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Abstract

The interaction of activated leukocytes and renal resident cells are thought to play a crucial role in the pathogenesis of renal diseases. Recent investigations of the pathophysiological roles of chemokines and their cognate receptors have shed light on the detailed molecular mechanisms of leukocyte trafficking and activation in the diseased kidneys. Chemokine/chemokine receptor systems may be essentially involved in the pathogenesis of phase-specific renal disorders and the measurement of urinary levels of chemokines may be clinically useful for monitoring the different disease phases and activities. In addition, chemokine receptors expressed in renal resident cells may be involved in proliferation, fibrogenesis as well as chemotaxis. The selective intervention of chemokines/chemokine receptor systems (anti-chemokine therapy) may have the potential as the particular therapeutic strategies for renal diseases in future.

Introduction

The interaction between leukocytes and renal resident cells may provide the key roles to the progression of the inflammatory processes. Moreover, leukocyte trafficking from peripheral blood into the diseased kidneys is a hallmark of almost any kind of renal diseases (1). Activated leukocytes are thought to play a crucial role in the pathogenesis of renal diseases from acute phases to chronic phases (2). Recent investigations of the pathophysiological roles of chemokines and their cognate receptors have shed light on the detailed molecular mechanisms of leukocyte trafficking and activation in various diseases (3-5). In addition, these chemokines exert overlapping but distinct actions on specific cell types through interacting with the cognate G protein-coupled receptors with seven transmembrane domains (2-5). Chemokine receptors are expressed not only on leukocytes, but also parenchymal cells, suggesting the possible autocrine/paracrine loop during the interaction of leukocytes and parenchymal cells. Therefore, detailed mechanisms of leukocyte recruitment and activation via chemokines/chemokine receptor systems may provide the better understanding of the pathogenesis of renal diseases.

This review will focus on 1) chemokine/chemokine receptor systems in the pathogenesis of phase-specific renal disorders (“chemokine cascade”), and 2) the measurement of urinary levels of chemokines useful for monitoring the different disease phases and activities of human renal diseases, and 3) the intervention of chemokines/chemokine receptor systems as the particular immunotherapeutic strategies to combat with the specific phases of renal diseases.

Chemokine superfamily

Chemotaxis and leukocyte activation

The chemokine superfamily is divided into four groups depending on conserved cysteine residues that form disulfide bonds in the chemokine tertiary structure (3-5). More than 40 chemokines and 17 chemokine receptors have been identified. Leukocyte trafficking at the inflammatory site consists of two major functions: first, the arrest, activation and firm adhesion of leukocytes on endothelial surfaces and, second, the diapedesis and transmigration through the endothelial cells into the renal tissue and from there to specific microenvironments (3-5). Evidence is accumulating that chemokines through their cognate receptors are of importance for these steps. In addition, during the first step, a selectin-mediated rolling followed by an integrin-mediated firm adhesion are involved when leukocytes bind to endothelium (6-7). Chemokines expressed on the surface of endothelial cells interact with their cognate receptors on specific leukocytes, which trigger the activation of adhesion molecules and result in firm adhesion. Once leukocytes migrate into the interstitium, chemokines produced by both tissue cells and infiltrated cells induce a variety of biological functions of leukocytes at the inflammatory sites. Selective expression of chemokine receptors contributes to cell specificity of chemokine actions. Thus, the chemokine systems provide sequential migratory patterns of the specific leukocytes with their cognate receptors in a multistep manner.

Other biological functions of chemokines

Recent studies revealed that chemokines through their cognate receptors act as growth factors for mesangial cells (8) and are involved in respiratory burst, hematopoiesis, angiogenesis, development and fibrogenesis (3-5). Interferon-inducible protein (IP)-10 induced the proliferation of mesangial cells probably via the cognate receptor, CXCR3 (8). In addition, interleukin (IL)-8 and monocyte chemoattractant protein (MCP)-1 (also termed as monocyte chemotactic and activating factor (MCAF/MCP-1)) are closely related to the urinary excretion of protein in experimental

models (9-10) and human nephrotic syndrome (11), which may be related to the permeability of the glomerular capillaries. IL-8 has been shown to induce the migration of human umbilical endothelial cells and angiogenesis in rat cornea (12-13). Additional interest in chemokines and their cognate receptors is arising from recent identification of several chemokines as inhibitors and receptors as co-receptors for HIV infection (14). The blockade of chemokines/chemokine receptors as the clinical therapeutic applications have been anticipated in these fields.

