Rev Physiol Biochem Pharmacol (2020) 177: 1–24
https://doi.org/10.1007/112_2020_21

Published online: 9 August 2020

The Role of Chemokine Receptors in Renal Fibrosis

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Abstract Renal fibrosis is the final pathological process common to any ongoing, chronic kidney injury or maladaptive repair. Renal fibrosis is considered to be closely related to various cell types, such as fibroblasts, myofibroblasts, T cells, and other inflammatory cells. Multiple types of cells regulate renal fibrosis through the recruitment, proliferation, and activation of fibroblasts, and the production of the extracellular matrix. Cell trafficking is orchestrated by a family of small proteins called chemokines. Chemokines are cytokines with chemotactic properties, which are classified into 4 groups: CXCL, CCL, CX3CL, and XCL. Similarly, chemokine receptors are G protein-coupled seven-transmembrane receptors classified into

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4 groups: XCR, CCR, CXCR, and CX3CR. Chemokine receptors are also implicated in the infiltration, differentiation, and survival of functional cells, triggering inflammation that leads to fibrosis development. In this review, we summarize the different chemokine receptors involved in the processes of fibrosis in different cell types. Further studies are required to identify the molecular mechanisms of chemokine signaling that contribute to renal fibrosis.

Keywords Chemokine receptors · Macrophages · Myofibroblasts · Renal fibrosis · T cells

1 Introduction

Renal fibrosis is widely regarded as a common pathway contributing to end-stage renal disease, characterized by aberrant activation and the development of renal fibroblasts and overproduction of proteins of extracellular matrix (ECM) (Meng et al. 2014). During fibrosis, the kidney is stimulated by various pathogenic factors in diverse diseases including trauma, infection, inflammation, blood circulation disorder, and immune response. Fibrosis can be viewed as an aberrant wound healing, in which there is progression rather than scar recovery following damage, and fibroblasts are central to this process. Fibrosis is closely related to tissue regeneration and inflammation, which is mediated by specific types of cells, including epithelial, endothelial, fibroblast, pericyte, myofibroblast, and inflammatory cells (Duffield 2014). Pathogenic factors such as drug poisoning, high blood pressure, diabetes, and infection can cause damage to the intrinsic cells which can release some cytokines. These cytokines attract a series of inflammatory cells in blood to infiltrate the mesangial, vascular, and interstitial areas. In response to inflammatory mediators, the intrinsic cells release nephrotoxic cytokines and growth factors, causing the proliferation of fibroblasts and further differentiation to myofibroblasts in the renal interstitium. With the constant stimulation of cytokines and growth factors, fibroblasts continue to proliferate and synthesize extracellular matrix (ECM) components. Kidney-derived cells, such as mesangial cells, glomerular epithelial cells, and renal tubular epithelial cells, can also be differentiated into myofibroblasts. More than half of the renal myofibroblasts have been confirmed to be derived from local fibroblasts, while most of the remainder are derived from bone marrow, endothelial-to-mesenchymal transition program, and epithelial-to-mesenchymal transition program (LeBleu et al. 2013). The impaired imbalance in the synthesis and degradation of ECM components promotes the formation of fibrous tissue, eventually leading to glomerular sclerosis, renal fibrosis, and formation of persistent scars.

Abundant evidences have shown that most chemokines and their receptors are crucial participants in the progression of renal fibrosis. Chemokines are chemotactically categorized into four groups of cytokines based on the location of two

cysteine residues in their sequence: XCL, CCL, CXCL, and CX3CL (Griffith et al. 2014). Chemokine receptors are G protein-coupled seven-transmembrane receptors classified into four groups: XCR, CCR, CXCR, and CX3CR. Chemokine receptors are expressed in various leukocytes and immune cells. Chemokines and their receptors play an essential role in various physiological and pathological processes (Griffith et al. 2014).

The change of chemokine expression at the lesion site is also an important part of renal fibrosis. High expression of CCL2 in kidney has a very strong association with the progression of renal disease, and the blockade of CCL2 receptor (CCR2) reduces interstitial fibrosis (Kitagawa et al. 2004). High expression levels of CXCL10 and CXCL9 have been reported in glomerular cells in kidney biopsies of patients with membranoproliferative and crescentic glomerulonephritis (Romagnani et al. 2002). CCL18 is also identified as one of the central chemokines in glomerulonephritis (Brix et al. 2015). In hypertension mice, significantly CX3CL1 mRNA expression increases in whole kidney, and the protein localizes to tubular epithelial and vascular endothelial cells (Shimizu et al. 2011).

Chemokines are involved in the development of inflammatory cells in pathological and physiological processes. CXCR2 regulates neutrophils recruitment in response to CXCL1 (Drummond et al. 2019). CXCL8, as another ligand of CXCR1/2, can also modulate neutrophil migration (Zuniga-Traslavina et al. 2017). CXCR3 mainly expresses on activated Th1 cells, NK cells, macrophages, and other immune cells which may play an important role in renal fibrosis (Campanella et al. 2008). CXCR4 participates macrophages differentiation (Ding et al. 2019) and T cells recruitment, so as CXCL16/CXCR6 (Seo et al. 2019; Wehr et al. 2013; Zhang et al. 2009). CCL3 and CCL5 can interact with CCR1 to attract macrophages and T cells (Olszewski et al. 2000) (Fig. 1).

