CHAPTER 2

Pathological Significance of Renal Expression of Proinflammatory Molecules

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Abstract

Recent studies of cytokines, chemokines, adhesion molecules and growth factors have enhanced our understanding of molecular mechanisms of leukocyte trafficking and their activation in the inflammatory phase of various renal diseases. Interactions between infiltrated inflammatory cells and resident renal cells are actively involved in the pathogenesis of phase-specific renal disorders. Furthermore, a number of proinflammatory and fibrogenic cytokines, chemokines and growth factors exert their biological activities through their receptors expressed on resident renal cells, to induce inflammatory responses that eventually lead to the development of fibrosis in various renal diseases. Thus, measuring the levels of certain proinflammatory molecules might provide useful information about the inflammatory state of the diseased kidney and could have clinical importance and significance. The selective intervention of some of these molecules might have the therapeutic potential to modulate renal inflammatory responses, and thereby could alter disease progression. Despite the apparent redundancy, accumulating evidence supports this possibility. In this chapter, we will briefly summarize the specific roles of certain proinflammatory molecules in the pathogenesis of various human and experimental renal diseases.

Introduction

The interactions of activated infiltrated cells and resident renal cells are actively involved in the pathogenesis of renal inflammation. The trafficking of leukocytes from peripheral blood into the kidneys is an important inflammatory event that is encountered in the early phases of most renal diseases.[1] Proinflammatory molecules, through their interactions with receptors expressed on leukocytes and resident renal cells, can induce a number of cytokines, chemokines, adhesion molecules and growth factors, both by autocrine and/or paracrine loops, during acute and chronic phases of various renal diseases.[2] Some of these secreted molecules are not only involved in the inflammatory phase of the disease, but also contribute to the development of subsequent renal fibrosis.

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Participants in Renal Inflammation

Inflammatory Infiltrates

The main inflammatory cells actively involved in the early phase of various renal diseases are neutrophils, macrophages, and lymphocytes. One of the mechanisms of neutrophil and macrophage infiltration into diseased kidneys is via activation of adhesion molecules to induce the release of lysosomal enzymes and generation of superoxide anions to initiate inflammatory events and subsequent tissue damage.[3] In contrast, macrophages also have a scavenging role in the clearance of nonself and/or altered-self materials, including glycated proteins and oxidized lipoproteins.[4] Macrophages exert dual effects in renal injury, i.e., damaging and protective effects. Therefore, infiltrated and activated macrophages play a crucial role in the pathogenesis of both inflammatory and fibrotic phases of the disease process. Certain chemokines, including monocyte chemoattractant protein (MCP-1), are involved in the recruitment of macrophages in diseased kidneys. In addition, macrophage colony-stimulating factor (m-CSF) is actively involved in monocyte and macrophage survival, proliferation, and chemotaxis.[5] Overexpression of m-CSF by tubular epithelial cells is closely associated with the interstitial accumulation and proliferation of macrophages, as demonstrated in experimental anti-glomerular basement membrane (GBM) nephritis and unilateral ureteral obstruction models.[6] A correlation between overexpression of m-CSF and accumulation of macrophages has also been demonstrated in various human and experimental diseases, including glomerulonephritis.[7,8] Similarly, increased expression of macrophage migration inhibitory factor (MIF) has been shown to be involved in human and experimental models of tubulointerstitial injury, possibly by facilitating the interstitial accumulation of macrophages and lymphocytes.[9,10] Infiltration of inflammatory cells, including lymphocytes, into diseased kidneys, exerts inflammatory responses by secreting certain proinflammatory cytokines and chemokines.[11] In kidneys of autoimmune MRL-*Fas*^{lpr} mice, a dynamic interaction of macrophages and lymphocytes has been shown to be the result of nephritogenic cytokines.[11]