In vitro expression of chemokines and chemokine receptors

Renal parenchymal cells express chemokine receptors as well as their cognate ligands on stimulation (2). *In vitro* studies revealed that proinflammatory stimuli such as IL-1 β , tumor necrosis factor (TNF)- α , and interferon (IFN)- γ , immune complexes, growth factors including platelet-derived growth factor and basic fibroblast growth factor are able to induce IL-8, MCP-1, IP-10, macrophage inflammatory protein (MIP)-1 α and regulated upon activation, normal T cell expressed and excreted (RANTES) from renal resident cells (2). In turn, these stimuli may induce the expression of CCR1 and CXCR3 on renal resident cells, especially on mesangial cells (8, 15). These results suggest the certain roles of possible positive feedback loop dependent on chemokines/chemokine receptors which results in progressive renal diseases. In fact, the C-X-C chemokines, MIP-2 and KC up-regulated MCP-1 and RANTES expression in mesangial cells (16). Autoinduction of MIP-2 and KC mRNA were also noted. These indicate chemokine amplification probably via their cognate receptors in mesangial cells, which may contribute to the maintenance and chronic course of glomerular inflammation. In addition, vasoactive agents especially angiotensin (AG) II through its receptors can induce chemokine expression (17-18). In contrast, glucocorticoids, transforming growth factor (TGF)- β , Vitamin D and prostaglandins are able to inhibit the expression of chemokines (3-5). Supporting this notion, we have reported that glucocorticoid therapy including methylprednisolone pulse therapy

reduced the renal expression of chemokines and their cognate receptors in accordance with the decrease in the clinical activities of human renal diseases (19-25).

Chemokines/chemokine receptors in recent animal models

Lessons from gene targeting mice

Data from gene targeting mice can give rise to the identification of the actions of chemokines and their cognate receptors (2). Accumulating data suggest that chemokines and their cognate receptors expressed in the diseased kidneys govern critical aspects of acute and chronic renal inflammation leading to glomerulosclerosis and interstitial fibrosis (2). Lack of CCR1 enhanced Th1 responses and glomerular injury induced by the administration of nephrotoxic serum (26). Considering the expression of CCR1 on mesangial cells (15) and the probable involvement of CCR1 in interstitial fibrosis (24), CCR1 may protect glomerular and interstitial injury after the initial insults. On the other hand, anti CCR1 antibodies significantly reduced the accumulation of inflammatory cells and collagen deposition, resulting in dramatic improvement of survival in bleomycin-induced lung fibrosis in mice (27). The identification of organ- and phase-specific roles of CCR1 will be required. Similarly, deleting MCP-1 dramatically reduces M ϕ and T cell recruitment, protects kidney pathology, reduces proteinuria and prolongs survival in MCP-1-deficient MRL-*Fas*^{lpr} mice (28-29). In contrast, the intensity of glomerulonephritis in CCR2 knockout mice was more severe induced by nephrotoxic serum. This result suggests glomerulonephritis is not solely dependent on the presence of CCR2 for progression of disease and that the intriguing possibility that a CCR2 gene product ameliorates glomerulonephritis in this murine model. (30). Further studies, therefore, will be required to identify the detailed molecular mechanisms of chemokine and chemokine receptor actions in renal diseases *in vivo*.

Establishment of cell-mediated renal injury via ex-vivo gene transfer of chemokine

Few studies revealed the direct evidence that locally or systematically produced chemokines in the kidneys induced the leukocyte infiltration and activation. RANTES may explain the cellular infiltration including Th1 T cells in the interstitium in human renal diseases via its cognate receptors, CCR1 and CCR5 (24). In addition, RANTES was upregulated in the kidneys of a murine lupus nephritis model, MRL-*Fas*^{lpr} mice prior to renal injury and increased with progressive injury (31). To explore whether locally produced RANTES incites renal injury with T cell infiltration, tubular epithelial cells genetically modified to secrete RANTES infused under the renal capsule incites interstitial nephritis in MRL-*Fas*^{lpr} mice (31). RANTES fostered the accumulation of a distinct subset of T cells (e.g. CD4 T cells), which would be compatible to clinical findings. Supporting this notion, circulating components including CD4⁺ T cells are required to incite renal injury in MRL-*Fas*^{lpr} mice via both cellular and humoral immune responses (32). The manipulation of T cells dependent on chemokines/chemokine receptors would be of therapeutic importance in renal diseases.