Myeloid cells and organ-resident cells are also involved in the process of tissue fibrosis. Circulating bone marrow-derived fibroblast precursors were chemotactic and differentiated under the control of CXCL16/CXCR6 and CCL2/CCR2 (Chen et al. 2011; Xia et al. 2013). CXCR4 is well known for its role in the homing of progenitor cells into the bone marrow (Doring et al. 2014) (Table 1).

Some fibrosis-related molecule productions are also directly or indirectly regulated by chemokines. CXCL8 was a potent suppressor of MMPs which acted their proteolytic activity in tissue fibrosis (Milovanovic et al. 2017). CXCR4 could induce pro-fibrotic collagen in some diseases such as cancer (Dong et al. 2019). CXCR4 induced platelet-derived growth factor-β to promote pulmonary fibrosis by trafficking of circulating fibrocytes (Aono et al. 2014). Th17-derived cytokines were related to fibrosis and could be induced by CCR2 (Gurczynski et al. 2019). CXCR6 could activate human pulmonary fibroblasts to produce collagen production (Ma et al. 2019).

Accumulating evidences indicate that chemokine receptors are key regulators of renal fibrosis in diseased kidneys. Therefore, the purpose of this summary is to provide a succinct overview of recent progress in the pathogenesis of renal fibrosis on chemokine receptors.

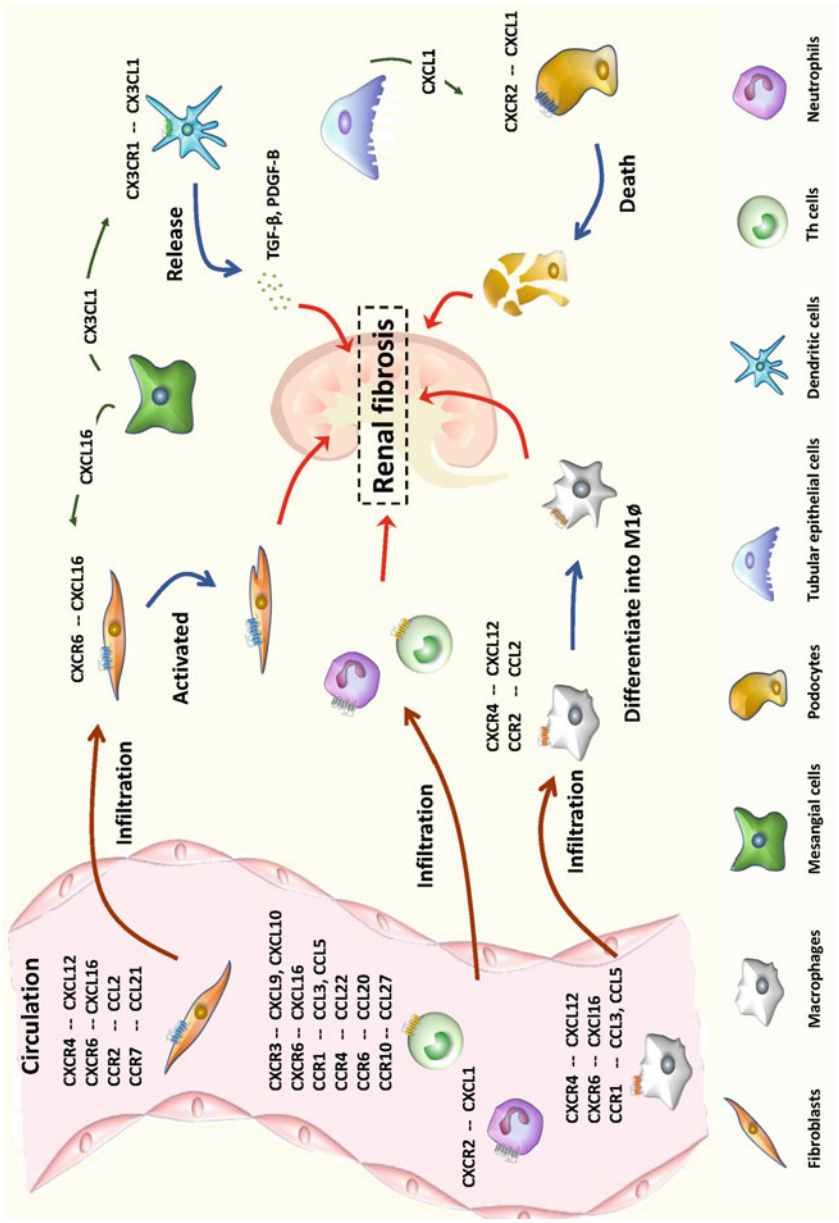

Fig.1 The role of chemokine receptors in renal fibrosis. Bone marrow-derived fibroblasts infiltrated into kidney by CXCR4, CXCR6, CCR2, and CCR7. Fibroblasts in kidney could be activated by CXCL16/CXCR6. Helper T cells in circulation expressed CXCR3, CXCR6, *CCR1* CCR4, CCR6, and CCR10 while

