, the interaction between endothelial cells and leukocytes is initiated. Recruited leukocytes roll along the activated endothelium that is mediated by selectins, E-selectin and P-selectin, and leukocyte surface antigens. Leukocyte adhesion is facilitated by endothelial expression of ICAM-1, VCAM-1 and PECAM; leukocytes transmigrate to injured tissue and exert proinflammatory functions (Guerrot et al. 2012). Evidence of this comes from a study that showed blocking P-selectin increased renal blood flow and promoted recovery of renal function in an ischemic model of renal failure (Bojakowski et al. 2001). Consistently, another study showed deficiency of CD147, a ligand for E-selectin, impaired neutrophil recruitment and

attenuated kidney damage (Kato et al. 2009). Similarly, inhibition of ICAM-1 with monoclonal antibody or genetic knockdown techniques also protected against renal injury (Kelly et al. 1994, 1996). Taken together, these findings underscore the importance of endothelial activation in local inflammation at an early stage.

Endothelial activation and subsequent leukocyte adhesion create hemodynamic resistance that reduces regional blood flow (Guerrot et al. 2012). In such conditions, ischemia and oxidative stress trigger endothelial apoptosis that leads to rarefaction of peritubular capillaries (Kelly et al. 2009; Venkatachalam et al. 2010). A pathogenic role for endothelial dysfunction was described in a study that found Crim1 deficiency, a protein involved in endothelial maintenance and integrity, resulted in excessive deposition of collagen, dysfunction and permeability of peritubular capillaries, and eventually renal fibrosis (Wilkinson et al. 2009). Importantly, rarefaction of peritubular capillaries induces hypoxia, which has significant impacts on progression of renal fibrosis by triggering EMT and/or promoting matrix production from myofibroblasts (Higgins et al. 2007). Compelling evidence for the pathogenic role of hypoxia in renal fibrosis was provided by studies showing that degradation or inhibition of hypoxia-induced factor1α (HIF1α), a central regulator of cellular responses to hypoxia (Higgins et al. 2008), largely reduced renal fibrosis (Higgins et al. 2007; Kimura et al. 2008). The correlation between HIF1α and tubulointerstitial fibrosis was also confirmed in biopsy samples from patients (Higgins et al. 2007). Chronic hypoxia is accompanied by increased oxidative stress and generation of ROS, which trigger advanced glycation end products, advanced oxidative protein products and advanced lipoperoxidation end products (D'Agati and Schmidt 2010; Negre-Salvayre et al. 2008). These may target kidney cells as pathogenic mediators and enhance renal inflammation and fibrosis (Daroux et al. 2010; Shanmugam et al. 2008; Shi et al. 2008; Zhou et al. 2009).

Finally, inflammatory endothelial cells also contribute to renal fibrosis through transdifferentiation into collagen-producing cells via EndoMT in response to stimuli (Zeisberg et al. 2008). Of note, TGF-β1 is the key mediator inducing EndoMT via Smad3-dependent mechanisms (Li et al. 2010; Xavier et al. 2015). A recent study showed EndoMT is regulated by SIRT (sirtuin)3/Foxo3a axis and integrin β1/dipeptidyl peptidase (DPP)-4 in vivo (Lin et al. 2018). Moreover, loss of heparin-binding EGF-like factor (HB-EGF) in endothelial cells attenuates angiotensin II (Ang II)-induced renal inflammation and fibrosis (Zeng et al. 2016). This emphasizes the critical role endothelial cells play in linking inflammation and fibrosis.

18.4 Key Fibrosis-Correlated Growth Factors Released by Inflammatory Cells

Resident and recruited inflammatory cells secrete growth factors such as TGF-β, PDGF, FGF, HGF, EGF and CTGF that exert pro- or anti-fibrotic roles in renal fibrosis (Boor and Floege 2011; Lv et al. 2018). TGF-β1 is the most abundant isoform

of TGF-β family members and is secreted by all types of resident renal cells and infiltrated inflammatory cells. It is secreted as a latent precursor, called latent TGF-β1 that binds to latent TGF-β-binding protein (LTBP). When exposed to stimuli, including ROS, plasmin and acid (Meng et al. 2015, 2016a), TGF-β1 is released from latency-associated peptide (LAP) and LTBP (Lyons et al. 1990; Meng et al. 2013; Munger et al. 1999). Mature TGF-β1 then binds to its type II receptor to recruit type I receptors and activates downstream signals. The major source of TGF-β1 includes macrophages, tubular epithelial cells and myofibroblasts (Fukuda et al. 2001; Lee and Kalluri 2010; Ma et al. 2003). After release and activation, TGF-β1 activates Smad and non-Smad signaling in renal fibrosis, inflammation, cell growth, apoptosis and differentiation (Bottinger and Bitzer 2002). In general, TGF-β1 has both pro- and anti-inflammation properties (Huang et al. 2008a, b; Kitamura and Suto 1997; Zhang et al. 2009). In renal fibrosis, TGF-β and downstream Smad3 are pathogenic, while Smad2 and Smad7 seem to be renoprotective (Meng et al. 2013).

TGF-β1 behaves in renal disease in a cell-specific and dosage-dependent manner (Hathaway et al. 2015; Meng et al. 2016a). TGF-β1 recruits macrophages by secreting chemokines, including MCP-1 and OPN (Lan 2011; Zhang et al. 2009), and promotes macrophage polarization toward M2 phenotype (Sica and Mantovani 2012). Our recent results also show TGF-β1 initiates transdifferentiation of macrophages into myofibroblast-like cells (Wang et al. 2016b). In addition, TGF-β1 induces the production of Foxp3+ T regulatory cells (Tregs) (Fu et al. 2004) and inhibits the progression of autoimmune kidney disease (Wang et al. 2006). A recent study showed that combination treatment of rhTGF-β and ICG-001, an inhibitor of β-catenin/TCF, suppressed both renal inflammation and fibrosis in UUO nephropathy and kidney ischemia/reperfusion (Qiao et al. 2018). Several other studies confirm TGF-β1 plays regulatory roles in other types of T cells (Gorelik and Flavell 2002; Kitching and Holdsworth 2011; Turner et al. 2010). In addition, TGF-β mediates mast cell chemotaxis (Gruber et al. 1994) and production of mast cell protease (Funaba et al. 2006).