Chemokines in human renal diseases

Chemokine cascades

In inflammatory renal diseases, the types of leukocytes migrated to the diseased kidneys depend on the types of insults; neutrophils in acute inflammation, macrophages, lymphocytes and plasma cells in chronic inflammation, resulting in renal sclerosis/fibrosis. To clarify the mechanism of specific leukocyte infiltration into the diseased kidneys and the involvement of chemokines and their cognate receptors in renal diseases, both urinary and plasma levels of chemokines were measured in patients with various renal diseases at different phases. Firstly, urinary IL-8 levels were elevated in the acute phase and acute exacerbation of inflammatory renal diseases including IgA nephropathy, acute glomerulonephritis, lupus nephritis and crescentic glomerulonephritis (19-20). Urinary levels of IL-8 were correlated with glomerular endocapillary proliferation and the degree of hematuria (19-20). Elevated urinary IL-8 levels during the acute phase or exacerbation was found to be decreased during

spontaneous or glucocorticoid therapy-induced convalescence in all patients examined. Taken together, locally produced IL-8 in the diseased kidneys may reflect acute renal disease status based on leukocyte infiltration in the diseased kidneys (Table 1).

Secondly, urinary MCP-1 levels were significantly higher in patients with advanced renal diseases, and were correlated with pathological progressive factors such as mesangial proliferation, crescentic formation and interstitial lesions associated with CD68 positive M ϕ in patients with IgA nephropathy, lupus nephritis, crescentic glomerulonephritis and other inflammatory renal diseases (20, 22-23).

Urinary MCP-1 levels in lupus nephritis patients with active lesions were significantly higher than those with inactive lesions. Moreover, elevated urinary MCP-1 levels were dramatically decreased during steroid therapy-induced convalescence.

MCP-1 was mainly detected in vascular endothelial cells, tubular epithelial cells and infiltrated mononuclear cells in the interstitial lesions via both immunohistochemical and *in situ* hybridization analyses (20, 22-23). Collectively, these observations suggest that MCP-1 is probably involved in the pathogenesis of progressive inflammatory renal diseases, especially tubulointerstitial lesions possibly through the recruitment and activation of M ϕ . Moreover, the measurement of urinary MCP-1 levels may be a useful clinical tool for monitoring the disease activity of inflammatory renal diseases (Figure 1). Considering the presence of chemokine amplification that C-X-C chemokines induced C-C chemokines and C-X-C chemokines as well in mesangial cells *in vitro* (16), Switches from acute inflammation to chronic inflammation in human renal diseases may be dependent on the subsequent expression of C-C chemokines (e.g. MCP-1) followed by C-X-C chemokines (e.g. IL-8). In addition, MCP-1 mediates collagen deposition in experimental glomerulonephritis by TGF- β (33), MCP-1 expression in chronic inflammation may result in renal sclerosis/fibrosis. Supporting this notion, the administration of anti-MCP-1 antibodies prevented glomerular sclerosis and interstitial fibrosis as well as the leukocyte infiltration (10). Therefore, the possible positive amplification loop from C-X-C chemokines to C-C chemokines

resulting in sclerosis/fibrosis (“chemokine cascade”) may play a crucial role in the pathogenesis of human renal diseases (Table 1).

MCP-1: a common regulatory molecule of chronic inflammation resulting in renal sclerosis/fibrosis

MCP-1 may be involved in progressive glomerular and interstitial damage resulting in renal sclerosis/fibrosis in inflammatory renal diseases. Recent studies revealed that MCP-1 may play an important role in the pathogenesis of metabolic disorders, such as diabetic nephropathy and non-inflammatory nephrotic syndrome. Locally expressed MCP-1 in interstitium participates in human diabetic nephropathy especially in interstitial lesions via recruiting and activating M ϕ (34). Urinary MCP-1 levels were significantly elevated in patients with diabetic nephrotic syndrome and advanced tubulointerstitial lesions. Moreover, urinary levels of MCP-1 were well correlated with the number of CD68-positive infiltrating M ϕ in the interstitium. In contrast, serum MCP-1 levels remained as similar as those of healthy volunteers. Furthermore, MCP-1-positive cells were detected in the interstitium of diabetic nephropathy via both immunohistochemical and *in situ* hybridization analyses. These observations suggest that locally produced MCP-1 may be involved in the development of advanced diabetic nephropathy, especially in the formation of tubulointerstitial lesions possibly through M ϕ recruitment and activation. In addition, overexpression of MCP-1 and other fibrogenic cytokines including platelet derived growth factor and TGF- β were associated with an interstitial accumulation of mononuclear cells and an increase in myofibroblastic activity in patients with membranous nephropathy, non-inflammatory nephrotic syndrome (35). In contrast, patients with minimal change nephrotic syndrome showed undetectable levels of urinary MCP-1, similarly as those of healthy volunteers (22-23). These results suggest that there might be no correlation between levels of urinary MCP-1 and proteinuria caused by non-inflammatory glomerular capillary lesions, such as minimal change nephrotic syndrome. Therefore, some additional factors in patients with membranous nephropathy may be responsible

for the up-regulation of MCP-1 resulting in interstitial inflammation and fibrosis. Taken these together with the results in inflammatory renal diseases, up-regulation of MCP-1 may be a common regulatory pathway involved in the progressive renal damage with any etiologies leading to interstitial fibrosis (Figure 1). Thus, the development of therapeutic approaches via MCP-1/its cognate receptors will be anticipated for the prevention of progressive renal injury in near future.