Fig.1 (continued) neutrophils expressed CXCR2. They could be attracted into fibrosis site by corresponding ligands. Macrophages were appealed to CXCR4, CXCR6, and *CCR1* and differentiated into M1 macrophages through CXCL12/CXCR4 and CCL2/CCR2. CX3CR1+ dendritic cells could release pro-fibrotic factors such as TGF-β and PDGF-β. CXCL2 combined with CXCR2 to facilitate podocytes loss. Tubular epithelial cells were considered as the source of CXCL2

Table 1 The role of chemokine receptors in renal fibrosis

Chemokine receptors	Ligands	Pro-fibrosis	Anti-fibrosis
CXCR1/ CXCR2	CXCL8, CXCL1, CXCL2	CXCL8 increased in both urinary and serum levels (Wong et al. 2007) G31P, an antagonist of CXCL8, inhibited fibrotic factor upregulation in human renal mesangial cells through JAK2/ STAT3 and ERK1/2 pathways (Cui et al. 2017) The GP31 improved kidney fibrosis by reduction in ECM (Cui et al. 2017; Ye et al. 2018) CXCL1 induced podocyte death and adhesion dysfunction in podocytes via CXCR2 (Zhu et al. 2013) TLR4 on intrinsic renal cells contributes to the induction of antibody-mediated glomerulonephritis via CXCL1 and CXCL2 (Brown et al. 2007) MiR-146a prevented the development of inflammation and fibrosis by targeting CXCL8 in ischemia-reperfusion injury (Amrouche et al. 2017) CXCL1 levels were positively associated with fibrosis in IgA nephropathy (Zhao et al. 2015; Zhu et al. 2013)	
CXCR3	CXCL9, CXCL10, CXCL11	CXCL9/CXCL10 in macrophages was induced by biglycan via TLR/TRIF/MyD88-signaling (Nastase et al. 2018) CXCR3+ Th1 and Th17 cells can be recruited into the kidney in fibrosis progress (Nastase et al. 2018; Steinmetz et al. 2009)	CXCL10 prevented fibrosis in diabetic kidney disease in mice (Zhang et al. 2018) Blockade of CXCL10 via CXCR3 contributes to renal fibrosis by upregulation of TGF-β1 (Nakaya et al. 2007)
CXCR4	CXCL12	CXCR4 was overexpressed in renal fibrosis samples (Maluf et al. 2008; Togel et al. 2005) Administration of AMD3100, the CXCR4 inhibitor, reduced renal fibrosis in oxidative stress-induced podocyte injury (Mo et al. 2017) CXCR4 antagonist blunts the increase in classic indicators of	Continuous AMD3100 treatment exacerbates the renal fibrosis by attracting T cell in unilateral ureteral obstruction mice (Yang et al. 2016)

(continued)

Table 1 (continued)

Chemokine receptors	Ligands	Pro-fibrosis	Anti-fibrosis
		fibrosis and fibroblast activation (Yuan et al. 2015)	
CXCR6	CXCL16	CXCL16/CXCR6 promoted the recruitment, activation, and differentiation of bone marrow-derived fibroblasts precursors and contribute to the pathogenesis of renal fibrosis (Chen et al. 2011; Xia et al. 2014b) CXCL16 deficiency impaired myeloid fibroblast accumulation and myofibroblasts formation (Ma et al. 2016a, b) CXCR6 regulated the infiltration of macrophage and T cell in renal fibrosis (Xia et al. 2014a)	
CCR1	CCL3, CCL5	CCR1 was expressed on infiltrating macrophages and T cells in the development of renal fibrosis (Vielhauer et al. 2001) CCR1 antagonist BX471 treatment significantly reduced markers of renal fibrosis (Vielhauer et al. 2004)	
CCR2	CCL2	CCL2/CCR2 accelerated renal fibrosis through bone marrow-derived myofibroblast infiltration (Xia et al. 2013) CCL2/CCR2 blockage improves renal fibrosis by inhibiting pro-fibrotic M1 macrophage (Saito et al. 2018)	
CCR7	CCL21	CCL21/CCR7 induced the trafficking of circulating fibrocytes, contributing to the pathogenesis of renal fibrosis (Wada et al. 2007; Habiel and Hogaboam 2014)	
CX3CR1	CX3CL1	CX3CR1 regulates macrophage infiltration and led to increased expression of α-SMA, TGF-β, and PDGF-B (Furuichi et al. 2006)	CX3CR1 attenuated renal fibrosis with accumulation of macrophages in UUO model (Engel et al. 2015)