Resident Renal Cells

In addition to inflammatory infiltrates, there are at least two groups of resident renal cells that actively participate in the inflammatory phase of various renal diseases; these are glomerular cells (mesangial cells, endothelial cells and epithelial cells), and tubulointerstitial cells (tubular epithelial cells, interstitial cells and peritubular capillary endothelial cells). These intrarenal cells are capable of proliferation, differentiation, and synthesis of various proinflammatory cytokines, chemokines, and growth factors in response to various stimuli, which in turn augment inflammatory responses. In addition, activated and transformed resident renal cells regulate extracellular matrix (ECM) remodeling by inducing the synthesis of fibrogenic molecules. Recently, it has been suggested that injury to the renal microvasculature contributes to the progression of a number of renal diseases. For instance, Ohashi et al demonstrated that early angiogenic responses, such as peritubular capillary regression, were followed by progressive deletion of endothelial cells by apoptosis in experimental obstructive nephropathy.[12]

Using a bone marrow transplantation model, Imasawa et al[13] recently reported the potential of bone marrow-derived cells to differentiate into glomerular mesangial cells. In an experimental model of anti-Thy1 nephritis, Ito et al[14] reported an increased number of bone marrow-derived Thy1(+) cells constituting about 7 to 8% of glomerular cells. These reports are interesting, and suggestive of the presence of bone marrow-derived mesangial cells in nephritis. Further studies are needed to determine the pathogenic role of these marrow-derived mesangial cells in various renal diseases.

Major Mediators Involved in Renal Inflammation

Chemokines

The chemokine family is divided into four groups depending on conserved cysteine residues that form disulfide bonds in the chemokine tertiary structure.[15,16] The CXC subfamily contains a single nonconserved amino acid separating the first two cysteine residues. The CC and CXXXC subfamilies have either none or exactly three nonconserved amino acids between the cysteines, respectively. The C chemokine subfamily, is unique in that only two of the four cysteine residues (i.e., the first and third) are present. More than 44 chemokines and 18 chemokine receptors have been identified. Recent studies have documented that chemokines, through the binding of their cognate receptors, play an important role in the pathogenesis of various renal diseases by regulating leukocyte trafficking at inflammatory sites.

Interferon-inducible protein (IP)-10/CXCL10 is a mitogenic factor for mesangial cells and possibly acts via the cognate receptor, CXCR3.[17] The constitutive glomerular expression of CCR7 and its ligand, secondary lymphoid tissue chemokine (SLC/CCL21), by adjacent renal cells suggests the involvement of this specific chemokine/chemokine receptor interaction in regulating glomerular homeostasis and regeneration.[18] In addition, the regulation of interleukin (IL)-8/CXCL8 and MCP-1 (also known as monocyte chemotactic and activating factor [MCAF])/CCL2 are closely related to the urinary excretion of protein in experimental models[19,20] and human nephrotic syndrome;[21] the glomerular protein leakage is possibly due to increased permeability of the glomerular capillaries. A recent report described the expression of CCR4, CCR8, CCR9, CCR10, CXCR1, CXCR3, CXCR4, and CXCR5 in cultured podocytes; the expression of CXCR1, CXCR3, and CXCR5 was also detected in podocytes of human kidney sections.[22] 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.[22]

Recent studies have documented a direct link between locally and systemically produced chemokines and the infiltration and activation of leukocytes in the kidneys. The infiltration of Th1 T cells in the interstitium in human renal diseases is partly regulated upon activation of normal T cells that express and secrete (RANTES)/CCL5, through its interaction with its cognate receptors, CCR1 and CCR5.[23] RANTES was also upregulated in the kidneys of a murine lupus nephritis model, MRL-*Fas*^{lpr} mice, prior to renal injury, and increased with progression of the injury.[24] When tubular epithelial cells genetically modified to secrete RANTES were infused under the renal capsule, features of interstitial nephritis developed in MRL-*Fas*^{lpr} mice.[24] RANTES fostered the accumulation of $CD4^+$ cells. In addition, circulating components, including $CD4^+$ cells, were required to incite renal injury in MRL-*Fas*^{lpr} mice via both cellular and humoral immune responses.[11] Therefore, the manipulation of lymphocyte trafficking by blocking the bioactivities of certain chemokines could have a potential therapeutic effect in renal diseases.

