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The role of chemokines in glomerulonephritis

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1. ABSTRACT

Leukocyte infiltration to glomeruli plays an essential role in the pathogenesis of glomerulonephritis. Pathophysiological roles of chemokines and their cognate receptors have shed light on the detailed molecular mechanisms of leukocyte trafficking and activation both in clinical and experimental settings of glomerulonephritis. Infiltrating leukocytes and glomerular resident cells interact to promote and exacerbate glomerular injury, eventually leading to glomerulosclerosis. Further, recent studies on chemokines have expanded their universe beyond leukocyte migration to glomeruli, to include homeostasis, development and protection of resident cells in glomeruli. New insights into proteinuria have been uncovered by the regulation of chemokine system. The intervention of chemokines and their cognate receptors may have therapeutic potential to slow the progression of glomerulonephritis.

2. INTRODUCTION

Most glomerular diseases are immune-mediated, and described by the generic term glomerulonephritis. Leukocytes with directed infiltration and activation by chemokines, play a key role in the pathogenesis of glomerulonephritis from the acute phase to eventual glomerulosclerosis. Recent studies have uncovered that chemokine receptors are expressed not only on infiltrating immune competent cells, but also on glomerular cells, suggesting their involvement in development, homeostasis, pathogenesis and regeneration of diseases. Selective intervention via chemokine/chemokine receptor systems may have potential as therapeutic strategies for glomerulonephritis. Here we review the key role of chemokines in the progression of glomerulonephritis.

3. GLOMERULONEPHRITIS AND IMMUNE COMPETENT CELLS

Most glomerular diseases are immune-mediated, and described by the generic term glomerulonephritis (1). Immune mediated glomerular injury results from autoimmunity, immune complex deposition and cell-mediated disorder. Many forms of glomerulonephritis are characterized by the deposition of immunoglobulin and complements in the glomerulus, which is accompanied by glomerular inflammation and injury. Immune mechanisms orchestrate intrinsic effector cells, extrinsic effector cells and biological mediators, such as chemokines, which result in glomerulonephritis in this setting.

In fact, after disease onsetthere are a wide range of possible outcomes of glomerulonephritis, although more severe initial injury results in less likelihood of recovery. Outcomes range from complete resolution of glomerulonephritis without functional or morphological consequences, (for example in poststrepotococal glomerulonephritis) to the presence of severe glomerulosclerosis and tubuointerstitial fibrosis with established renal failure.

The main immune competent cells actively involved in glomerulonephritis are consisting of neutrophils, macrophages, and lymphocytes (2). Once glomerular injury is evoked, neutrophils are recruited within a few hours to reach a peak in numbers at -24 hours; monocytes are recruited rather more slowly, the maximum number typically being reached at 48 hours when maturation into macrophages is already well advanced. The kinetics of lymphocyte recruitment is slower still and occurs over several days. There is strong evidence that such sequential recruitment reflects sequential expression of chemoattractant cytokines, adhesion molecules and chemokines (1). One of the mechanisms of neutrophil and macrophage infiltration into the diseased kidneys is via activation of adhesion molecules to induce the release of lysosomal enzymes and generate superoxide anions to initiate inflammatory events and subsequent tissue damage (2). However, macrophages may exert dual effects on renal injuries, in addition to the promotion of injury and progression of inflammation and fibrosis. Macrophage subsets may direct the resolution of inflammatory injury. However, with continuation of the trigger for the development of glomerulonephritis and/or a severe initial insult, infiltration of inflammatory cells, including lymphocytes, promote inflammatory injury through several pathways including the secretion of proinflammatory cytokines and chemokines (3).

4. ROLE OF CHEMOKINES IN THE ACUTE PHASE OF GLOMERULONEPHRITIS

Detailed molecular mechanisms involved in leukocyte migration to the kidney via chemokines have shed light on the pathogenesis of glomerulonephritis. Chemokines expressed on the surface of glomerular endothelial cells interact with their cognate receptors on specific infiltrates. Once leukocytes migrate to glomeruli, chemokines and proinflammatory cytokines produced by both resident cells and immune competent cells exert a wide range of biological activities at inflammatory sites. Selective expression of chemokine receptors and adhesion molecules on specific cell populations may determine the specific phenotypes of infiltrating cells in inflamed glomeruli.