2 CXC Chemokine Receptors

2.1 CXCR1/CXCR2

CXCR1and CXCR2 share 76% of their sequence homology and bind to CXCL8 with similar affinity (Holmes et al. 1991; Kunsch and Rosen 1993). Interleukin (IL)-8 (CXCL8) and granulocyte chemotactic protein 2 (GCP-2, CXCL6) are known to be ligands of both CXCR1 and CXCR2 (Wuyts et al. 1998; Ha et al. 2017). CXCL8 is commonly expressed in activated monocytes and macrophages, epithelial and endothelial cells, fibroblasts and neutrophils (Wolff et al. 1998). Growing evidences have shown that CXCL8 participates in the pathological processes of fibrosis, angiogenesis, arteriosclerosis, infection, and tumor growth (Kormann et al. 2012; Higurashi et al. 2009). In diabetic nephropathy patients, CXCL8 was seen to increase both urinary and serum levels (Wong et al. 2007). G31P is a mutant protein of CXCL8, which can selectively bind to CXCR1 and CXCR2 without agonist activity (Li et al. 2002). Recent studies have revealed that G31P can effectively improve renal fibrosis (Svensson et al. 2011). In diabetic nephropathy mice, G31P treatment reduced phosphorylation of ERK1/2, JAK2, and STAT3. Meanwhile, G31P treatment inactivated JAK2/STAT3 and ERK1/2 pathways in high-glucose-treated mesangial cells (Cui et al. 2017). Also, JAK2/STAT3 and ERK1/2 pathways were implicated in the pathogenesis of progressive diabetic nephropathy (Chuang and He 2010). JAK2/STAT3 pathways were reported to participate in the fibrosis in dermis, lung, and liver (Li et al. 2018; Zehender et al. 2018). ERK1/2 pathways were also demonstrated to be directly involved in renal fibrosis (Andrikopoulos et al. 2019). Furthermore, the administration of G31P improved kidney fibrosis as confirmed by reduction in ECM. In the diseased kidney observed in another study, the extracellular matrix degradation-related protein matrix metalloproteinases (MMP)-9 decreased while TIMP-1, known as an inhibitor of metalloproteinase, was upregulated. However, G31P treatment reversed their altered expression (Ye et al. 2018). G31P treatment was also associated with improvement in MMP-2 (Cui et al. 2017). MMPs are believed to suppress fibrosis because of their proteolytic activity (Giannandrea and Parks 2014). It has been reported that miR-146a is most induced in tubular cells in response to ischemia-reperfusion, thereby preventing the development of inflammation and fibrosis by targeting CXCL8 (Amrouche et al. 2017).

CXCL1, known as a ligand of CXCR2, has been positively associated with interstitial fibrosis in IgA nephropathy (IgAN) progression (Zhao et al. 2015). Both clinical samples and cell experiments showed the elevated expression of CXCL1 (Zhu et al. 2013). It was reported that toll-like receptor 4 in kidney-resident cells induced the antibody-mediated glomerulonephritis via CXCL1 which promotes glomerular neutrophil infiltration (Brown et al. 2007). Additionally, mesangial-induced CXCL1 and TGF-β1 synergistically increased podocyte death and decreased podocyte adhesion via CXCR2 (Zhu et al. 2013). Studies have proven that podocytes loss can impair the glomerular filtration barrier which leads to proteinuria and glomerulosclerosis in IgAN (Wharram et al. 2005).

2.2 CXCR3

CXCR3 is widely expressed in different subtypes of T and NK cells. The ligands are CXCL9, CXCL10, and CXCL11, and their secretion is predominantly driven by IFN-γ (Sallusto et al. 1998). IFN-γ, known as aa Th1-related cytokine, has been proposed to be an antifibrotic effector that inhibits fibroblast activation and proliferation and reduces collagen synthesis (Gao et al. 2007).

It was reported that increased levels of IFN-γ and IFN-γ-responsive genes (CXCL9 and CXCL10) in Sphk2$^{-/-}$ (sphingosine kinase 2) mice inhibited the progression to fibrosis (Bajwa et al. 2017). TGF-β and high glucose contributed to the development of fibrosis in diabetes. CXCL10 attenuated both high glucose and TGF-β-induced collagen synthesis (Zhang et al. 2018). CXCR3 ligands are a potent chemoattractant for activated Th1 cells, NK cells, macrophages, and other immune cells (Campanella et al. 2008). The ureter is ligated in the case of unilateral ureteral obstruction (UUO), leading to hydronephrosis and interstitial inflammatory infiltration, myofibroblast activation, and extracellular matrix deposition, ultimately leading to renal fibrosis (Verbeke et al. 2016). Although CXCL10 and CXCR3 were observed to be upregulated in the progressive renal fibrosis in UUO mice (Nakaya et al. 2007), CXCL10 blockade affected neither macrophage nor T cell infiltration. Despite this, CXCL10 blockade was also shown to promote renal interstitial fibrosis in the kidney via hepatocyte growth factor (HGF) which is a potent antifibrogenic factor (Nakaya et al. 2007). HGF created by mesangial cells prevents peritubular capillaries (PTCs) from decreasing, preserves renal blood flow, and effectively suppresses myofibroblast progression induction and collagen synthesis (Oka et al. 2019). In addition, CXCL10 blockage has also been demonstrated to reduce transcripts of CXCL9 and CXCL11 in diseased kidneys (Nakaya et al. 2007).