Cytokines

The renal inflammatory response is a multistep and multifactorial process, mainly orchestrated by the cross-talk of cytokines. Among the cytokines, IL-1 and tumor necrosis factor (TNF)-α are the most extensively studied molecules, and have been found to play an important role in the inflammatory phase of various renal diseases. These two cytokines are capable of, (1) regulating proliferation of resident renal cells (mesangial cells, endothelial cells), (2) augmenting production of inflammatory mediators (cytokines, chemokines, prostaglandins, free radical oxygen and superoxide anions), and (3) facilitating recruitment of inflammatory

cells into the injured kidneys via the expression of chemokines.[25] In addition, the upregulation of these proinflammatory cytokines is closely related to the degree of apoptosis during inflammation.

The two different subsets of $CD4^+$ lymphocytes (Th1 and Th2 subsets) produce different groups of cytokines.[26] Th1 cytokines include IL-2, IL-12, IL-18 and interferon (IFN)-γ, while IL-4, IL-5, IL-10, and IL-13 represent Th2 cytokines. Th1 cytokines are capable of activating monocytes, lymphocytes and resident renal cells, which augment immunoinflammatory responses via cellular immunity. In contrast, Th2 cytokines directly activate B cells to switch on humoral immunity and induce human endothelial cell adhesiveness for T cells via generation of adhesion molecules.[27] In particular, Th1-predominant nephritogenic immune responses are associated with severe proliferative and crescentic glomerulonephritis. In contrast, Th2 predominance is presumed to contribute to minimal change nephrotic syndrome and membranous nephropathy. Interestingly, lupus nephritis and IgA nephropathy have aspects of both Th1 and Th2 predominance in a phase-specific manner.

The transition from neutrophil infiltration to mononuclear cell infiltration is an important feature of inflammation. Recently, a role for IL-6 and its soluble receptor has been suggested in the transition from neutrophil to monocyte recruitment during inflammation.[28] During acute inflammation, IL-6 might help in the resolution of the neutrophilic infiltrates. In contrast, during chronic inflammation, IL-6 might contribute to increased infiltration of mononuclear cells. These findings are suggestive of a new role for IL-6 in the inflammatory process.

Leukocyte Trafficking During Renal Inflammation

Cell-cell interaction has an enormous impact on renal inflammation. Leukocyte trafficking at the inflammatory site comprises two major events: first, the activation and firm adhesion of leukocytes on endothelial surfaces and, secondly, the diapedesis and transmigration through the endothelial cells into the inflammatory sites of the renal tissue (Fig. 1). Leukocyte adhesion molecules are responsible for these steps and/or events. Major molecules involved in leukocyte trafficking include the selectin family of molecules and their glycoprotein ligands, integrins and immunoglobulin-like leukocyte adhesion molecules.[29] Selectin-mediated rolling and integrin-mediated firm adhesion is involved in the binding of leukocytes to the endothelium. In addition, recent studies have shown that chemokines, through their cognate receptors, play an important role in these steps. Chemokines expressed on the surface of endothelial cells interact with their cognate receptors on specific leukocytes, a process that triggers activation of adhesion molecules and result in firm adhesion of leukocytes to the surface of endothelial cells. Once leukocytes migrate into the interstitium, chemokines and proinflammatory cytokines produced by both resident cells and infiltrated inflammatory cells exert a wide range of biological activities at the inflammatory sites. Selective expression of chemokine receptors and adhesion molecules on specific cell populations determines the specific types of infiltrating cells in inflamed kidneys. Thus, the interaction of infiltrating cells and endothelial cells orchestrated by chemokines and adhesion molecules regulates sequential migratory patterns of specific types of leukocytes in a multistep manner.