4.1. *In vitro* studies

The acute phase of glomerulonephritis is pathologically characterized by infiltration of inflammatory cells into glomeruli, and proliferation of mesangial cells in the glomerulus. *In vitro* studies revealed that proinflammatory stimuli such as interleukin-1beta (IL-1beta), tumor necrosis factor-alpha (TNF-alpha) and interferon-gamma (IFN-gamma), immune complexes, growth factors including platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) are able to induce IL-8/CXCL8, monocyte chemoattractant protein-1 (MCP-1)/macrophage chemotactic and activating factor (MCAF)/CCL2, interferon-inducible protein-10 (IP-10)/CXCL10, macrophage inflammatory protein-1alpha (MIP-1alpha/CCL3 and regulated upon activation of normal T cells that express and secrete (RANTES)/CCL5 from glomerular resident cells (4). Interestingly, a recent study revealed that binding of polymeric IgA to mesangial cells resulted in increased production of IL-8/CXCL8, predominantly with IgA from patients with IgA nephropathy (5). In turn, these stimuli may induce the expression of CCR1 on kidney resident cells, especially on mesangial cells (6). These findings may indicate a possible positive feedback loop dependent on chemokines/chemokine receptors, which results in the escalation of glomerulonephritis.

4.2. Lessons from experimental animal models

Activated mesangial cells are a source for the augmented glomerular fractalkine/CX3CL1 expression during the proliferative phase of acute anti-Thy1 glomerulonephritis. Up-regulation of mesangial fractalkine/CX3CL1 by TNF-alpha, IL-1beta, PDGF-AB and bFGF is mediated, at least in part, via NF-kappaB signaling pathway. The differential expression of MCP-1/CCL2 and fractalkine/CX3CL1 may sequentially recruit distinct subsets of monocytes to the glomerulus during acute anti-Thy1 glomerulonephritis (7). It is of note that toll-like receptor (TLR) is closely related to the expression of chemokines in glomerular resident cells. Glomerular inflammation induced by passive administration of nephrotoxic antibodies does not occur in the absence of TLR2 stimulation, with a strong synergy when antibody deposition and TLR2 stimulation occur together. Wild-type but not TLR2-deficient mesangial cells produced CXC chemokines in response to stimulation with Pam(3)CysSK. These results demonstrate that TLR2 stimulation on both bone marrow-derived and resident tissue cells plays a role in amplifying the inflammatory effects of antibody deposition in the glomerulus (8).

Table 1. Chemokines/chemokine receptors in human glomerulonephritis

	Chemokines (Chemokine receptors)
IgA nephropathy	Mig/CXCL9 (CXCR3)
	IP-10/CXCL10 (CXCR3)
	I-TAC/CXCL11 (CXCR3)
	IL-8/CXCL8 (CXCR1)
	BCA-1/CXCL13 (CXCR5)
	MCP-1/CCL2 (CCR2)
	MIP-1alpha /CCL3, RANTES/CCL5
	(CCR1, 5)
	TECK/CCL25 (CCR9)
	MEC/CCL28 (CCR10)
	Lymphotactin/XCL1
Crescentic glomerulonephritis	IL-8/CXCL8 (CXCR1)
	MCP-1/CCL2 (CCR2)
	MCP-4/CCL13 (CCR2, CCR3)
	MIP-1alpha /CCL3, MIP-1beta/CCL4
	RANTES/CCL5
	(CCR1, CCR5)
	Mig/CXCL9
	IP-10 /CXCL10(CXCR3)
	Fractalkine/CX3CL1 (CX3CR1)
	Lymphotactin/XCL1
	DARC
Membranoproliferative glomerulonephritis	IL-8/CXCL8 (CXCR1)
	Mig/CXCL9 (CXCR3)
	IP-10/CXCL10 (CXCR3)
	I-TAC/CXCL11 (CXCR3)
	MCP-1/CCL2 (CCR2)
	RANTES/CCL5 (CCR5)
	CX3CR1