The results in diabetic nephropathy and lupus nephritis are controversial. Biglycan, a class I member of the small leucine-rich proteoglycans, was found to be upregulated in diabetic nephropathy and lupus nephritis. Meanwhile, CXCL9/CXCL10 in macrophages was induced by biglycan via TLR/TRIF/MyD88-signaling and then recruited CXCR3^{+} Th1 and Th17 cells into the kidney (Nastase et al. 2018). Another study showed that CXCR3 deficiency in lupus-prone mice improved the renal damage by decreasing the numbers of Th1 cells and Th17 cells in the inflamed kidneys (Steinmetz et al. 2009). Th1 and Th17 cells have been shown to play an important role in the development and progression of inflammatory and autoimmune diseases (Zheng and Zheng 2016; Stockinger and Omenetti 2017). Th1 and Th17 cells, which are Th subtypes, are key inducers of renal fibrosis (Wen et al. 2017).

2.3 CXCR4

CXCR4 is mainly expressed in hematopoietic and immune cells. CXCR4 is highly expressed in embryonic kidneys but the expression is significantly low in adult

kidneys (Takabatake et al. 2009). In tubular atrophy and interstitial fibrosis samples, however, CXCR4 genes were found to be overexpressed compared with normal allografts and normal kidneys (Maluf et al. 2008). Increased CXCR4 expression has also been observed in tubular segments after renal ischemia-reperfusion injury (IRI) (Togel et al. 2005). Thus, increased CXCR4 expression seems to be closely associated with kidney disease. Another report showed that the stimulation of CXCR4 in macrophages activated STAT and NF-κB pathways which acted as important roles in macrophage activation. Meanwhile, the administration of AMD3100, a CXCR4 inhibitor, reduced renal fibrosis in mice and was accompanied by a significant reduction in macrophage infiltration (Mo et al. 2017). In a UUO model, a lack of CXCR4 protected against renal fibrosis by suppressing macrophage activation. AMD3100 treatment downregulated the mRNA levels of multiple pro-fibrotic molecules including collagen-1a1 (Col1a1), collagen-3a1 (Col3a1), and collagen-4a1 (Col4a1) by inhibiting downstream signaling and fibroblast activation (Yuan et al. 2015).

In another study, AMD3100 treatment did not mitigate renal fibrosis but promoted tissue damage and renal fibrosis by increasing pro-fibrotic molecules expression, such as α-SMA, PDGFR-β, and collagen-IV (Yang et al. 2016). α-SMA was found to be a marker of activated fibroblasts. PDGF-β and collagen-IV is the well-characterized factor that promotes fibrosis in many diseases and organs, including the kidney (Border and Noble 1994; Hugo 2003; Li et al. 2019). This difference may be attributed to the mechanism of AMD3100 and the chemotaxis of CXCR4 ligands. The factor-1-derived chemokine stromal cell (SDF-1, also known as CXCL12) is constitutively expressed in pro-angiogenic cells and regulates embryonic development and homeostasis of the organ (Ratajczak et al. 2006). Evidence indicates that continuous AMD3100 treatment disrupts SDF-1-CXCR4 binding leading to a decrease in bone marrow-derived pro-angiogenic cell homing. Besides, the infusion of pro-angiogenic cells not only decreases vascular rarefaction but also reduces damage to the tissue and the invasion of inflammatory cells. A few studies have shown that bone marrow-derived pro-angiogenic cells participate in renal fibrosis controlled by the SDF-1/CXCR4 system (Shen et al. 2011; Petit et al. 2007). CXCR4 is also highly expressed in T cells which are major inducers of fibrosis (Arieta Kuksin et al. 2015). In Kuksin's study, AMD3100 administration increased renal T cell infiltration. This result may due to AMD3100 redistributing T cells from the bone marrow and thymus to the blood and peripheral tissues in mice (Liu et al. 2015). It suggests that AMD3100 should be more cautiously used in patients with renal disease and additional studies should be performed on this issue in the future.

2.4 CXCR6

CXCL16 has been described as a CXCR6 ligand consisting of a molecular domain accompanied by a glycosylated mucin-like stalk, a long transmembrane helix, and a short cytoplasmic tail (Matloubian et al. 2000). The CXCL16/CXCR6 pathway is