TGF-β1 also functions in resident inflammatory cells by enhancing ECM production from TECs and promoting EMT. TGF-β1 also induces apoptosis in tubular epithelial cells (Lopez-Hernandez and Lopez-Novoa 2012). In vitro, data indicate that podocytes produce ECM in response to TGF-β1 (Gruden et al. 2005). In TGF-β1 transgenic mice, apoptosis of podocytes is induced by overactivation of Smad7 (Schiffer et al. 2001). Further, a previous study indicated that TGF-β-induced apoptosis in cultured mouse podocytes acted through upregulation of mitochondrial Nox4 via Smad2/3-dependent mechanisms (Das et al. 2014). As terminally differentiated epithelial cells, podocytes also undergo EMT in response to TGF-β1 (Li et al. 2008). Furthermore, emerging evidence indicates that TGF-β1 stimulates mesangial cells to secrete type I, III and IV collagen, laminin and fibronectin, supporting glomerular ECM accumulation (Gruden et al. 2005; Lopez-Hernandez and Lopez-Novoa 2012). TGF-β1 also induces hypertrophy and proliferation of mesangial cells to accelerate glomerulosclerosis (Gruden et al. 2005). Additionally, TGF-β1 has an impact on apoptosis, proliferation and migration of endothelial cells (Lebrin et al. 2005). Although TGF-β1 has a proapoptotic effect on endothelial cells in most scenarios (Loeffler and Wolf 2013), it also promotes the release of VEGF from podocytes and

TECs which protect endothelial cells from apoptosis (Kang et al. 2002). Notably, as a downstream molecule of TGF-β1, Smad2 triggers expression of antiangiogenic factors like TSP-1 and VEGF-A antagonist. In comparison, TGF-β1-induced VEGF mRNA and protein expression are Smad3-dependent (Nakagawa et al. 2004a, b). TGF-β1 is known classically to stimulate EndoMT (Zeisberg et al. 2008). Thus, data clearly show TGF-β1 could be secreted by inflammatory cells and may be one of the key growth factors that drives renal fibrogenesis.

The PDGF family contains four isoforms, PDGF-A, -B, -C and -D, and two receptor chains, PDGFR-α and -β, that are constitutively or inducibly expressed in most renal cells (Floege et al. 2008). PDGF exerts numerous biological functions in renal diseases, including production of pro- and anti-inflammatory mediators, ECM accumulation, cell proliferation and migration (Ostendorf et al. 2012). PDGF signaling is a crucial mediator in renal fibrosis (LeBleu and Kalluri 2011), as evidenced by the findings that show blocking PDGF-D attenuates tubulointerstitial fibrosis in both early and late stages of glomerulonephritis (Boor et al. 2007; Ostendorf et al. 2006). PDGF-D has a direct profibrotic effect on the tubular interstitium by promoting EMT (Kong et al. 2009) or by triggering expression of PDGFR-β from resident fibroblasts or pericytes, which are the major source of interstitial myofibroblasts (Humphreys et al. 2010; Lin et al. 2008). Inhibition of PDGFR signaling reduces the number of myofibroblasts and ameliorates renal damage in obstructive nephropathy (Chen et al. 2011b). This indicates a key role for PDGFR signaling in myofibroblast generation from pericytes. Compelling evidence for a role of PDGFRα and its ligand PDGF-CC in renal fibrosis is provided by results showing that inhibition of PDGF-CC suppresses renal fibrosis in obstructive nephropathy (Eitner et al. 2008). PDGF-CC also exerts profibrotic effects by directly enhancing fibroblast proliferation, as well as accelerating leukocyte infiltration (Eitner et al. 2008). Moreover, PDGF-CC serves as a pro-angiogenic mediator in glomeruli (Boor et al. 2015). In contrast to PDGF-A, which has limited effects in renal fibrosis (Tang et al. 1996), PDGF-B and PDGFR-β mediate mesangial proliferation both in vitro and in vivo; high doses of PDGF-BB induce proliferation of tubulointerstitial cells and promote the myofibroblast generation and fibrosis (Boor et al. 2014; Buhl et al. 2016; Das et al. 2017; Tang et al. 1996). Collectively, renal inflammatory cells produce plenty of PDGF, driving the progression of renal fibrosis.

18.5 Conclusion

Inflammation is the initial response to cellular injuries and is the key process in wound healing and renal repair. However, unresolved renal inflammation leads to fibrosis with loss of renal function. In this process, both circulating leukocytes and intrinsic kidney cells are key inflammatory cell types and play critical roles in driving acute renal inflammation to chronic fibrosis, leading to the end-stage kidney disease. There are two primary mechanisms regulating the pathway from renal inflammation to fibrosis. First, fibrogenetic growth factors produced by inflammatory cells

promote local fibroblasts, or inflammatory cells themselves, to proliferate and produce ECM. Second, inflammatory cells convert into collagen-producing fibroblasts or myofibroblasts directly from EMT, EndoMT, pericytes, fibrocytes or MMT. Many inflammatory cytokines and growth factors, like TGF-β, are involved in the inflammation–fibrosis process. Collectively, blocking excessive inflammatory responses may represent an effective therapy for renal fibrotic diseases.

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