In contrast, a certain chemokine may play a protective role against the insult. For example, the anti-IP-10 treatment given to the rats with Thy1 nephritis disturbed the podcyte function, resulting in exacerbated proteinuria, and accelerated mesangiolysis and matrix expansion (9). A very recent study suggests that C-reactive protein (CRP) mediates protection from accelerated nephrotoxic nephritis through the induction of IL-10 with concomitant reduction of chemokine expression. In addition, FcgammaRI plays an important role in but is not the sole mediator of CRP-mediated protection (10).

4.3. Human glomerulonephritis

IL-8/CXCL8 is detected in diseased glomeruli in patients with acute glomerulonephritis and urinary levels of IL-8/CXCL8 correlate well with neutrophils in glomeruli and the presence of hematuria (11)(Table 1). Supporting these observations, by immunohistochemistry, CXCR1 expression was found on infiltrating inflammatory cells (predominantly polymorphonuclear leukocytes), as well as on intrinsic kidney cells (arterial smooth muscle cells, endothelial cells of peritubular capillaries). The highest numbers of glomerular CXCR1-positive cells were present in biopsies with mesangioproiferative glomerulonephritis, followed by lupus nephritis, and crescentic glomerulonephritis. CXCR1 might be involved in the recruitment of polymorphonuclear leukocytes to the glomerular tuft (12). In addition, CC chemokines play a role in human acute glomerulonephritis. For instance, MCP-1/CCL2 is reported to be pivotal in the acute setting of glomerulonephritis, and is detected in glomeruli (13-14).

5. ROLE OF CHEMOKINES IN PROTEINURIA

Glomerular injury induces the excretion of protein in urine, which, in turn, incites further kidney injury. In humans, chemokines, such as IL-8/CXCL8 and MCP-1/CCL2, have been reported to be involved in proteinuria in nephritic glomerular diseases and diabetic nephropathy (11, 15-16) (Table 1). Therefore, deeper knowledge of the detailed mechanisms and the blockade of urinary protein excretion in this area may be beneficial for the long-term kidney protection.

Results from experimental animal models and *in vitro* studies support these observations. Anti-IL-8 antibody treatment dramatically prevented the fusion of epithelial cell foot process and completely normalized the urinary levels of protein and albumin (17). In addition, neutralizing antibodies for MCP-1/CCL2 returned proteinuria to almost normal levels in rat crescentic glomerulonephritis (18) (Figure 1A). These phenomena might be explained, at least in part, by the presence of chemokine receptors on podocytes. Rao *et al.* reported that macrophage metalloelastase 12, induced by MCP-1/CCR2 from glomerular podocytes may induce podocyte injury and glomerular basement membrane destruction and finally cause proteinuria (19). In addition, it is likely that the release of oxygen radicals that accompanies the activation of CCRs and CXCRs may contribute to podocyte injury and the development of proteinuria (20).

6. ROLE OD CHEMOKINES IN THE CHRONIC PHASE OF GLOMERULONEPHRITIS LEADING TO GLOMERULOSCLEROSIS

In vitro studies suggest the presence of chemokine amplification such that CXC chemokines induce CC chemokines and CXC chemokines in cultured mesangial cells (21). This suggests that sequential expression of CC chemokines and CXC chemokines may be responsible for switches from acute inflammation to chronic inflammation in glomeruli. In addition, an intrinsic regulatory loop, in which MCP-1/CCL2 stimulates transforming growth factor-β (TGF-beta) production by isolated glomerular resident cells, has been suggested in the absence of infiltrating immune competent cells (22). These results suggest an additional role for MCP-1/CCL2 in fibrotic kidney diseases, possibly by interacting with TGF-beta. This was supported by *in vivo* studies showing that administration of anti-MCP-1 antibodies prevented glomerulosclerosis and kidney failure (18). Thus, the axis from CXC chemokines and CC chemokines to TGF-beta may play a central role both in early inflammatory events and in late fibrotic events of glomerulonephritis.