involved in tissue injury and inflammation (Wang et al. 2017). CXCL16 protein has been documented to be expressed at low levels in normal kidney epithelial cells while being upregulated in obstructive injury (Okamura et al. 2007). Recent studies have shown that precursors of fibroblasts originating from bone marrow contribute significantly to the pathogenesis of renal fibrosis. In response to kidney injury, bone marrow-derived fibroblast precursors in the circulation are recruited to the site of injury to participate in a wound healing response (Yan et al. 2016). Bone marrow-derived fibroblast precursors will differentiate into myofibroblasts that have been implicated in fibrosis pathogenesis (Gerarduzzi and Di Battista 2017). Circulating CXCR6-positive fibroblast precursors have been found in injured kidneys, with CD45 and α-SMA dual-positive myofibroblasts accumulating in the injured kidney in a CXCL16-dependent manner. Meanwhile, CXCL16 has been significantly implicated in the activation and differentiation of bone marrow-derived fibroblasts (Chen et al. 2011). In a renal artery stenosis study, CXCL16 protein was mainly distributed in tubular epithelial cells. They also found that CXCL16 deficiency impaired myeloid fibroblasts accumulation and myofibroblasts formation. Furthermore, CXCL16 deficiency inhibited the infiltration of $F4/80^+$ macrophages and $CD3^+$ T cells (Ma et al. 2016b). In Ang II-induced renal injury and fibrosis, CXCR6 plays a pivotal role in the regulation of macrophage and T cell infiltration and bone marrow-derived fibroblast accumulation (Xia et al. 2014a). In deoxycorticosterone acetate/salt hypertension, CXCR6 deficiency inhibited the accumulation of bone marrow-derived fibroblasts and myofibroblasts in the kidney (Wu et al. 2020). Given the evidence above, CXCL16/CXCR6 may play important roles in the recruitment into the kidney of bone marrow-derived fibroblast precursors, which contribute to renal fibrosis pathogenesis (Xia et al. 2014b).

3 C-C Chemokine Receptors

3.1 CCR1

CCR1 was found in the peripheral blood of mice and humans in the circulation of macrophages and lymphocytes (Murphy et al. 2000), and one of the symptoms of interstitial fibrosis was found to be the aggregation of macrophages and lymphocytes that lead to ECM development and renal fibrosis (Yan et al. 2016). Studies on UUO mice have shown that, in tandem with the growth of renal fibrosis, the CCR1 was expressed in infiltrating macrophages and T cells. Furthermore, the mRNA expression of CCR1 ligands CCL3 (MIP-1a) and CCL5 (RANTES) was revealed to be upregulated in diseased kidneys (Zeisberg et al. 2000; Ratajczak et al. 2006; Vielhauer et al. 2004). In UUO mice, loss of CCR1 decreased macrophage and lymphocyte infiltration in the obstructed kidney and the associated interstitial fibrosis had diminished renal production of TGF-β1 mRNA (Eis et al. 2004). In a murine model of Adriamycin-induced focal segmental glomerulosclerosis, the small-molecule CCR1 antagonist BX471 treatment significantly reduced markers of

renal fibrosis including interstitial fibroblasts and interstitial volume (Vielhauer et al. 2004). BX471 prevents the binding of MIP-1α/CCL3 to murine CCR1 but not CCR5 and blocks the activation of receptors as determined by the mobilization of Ca2+.

3.2 CCR2

CCL2 is a member of the CC chemokine subfamily that controls recruitment of monocytes through CCR2 (Gerard and Rollins 2001). It has been demonstrated that CCL2 and CCR2 are positively correlated with kidney fibrosis. Similar to CXCR6, CCR2 was shown to be expressed in bone marrow-derived fibroblasts expressing CD45 and procollagen I or PDGFR-β. And CCR2 deficiency could impair myeloid fibroblast accumulation and myofibroblast formation (Xia et al. 2013). Meanwhile, it was demonstrated that CCR2-knockout mice could be shielded from bone marrow-derived myofibroblast infiltration in the kidneys (Xia et al. 2013). CCR2 deficiency also affects CCL2, CCL5, CCL7, CCL8, and CXCL16 gene expression, and the M2 macrophage marker CD206 also being affected (Xia et al. 2013). CCL2/CCR2 may promote the activation of NF-κβ and AP-1 which increases the expression of inflammatory factors including MCP-1 production in diseased kidneys (Kitagawa et al. 2004). Activation of Notch pathway has been described in many human chronic renal diseases. M1 macrophages have been reported to play a pro-fibrotic function in renal fibrosis, whereas M2 macrophages are antifibrotic. Notch signaling is critically involved in macrophage differentiation and activation. Studies have revealed that Notch signaling regulates renal fibrosis mainly through $CD11b^{+}F4/80^{+}CCR2^{+}$ monocytes-derived macrophages in UUO mice with monocytes being recruited through CCL2-CCR2 chemotaxis (Jiang et al. 2019). In unilateral IRI mice, CCR2 inhibition was observed reducing the mRNA expression of M1 macrophages, while the blockade of the CCL2/CCR2 signaling improved fibrosis (Saito et al. 2018). Meanwhile, CCR2 deficiency has been found to lead to a decrease of Th17-related cytokine production and VEGF production with both processes being directly related to renal fibrosis (Braga et al. 2018). These findings suggest that the therapeutic strategy of blocking CCR2 might prove beneficial for progressive fibrosis in the diseased kidneys.