Chemokine Systems in the Kidney from Acute Injury to Renal Scarring: The Chemokine Cascade

In renal inflammation, the type of leukocytes that infiltrate into the kidneys depends on the type of insult and phase of the disease; neutrophils are the predominant cells in acute inflammation, while macrophages, lymphocytes and plasma cells comprise the dominant cell populations in chronic inflammation. Fibrogenic factors released by some of these chronic inflammatory cells are involved in subsequent renal fibrogenesis (Fig. 2). Given the presence of a biologically active chemokine amplification cascade in the kidney,[30] a switch from acute

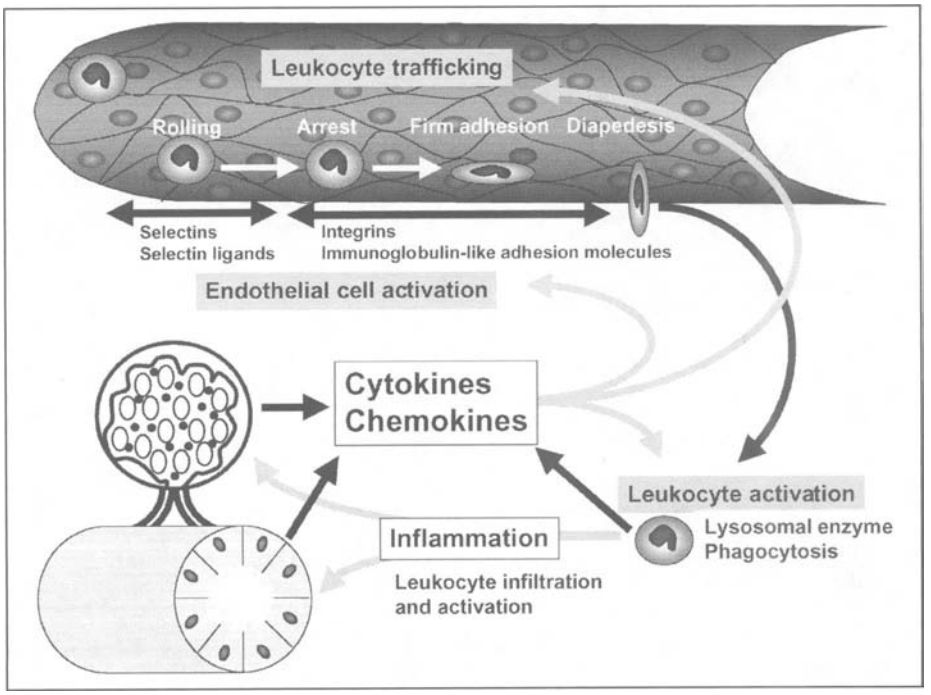

Figure 1. Proinflammatory molecules and kidney.

inflammation to chronic inflammation in various renal diseases may depend on the expression and bioactivity of specific chemokines. In human renal diseases, the presence of IL-8 in diseased kidneys reflects an acute disease stage, associated with neutrophil infiltration and hematuria[2] (Fig. 2). In contrast, the presence of elevated MCP-1 expression is suggestive of a chronic stage of disease, especially in tubulointerstitial lesions through the recruitment and activation of macrophages. Moreover, the measurement of urinary MCP-1 levels is a useful clinical tool for monitoring the disease activity of inflammatory renal disorders.[2] In addition, MCP-1 has been shown to mediate collagen deposition in an experimental model of nephritis, through its interaction with TGF-β[31] It is therefore likely that increased expression of MCP-1 in the chronic inflammatory stage of a particular disease may contribute to subsequent renal fibrosis, by regulating the synthesis of collagens. In support of this notion, the administration of anti-MCP-1 antibodies prevented the infiltration of leukocytes and development of renal fibrosis in a rat model of crescentic glomerulonephritis.[20] Thus, the positive amplification loop from CXC chemokines to CC chemokines (the "chemokine cascade") plays a crucial role, not only in early inflammatory events, but also in late fibrotic events of various renal diseases (Fig. 3).