7. ROLE OF CHEMOKINES IN CRESCENTIC GLOMERULONEPHRITIS

Crescentic glomerulonephritis is a prominent feature in rapidly progressive glomerulonephritis and

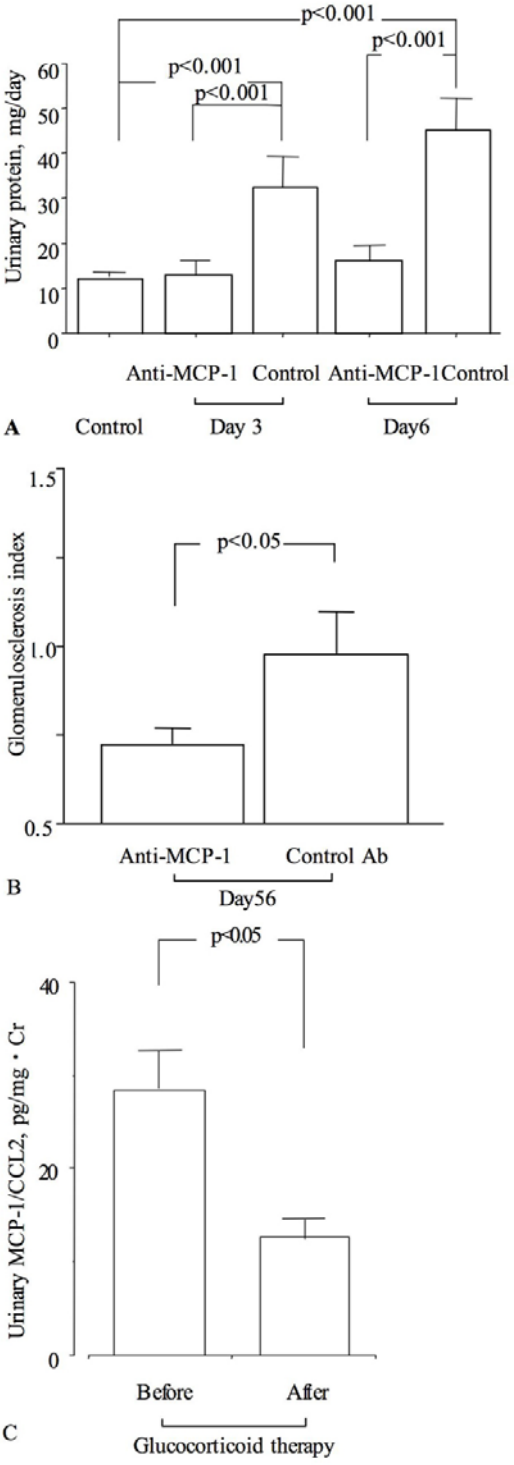

Figure 1. Effect of anti-MCP-1 antibodies on urinary protein excretion (A). The inhibition of MCP-1/CCL2 reduced glomerulosclerosis at 56 days in rat crescentic glomerulonephritis (B).Alteration of urinary levels of MCP-1/CCL2, following glucocorticoid therapy including methylprednisolone pulse therapy in patients with human crescentic glomerulonephritis (C).

may result in end-stage kidney failure. Macrophages and T lymphocytes preferentially migrate to both glomeruli and interstitium in crescentic glomerulonephritis. Many chemokines and their cognate receptors have been reported to be involved in human crescentic glomerulonephritis (Table 1). For example, urinary MIP-1alpha/CCL3 levels in patients with crescentic glomerulonephritis correlated well with the percentage of cellular crescents and the number of CD68-positive infiltrating cells, and CCR1- and CCR5-positive cells in the glomeruli (23-24). Moreover, elevated urinary levels of MIP-1alpha/CCL3 and the number of CCR5-positive cells were dramatically decreased during glucocorticoid therapy-induced convalescence (24). It is of note that CCR1 and CCR5 are preferentially expressed on Th1 T cells. It is therefore likely that MIP-1alpha/CCL3 plays a significant role in crescentic glomerulonephritis, by recruiting and activating macrophages and T lymphocytes positive for CCR1 or CCR5. In addition, the measurement of urinary MIP-1alpha may be an excellent system for monitoring the clinical activity of human crescentic glomerulonephritis.