Crescentic glomerulonephritis: Th1 type immune responses

In rapidly progressive glomerulonephritis, crescentic glomerulonephritis, associated with a comparable degree of tubulointerstitial nephritis and anemia, is a prominent feature which leads to eventual loss of renal function (23). Therefore, specific molecule(s) involved in the pathogenesis and the development of clinical monitoring systems for disease activities are required for the better understanding of crescentic glomerulonephritis. Urinary MIP-1 α was specifically detected in patients with crescentic glomerulonephritis, even though it was below detectable levels in healthy subjects and patients with renal diseases without crescentic formation (23). MIP-1 α -positive cells were mainly detected in crescentic lesions. In addition, recent studies revealed that chemokine receptors, CXCR3 and CCR5 are preferentially expressed on Th1 T cells (36-40). CCR1, and CCR5-positive cells, cognate receptors for MIP-1 α were detected in diseased glomeruli and interstitium (24). Using a dual staining technique, these positive cells were mainly CD3-positive T cells and CD68-positive M ϕ . Urinary MIP-1 α levels in the patients with crescentic glomerulonephritis were well correlated with percentage of cellular crescent and the number of CD68 positive infiltrating cells, CCR1 and CCR5 positive cells in the glomeruli (24). Moreover, elevated urinary levels of MIP-1 α and the increased number of CCR5 positive cells dramatically decreased during glucocorticoid therapy-induced convalescence. These data suggest that MIP-1 α may be involved specifically in the pathogenesis of crescentic glomerulonephritis via recruiting and activating M ϕ and T cells as Th1 type immune responses and the measurement of urinary MIP-1 α may be

the excellent system for monitoring the clinical activities of crescentic glomerulonephritis. In contrast, urinary MCP-1 levels were well correlated with the percentage of both total crescents and fibrocellular/fibrous crescents and the number of CD68-positive infiltrating cells in the interstitium. Moreover, MCP-1 was detected mainly in the interstitium (23). These observations suggest that locally produced MIP-1 α may be involved in the development of cellular crescents in acute phase via CCR1 and CCR5 and that MCP-1 may be involved mainly in the development of interstitial lesions in the chronic phase when fibrocellular/fibrous crescents are present possibly through M ϕ recruitment and activation.

Chemokines and Th2-type immune responses

Little is known about chemokines/chemokine receptors toward Th2 immune responses in kidney diseases (40). Locally produced eotaxin, the cognate ligand for CCR3, may contribute to renal eosinophil infiltration in the interstitium and that the elevated urinary levels of eotaxin fell dramatically during the glucocorticoid-induced convalescence, suggesting that they may reflect disease activities (41). Further investigations would be informative for our understanding of host immune responses and renal diseases based on Th1/Th2 immune responses.

Interstitial renal damage and chemokines

In addition to glomerular diseases, chemokines/chemokine receptor systems may be involved in interstitial renal diseases. Recently, fractalkine expressed in the interstitium was reported to be involved leukocyte influx including CD16 positive cells (25). Although, the intervention of fractalkine receptor, CX3CR1 showed the prevention of glomerular damage with the decrease in leukocyte infiltration (42), the blockade of fractalkine/its receptor may be beneficial to the prevention of interstitial damage as well as glomerular diseases. In addition, MCP-1, as anticipated, was involved in the interstitial nephritis (43). MCP-1 and other C-C chemokines were

involved in the pathogenesis of allograft rejection (44). Interestingly, Met-RANTES reduced vascular and tubular damage during acute allograft rejection (45).

Anti-chemokine therapy: novel therapeutic intervention to renal diseases

Based on *in vitro* and *in vivo* studies, selective intervention of chemokines/chemokine receptor systems and the adequate timing of anti-chemokine therapy may have the potential as the particular therapeutic strategies to combat with renal diseases culminating in renal sclerosis/fibrosis (46).