3.3 CCR7

Accumulated evidences suggest a strong candidate for tissue fibrosis activity with fibrocytes (Schmidt et al. 2003; Yoneyama et al. 2001). Recent studies indicated that the CCL21 and CCR7 signaling pathways induced the trafficking of circulating fibrocytes (Wada et al. 2007; Habiel and Hogaboam 2014). CCR7-positive fibrocytes infiltrated the kidney via CCL21-positive vessels, contributing to the

pathogenesis of renal fibrosis. Blockade of CCL21/CCR7 signaling reduced the number of CCR7-expressing fibrocytes as well as CCR2-expressing fibrocytes. Thus, the CCL21/CCR7 signaling of fibrocytes may provide therapeutic targets for combating renal fibrosis (Sakai et al. 2006).

4 CX3C Chemokine Receptor

4.1 CX3CR1

CX3CR1 was shown to be an important mediator in both acute and chronic kidney injury (Furuichi et al. 2009; Zhuang et al. 2017). In an IRI model, CX3CR1 regulated the macrophage infiltration and led to increased expression of α-SMA, TGF-β, and PDGF-B (Furuichi et al. 2006). Furthermore, α-SMA was found to be a marker of activated fibroblasts. TGF-β and PDGF-B are well-characterized factors that promote fibrosis in many diseases and organs, including the kidney (Border and Noble 1994; Hugo 2003). Meanwhile, dendritic cells (DCs) and macrophages were identified as key sources of TGF-β in renal tissue (Kassianos et al. 2013). It was also found that CX3CL1 expressed on activated proximal tubular epithelial cells (PTECs) could chemoattract $CX3CR1^+$ dendritic cells and subsequently promote adhesion of human DCs to PTECs (Kassianos et al. 2015). Given this evidence, it was hypothesized that CX3CR1 may promote renal fibrosis. However, renal fibrosis is promoted in the absence of CX3CR1 with the accumulation of macrophages and more TGF-β production in a UUO model (Engel et al. 2015). In this study, CX3CR1 was considered eligible to inhibit local macrophage proliferation (Engel et al. 2015). In contrast, another study showed that CX3CL1-CX3CR1 increased the population of macrophages contributing to UUO-induced fibrosis (Peng et al. 2015). Also, although CX3CR1 deficiency was not seen to affect monocyte trafficking or macrophage differentiation in vivo, CX3CR1 deficiency reduces renal fibrosis by inhibiting macrophage survival and extracellular matrix deposition in the obstructed kidney (Peng et al. 2015). Later research proposed that this inconsistency could be explained by the different methods for evaluating fibrosis. However, this does not account for the different outcomes of macrophages. We found that the above study had used different markers to identify the macrophages, which might be the cause of the discrepant results. Thus, further investigation is needed to clarify the role of CX3CR1 in renal fibrosis.

5 Other Chemokine Receptors

Data suggests that Th22 cells might be recruited into the kidneys via the CCL20-CCR6, CCL22-CCR4, and/or CCL27-CCR10 axes by mesangial cells and tubular epithelial cells in infection-related IgAN. Th22 cell overrepresentation has been

attributed to increases in levels of IL-1, IL-6, and TNF-α (Gan et al. 2018), thereby contributing to renal fibrosis. XCL1, the ligand of XCR1, was found to have a slight but significant increase (Vielhauer et al. 2001). Atypical chemokine receptor 2 (ACKR2) is also known as CCR10. It was reported that CCL2 levels and leukocyte counts increased in peripheral blood in Ackr2-deficient mice. Meanwhile, ACKR2 promoted renal leukocyte recruitment, the expression of inflammatory markers and fibrosis, and proinflammatory chemokine levels in autologous nephrotoxic nephritis (Bideak et al. 2018).

6 Discussion

Renal fibrosis is not a particular process, but a concept that describes various fibrotic processes of cellular and molecular structure in specific renal compartments. Throughout fibrogenesis, various chemokines and their receptors have been identified. Given the many obstacles that lie ahead, targeting chemokines remains one of the most promising ways to improve renal fibrosis treatment.

Renal fibrosis is characterized by excessive ECM deposition, which is primarily caused by myofibroblasts. Myofibroblasts are responsible for synthesizing and storing interstitial ECM components such as collagen type I and III and fibronectin during wound healing and at scar and fibrosis sites (Meran and Steadman 2011). Myofibroblasts also synthesize various ECM-degrading proteases known as MMPs, which control the turnover and remodeling of collagen and other ECM proteins (Pardo and Selman 2006). Differentiation of fibroblasts to myofibroblasts is regarded as a critical event in the pathogenesis of renal fibrosis (Strutz and Muller 2006). Myofibroblasts traditionally originate from resident renal fibroblasts and were recently found to also arise from bone marrow-derived cells (Broekema et al. 2007; Li et al. 2007). CXCL16 deficiency has been shown to impair aggregation and myofibroblast production of bone marrow-derived fibroblasts in the kidney and renal fibrosis development (Ma et al. 2016b), while CCR2 deficiency significantly reduced bone marrow-derived myofibroblasts formation by decreasing the protein expression levels of α-SMA and FSP-1 in fibroblasts (Xia et al. 2013).