Further, the p38 mitogen-activated protein kinase (MAPK)-NF-kappaB-chemokine axis contributes to progressive human and experimental crescentic glomerulonephritis (25-26). The phosphorylation of p38 MAPK associated with the activation of NF-kappaB may be involved in the up-regulation of intrarenal MIP-1alpha/CCL3 and the utilization of CCR5 signaling, which may result in human crescentic glomerulonephritis (25). Breakdown of this axis via the administration of p38 MAPK inhibitor(s) uncovered therapeutic benefit for crescentic glomerulonephritis (26-27).

8. INVOLVEMENT OF CHEMOKINES IN HOMEOSTASIS AND DEVELOPMENT OF GLOMERULI

Banas *et al.* reported the constitutive glomerular expression of CCR7 and its ligand secondary lymphoid tissue chemokine (SLC)/CCL21, which has functional roles for glomerular homeostasis and regenation, including mesangial migration, proliferation, survival and "wound healing"(28). In addition, chemokines and their receptors may be involved in human kidney development, although so far only one immunohistochemical study reported the expression of chemokines and their cognate receptors during kidney development (29). Mononuclear cell-like cells within the nephrogenic blastema focally express IP-10/CXCL10, a ligand for CXCR3. Mononuclear cell-like cells dispersed through the developing organ express CX3CR1. Expression of CXCR4, the receptor for stromal cell-derived factor-1 (SDF-1)/CXCL12, is limited to stromal CD34-positive cells. In contrast, the expression of SDF-1/CXCL12, fractalkine/CX3CL1, and CXCR3 is first observed in the comma- or S-shaped body stage (29). The intensity of this expression becomes stronger in the capillary loop stage, and the expression is mainly

Table 2. Intervention of chemokines/chemokine receptors on experimental glomerulonephritis

Anti-Thy-1 nephritis			
Target	Intervention	Outcome	References
IP-10/CXCL10	Neutralizing antibody	Worse	10
MCP-1/CCl2	Neutralizing antibody	Improved	30
RANTES/CCL5	Amino-oxypentane-RANTES	Improved	31
Crescentic glomerulonephritis			
Target	Intervention	Outcome	References
CINC	Neutralizing antibody	Improved	37
IL-8/CXCL8	Neutralizing antibody	Not affected	37
MIP-2/CXCL2	Neutralizing antibody	Improved	39
SR-PSOX/CXCL16	Neutralizing antibody	Improved	42
MCP-1/CCL2	Neutralizing antibody	Improved	18, 34-36
	Gene targeting	Not affected	43
CCR2	Gene targeting	Worse	44
MIP-1alpha /CCL3	Neutralizing antibody	Improved	38
RANTES/CCL5	Met-RANTES	Improved	34
CCR1	Gene targeting	Worse	44
MDC/CCL22	Neutralizing antibody	Improved	41
Immune complex glomerulonephritis			
Target	Intervention	Outcome	References
IL-8/CXCL8	Neutralizing antibody	Improved	8
RANTES/CCL5	Met-RANTES	Worse	46
	Amino-oxypentane-RANTES	Worse	46

observed in the mesangial stalk and endothelial cells of the glomeruli. In particular, IP-10/CXCL10 has been reported to have a protective and maintaining role for glomerular podocytes, by regulating the expression of podocyte-associated proteins such as nephrin and podocin that are reported to be essential for maintaining the podocyte function (10).