Neutralizing antibodies against chemokines

The pathophysiological role of IL-8 was explored in animal model of acute immune complex-mediated glomerulonephritis by administering a neutralizing antibody against IL-8 (9). Anti-IL-8 treatment decreased neutrophil number in glomeruli by 40 % and dramatically prevented the fusion of epithelial cell foot process. Furthermore, anti-IL-8 treatment completely reversed the urinary levels of protein and albumin to the normal levels. In addition, the specific inhibition of MCAF/MCP-1 may prevent long-term renal dysfunction in concomitant reduction of glomerulosclerosis and interstitial fibrosis in an animal model of crescentic glomerulonephritis (10). Administration of a small dose of nephrotoxic serum induced severe proliferative and necrotizing glomerulonephritis, with crescentic formation in the early phase and glomerulosclerosis and interstitial fibrosis in the later phase in Wistar-Kyoto rats. Anti-MCP-1 antibodies decreased the number of M ϕ in glomeruli, proteinuria and crescentic formation. Furthermore, this treatment remarkably reduced glomerulosclerosis and interstitial fibrosis and improved renal function on day 56. These results may suggest that 1) chemokines are essentially involved in the recruitment and activation of leukocytes in the diseased kidneys, 2) IL-8 and MCP-1 may be closely related to the function of

epithelial foot processes and the excreted amounts of protein, 3) MCP-1 may play an important role in the impairment of renal functions and renal sclerosis/fibrosis.

Approaches via chemokine /chemokine receptor systems

Accumulating data suggest that the blockade of select chemokines and/or their cognate receptors provide the key to the improvement of renal diseases. Antagonists against RANTES receptor using Met-RANTES (47) or APO-RANTES (48) decrease the cell infiltration in the diseased kidneys. In addition, a natural viral chemokine receptor antagonist of viral origin, vMIP-II reduce proteinuria as well as cell infiltration (49). Considering the importance of therapeutic approaches via chemokine/chemokine receptor systems in HIV infection, the development of these antagonists would be of use for the application to the renal diseases.

p38 mitogen-activated kinases (MAPK) and chemokines

Mitogen-activated protein kinase (MAPK) signal transduction pathway is thought to be involved in proliferation and apoptosis in various types of inflammatory diseases (50). The activation of MAPK isoform p38, detected also in mesangial cells is closely related to apoptosis, stress responses and inflammation (50-51). Moreover, the phosphorylation of p38 MAPK may contribute to the activation of nuclear factor (NF) κ B and activating protein (AP) 1, which may be essentially involved in inflammatory processes. FR167653 dramatically decreased the phosphorylation of p38 MAPK in cultured rat mesangial cells stimulated by interleukin-1 β (our unpublished data). The administration of FR167653 reduced glomerular damage, including crescentic formation and proteinuria (52). In addition, FR167653 markedly decreased renal expression of MIP-1 α and MCP-1. This study may provide evidence that p38 MAPK is a novel target for the therapy of glomerulonephritis.

Other approaches to chemokine /chemokine receptor systems

Agents that have impacts on cAMP (53) or NFκB such as antioxidants, glucocorticoids and aspirin can modulate chemokine expression, leading to improve renal pathology (54-55). Furthermore, already available agents such as prostaglandin E1 (56) and AT1 receptor antagonist (57) and hydroxymethylglutaryl CoA reductase inhibitor (58) inhibit chemokine expression and cell infiltration. Alternatively, the nonselective cyclooxygenase inhibitor upregulates chemokine expression (59). The development of humanized monoclonal antibodies, particular antagonists against chemokines/chemokine receptors or chemokine-specific signal transduction that would block intrarenal chemokines could well provide significant beneficial effects in renal diseases.

Concluding remarks and future directions

Based on the essential involvement of chemokine/chemokine receptor systems in the pathogenesis of phase-specific renal disorders, the intervention of chemokine/chemokine receptor systems may be therapeutically of importance to human renal diseases despite their redundancy. Numbers of chemokine receptor antagonists as the therapeutic tool are under development. Therefore, the selective blockade of chemokines/chemokine receptor systems may have the potential to become the particular therapeutic strategies in the specific phases of renal diseases in the near future.

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Figure legends

Figure 1

MCP-1: the common regulatory molecule of chronic inflammation resulting in renal sclerosis/fibrosis

Table 1

“Chemokine cascade”, in which chemokines may explain particular clinical symptoms and pathological findings of renal diseases.

Table 1

	Clinical symptoms	Pathological findings
IL-8	Acute onset or exacerbation Hematuria	Endocapillary proliferation Leukocyte infiltration
MIP-1α	Rapid progression Hematuria	Crescents Leukocyte infiltration
MCP-1/ MCAF	Acute onset or exacerbation Proteinuria, progression	Crescents, leukocyte infiltration Tubulointerstitial lesions

Figure 1