T cells accumulate in glomerular and tubulointerstitial compartments that can trigger kidney damage by immune-mediated mechanisms (Zohar et al. 2018). CXCR3 ligands are chemotactic for both leukocytes and have been found activating Th1 phenotype T lymphocytes expressing CXCR3 (Bonecchi et al. 1998). In another study, CXCL10/CXCR3 interactions promoted effector Th1 polarization via STAT1, STAT4, and STAT5 phosphorylation (Karin et al. 2016). Additionally, Th17 cells have been demonstrated to play an essential role in causing renal inflammation and tissue damage by secreting IL-17, IL-21, IL-22, and other cytokines (Paust et al. 2009). Several studies have revealed the significance of cytokine IL-17 in the end-stage aggravation of renal disease. Th17 cells are suspected to be able to transdifferentiate into regulatory T cells by modifying their transcription profile, further stressing their prominent role in inflammation and pro-fibrotic disease

resolution (Gagliani et al. 2015). Our review found that proinflammatory Th1 and Th17 lymphocytes were primarily drawn by the CXCR3 receptor to the location of inflammation in the diseased kidney (Nastase et al. 2018). Finally, CXCR3 has been reported to promote $CD4^+$ T cell polarization toward Th1/Th17 effector cells by binding CXCL9/CXCL10 (Zohar et al. 2014).

Macrophage infiltration, derived from circulating monocytes, occurs early after renal injury and plays a critical role in the initial inflammatory response and induction of fibrogenesis. Macrophages can be categorized into two phenotypes: M1 (activated classically) and M2 (activated alternatively). M1 macrophages are considered proinflammatory, releasing cytokines such as IL-1, IL-6, and TNF-α, whereas M2 macrophages are thought primarily to be anti-inflammatory, pro-fibrotic, and produce arginase. Research has found that in the initial stages, proinflammatory macrophages are present in damaged tissues, whereas in the chronic period of renal disease, the population of pro-resolving macrophages increases (Braga et al. 2016). The penetration of the macrophage is caused by induction and local blood monocyte proliferation, while both the level of renal injury and the extent of renal fibrosis are associated with the degree of macrophage infiltration. M2 macrophages can release insulin-like growth factor-1, fibroblast growth factor 2, and PDGF, which promote myofibroblast proliferation and survival (Wynes et al. 2004; Floege et al. 2008). Mouse monocytes have been reported to be divided into 2 populations marked by CX3CR1 expression. In this regard, it appears that kidney IRI induces several factors (perhaps fractalkine itself) that may selectively recruit the CX3CR1 + subset (Geissmann et al. 2003). CX3CR1, CXCR6, CCR1, and CCR2 play a vital role in macrophage infiltration. Thus, chemokine receptors can be considered as targets to inhibit macrophage function in renal fibrosis.

Dendritic cells, together with macrophages, form the axis of the kidney's mononuclear phagocytic network. Monocyte-derived dendritic cells are responsible for glomerular disease invasion and recruitment of T cells, thereby increasing the frequency of the kidney injury (Ma et al. 2013). Evidence in mice has shown that CX3CR1 contributes to the entry of DCs into the inflamed kidney and the adhesion to ECs (Inoue et al. 2005).

Recently, several chemokine receptor antagonists have been studied in human trials. CCX140-B is a small-molecule CCR2 antagonist that inhibits CCR2 and prevents the activation and chemotaxis of MCP-1-dependent monocytes. In a randomized, double-blind, placebo-controlled clinical trial, although eGFR was not significantly changed between the placebo group and the CCX140-B treatment group, it exhibited significant protective effects on patients with diabetic kidneys (de Zeeuw et al. 2015). Moreover, CCX140-B showed no side-effects like hyperkalemia or cardiovascular events after a 1-year-treatment of 5 mg CCX140-B (de Zeeuw et al. 2015). Reparixin is a non-competitive CXCR1 and CXCR2 allosteric blocker that has been studied in breast cancer patients (Schott et al. 2017) and pancreatic islet transplant patients with type 1 diabetes (Citro et al. 2012). Another study showed that sorafenib inhibited renal fibrosis via macrophage with CXCR3/CXCL11 pathway (Ma et al. 2016a). In a pilot study, reparixin

attenuated IRI and inflammation after on-pump coronary artery bypass graft surgery (Opfermann et al. 2015). Although reparixin has not been trialed in patients with renal diseases, it can effectively prevent granulocyte infiltration and renal function impairment in animal experiments (Cugini et al. 2005). Finally, TAK-779 is a synthetic, non-peptide CCR5 and CXCR3 antagonist which is used to cure HIV-1 (Takama et al. 2011). In IRI animal models, TAK-779 suppressed the infiltration of T cells and NK T cells and attenuated the kidney injury (Tsutahara et al. 2012). Cenicriviroc (CVC) is an oral, dual CCR2/CCR5 antagonist with nanomolar potency against both receptors. It showed antifibrotic effects with significant reductions in collagen deposition by significantly reducing monocyte/macrophage recruitment (Lefebvre et al. 2016).

In summary, these data suggest that chemokine receptors and their ligand signaling could constitute a novel therapeutic approach for renal fibrosis.

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