9. ANTI-CHEMOKINE THERAPY FOR GLOMERULONEPHRITIS

Selective intervention of chemokines/chemokine receptor systems may be therapeutically beneficial in several experimental nephritis models (Table 2). In addition to CXC chemokines (17), CC chemokines are of importance as therapeutic targets for acute glomerulonephritis. An antibody against MCP-1/CCL2 reduced the glomerular macrophage infiltration at 24 hours by 40%, but was without effect on glomerular neutrophil recruitment or growth of the glomerular resident cells. The reduction in macrophage infiltration might affect this glomerular injury in Thy1 nephritis (30). The CCR5 antagonist AOP-RANTES ameliorated monocyte/macrophage infiltration and improved glomerular pathology in experimental glomerulonephritis (31). Ninichuk *et al.* emphasized the impact of CCR1 as a potential therapeutic target for Alport's disease or other progressive nephropathies associated with interstitial macrophage infiltrates, since CCR1-mediated recruitment and local activation of macrophages contribute to disease progression in COL4A3-deficient mice (32). This effect is also confirmed by the evidence that blockade of CCR1 substantially reduced interstitial leukocyte accumulation and the subsequent kidney fibrosis in a murine model of nephrotic syndrome and focal segmental glomerulosclerosis (FSGS), which support a role for CCR1 in interstitial leukocyte recruitment and suggest that CCR1 blockade might be a new therapeutic strategy in progressive nephropathies such as FSGS (33).

Blockade of chemokine/chemokine receptors may have beneficial impacts on the treatment of crescentic glomerulonephritis. Anti-MCP-1 antibody treatment remarkably reduced eventual glomerulosclerosis and/or interstitial fibrosis and improved renal function (18, 34-36) (Figure 1B). Lloyd *et al.* reported that the antagonist, Met-RANTES when used in nephrotoxic serum nephritis in CD1 mice reduced urinary protein excretion, cell infiltration of T cells and mononuclear cells, whereas crescent formation was not affected (34). The inhibition of CXC chemokines also shows a beneficial effect on crescentic glomerulonephritis. Neutralizing antibodies against CINC attenuated the influx of neutrophils into the glomerulus and commensurately diminished proteinuria, whereas neutralizing antibody to MIP-1alpha/CCL3 attenuated proteinuria, but did not affect the accompanying influx of neutrophils (37-38). Similarly, anti-MIP-2 antibody administration was effective in reducing neutrophil influx and promoted functional improvement in the glomerular damage as evidenced by a reduction of abnormal proteinuria (39). Furthermore, vMIP-II, an antagonist for CC and CXC chemokine receptors as well as CX3CR1, the receptor for fractalkine/CX3CL1 significantly reduced leukocyte infiltration to the glomeruli, and markedly attenuated proteinuria in crescentic glomerulonephritis (40). Blocking the function of macrophage-derived chemokine (MDC)/CCL22 prevented crescentic formation, and preserved renal function impairment during days 7 to 14 in an anti-glomerular basement membrane antibody glomerulonephritis model (41). Very recently, Garcia *et al.* reported that blocking CXCL16 in the acute inflammatory phase or progressive phase of established glomerulonephritis significantly attenuated monocyte/macrophage infiltration and glomerular injury; proteinuria also improved (42).

In contrast, Tesch *et al.* investigated glomerular and interstitial lesions induced by

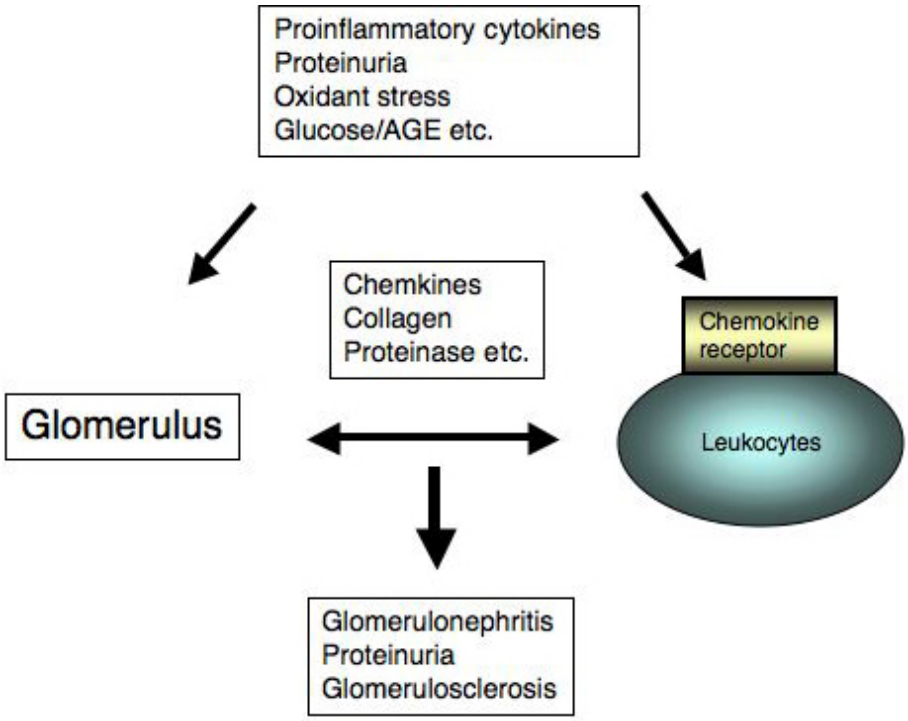

Figure 2. Involvement of chemokine/chemokine receptor systems in the progression of glomerulonephritis.

nephrotoxic serum in F1 generation littermates of MCP-1 knockout 129SV/J and wild-type C57BL/6 (43). Interestingly, there was a marked reduction in tubular injury in MCP-1-deficient mice, but no protection from glomerular injury. Moreover, aggravated kidney dysfunction and increased proteinuria have been detected in both CCR1 and CCR2 disrupted mice, compared to wild-type mice (44-45). Interestingly, horse apoferritin-induced glomerulonephritis mice treated with Met-RANTES and/or AOP-RANTES showed worse disease with mesangiolysis, capillary obstruction, and nephritic range proteinuria (46).

Recent studies further strengthen the idea that clinically available drugs including antagonists against renin-angiotensin-aldosterone system are of therapeutically importance in kidney diseases in accordance with decreased chemokine expression via NF-kappaB. Stahl *et al.* showed the inhibitory effects of AT1-receptor antagonists (47) and prostaglandin E1 (48) on glomerular expression of MCP-1/CCL2. In contrast, cyclooxygenase (COX) products might serve as endogenous repressors of MCP-1 formation in an anti-glomerular basement membrane model of glomerulonephritis (49). This study demonstrated that COX-1 and COX-2 products mediate these effects differently because the selective COX-2 inhibitors had less influence on chemokine expression. Further, pentoxifylline (PTX) is a phosphodiesterase inhibitor that possesses potent anti-inflammatory and immunomudulatory effects. Administration of PTX 800 mg per day is safe and effective for reducing proteinuria in patients with proteinuric primary glomerular diseases. This beneficial effect occurs in close association with a reduction of urinary MCP-1/CCL2 excretion (50). Further, Park *et al.* reported that while TNF-alpha-induced MCP-1 production is mediated by the cooperative action of NF-kappaB and AP-1 in human glomerular endothelial cells, dexamethasone represses TNF-α induced MCP-1 production via suppression of AP-1 binding activity (51). Supporting this notion, elevated urinary MCP-1/CCL2 levels were dramatically decreased during steroid therapy-induced convalescence in patients with glomerulonephritis in humans (52) (Figure 1C).

10. CONCLUDING REMARKS

Collectively, these findings suggest that chemokines and their cognate receptors participate in glomerular development, homeostasis, the initiation and/or progression of glomerulonephritis, resulting in glomerulosclerosis, which all provide a better conceptual understanding of glomerulonephritis (Figure 2). It is our hope that modulation of chemokines may provide new therapeutic potentials for glomerulonephritis.

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