The MCP-1/CCL2-TGF-β Axis: A Common Regulatory Pathway of Chronic Renal Inflammation Resulting in Renal Scarring

MCP-1 does not only regulate inflammatory events, but is also involved in progressive glomerular and interstitial damage resulting in renal scarring in various renal diseases. Recent studies suggest that MCP-1 plays an important role in the pathogenesis of metabolic renal disorders, such as diabetic nephropathy and noninflammatory nephrotic syndrome. Locally produced MCP-1, via recruiting and activating macrophages, contributes to the development

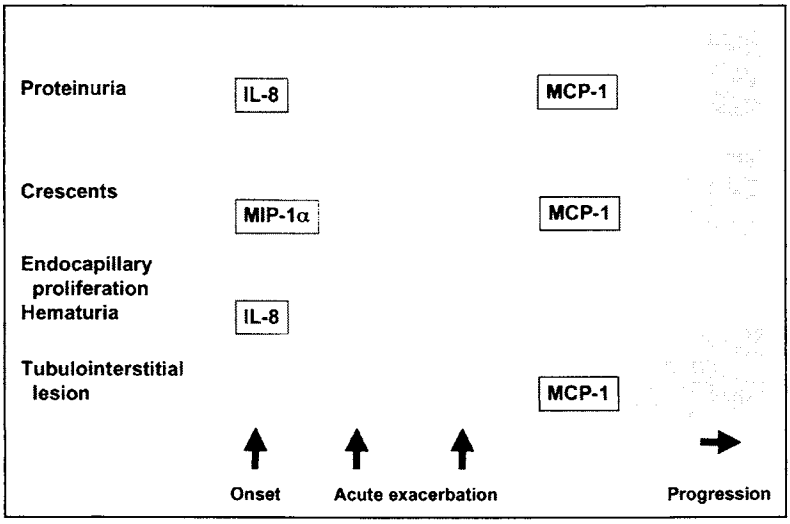

Figure 2. Relevance of the "chemokine cascade" in explaining the particular clinical symptoms and pathological changes in human renal diseases (modified from ref. 99).

of interstitial lesions in human diabetic nephropathy.[32] In diabetic nephropathy, urinary MCP-1 levels were significantly elevated in patients with advanced tubulointerstitial lesions. Moreover, urinary levels of MCP-1 showed a positive correlation with the increased infiltration of CD68-positive macrophages in the renal interstitium. Furthermore, studies using immunohistochemistry and in situ hybridization techniques showed increased number of MCP-1-expressing cells in the interstitium of kidneys affected by diabetes. These observations suggest that locally produced MCP-1 is involved in the development of tubulointerstitial lesions in diabetic nephropathy, possibly by regulating recruitment and activation of macrophages. Overexpression of MCP-1 and certain fibrogenic molecules, including platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-β), has been shown to be associated with interstitial accumulation of mononuclear cells and myofibroblastic transformation of resident cells in patients with membranous nephropathy.[33] Recently, an intrinsic regulatory loop, in which MCP-1 stimulates TGF-β production by resident glomerular cells, has been suggested in the absence of infiltrating immune competent cells.[34] Increased renal expression of TGF-β both at the mRNA and protein levels, was detected in isolated rat kidneys that were perfused with a polyclonal anti-thymocyte-1 antiserum and rat serum; this effect was attenuated by coperfusion with a neutralizing anti-MCP-1 antibody but was partly mimicked by perfusion with recombinant MCP-1 protein.[34] These results suggest an additional role for MCP-1 in fibrotic renal diseases, possibly by interacting with TGF-β.

Molecular Basis of Inflammation in Various Renal Diseases

Ischemia-Reperfusion Injury

Renal ischemia-reperfusion is usually encountered in renal transplantation, in patients with shock and circulatory collapse, or in renal artery stenosis. Ischemia-reperfusion injury in the kidney is pathologically characterized by tubular epithelial cell necrosis and/or apoptosis with marked inflammatory cell infiltration. Resident renal cell- and infiltrated inflammatory cell-secreted cytokines and chemokines, such as TNF-α, IL-1, IL-8, MCP-1 and RANTES play important roles in the induction and propagation of renal injury. Recently, a more specific

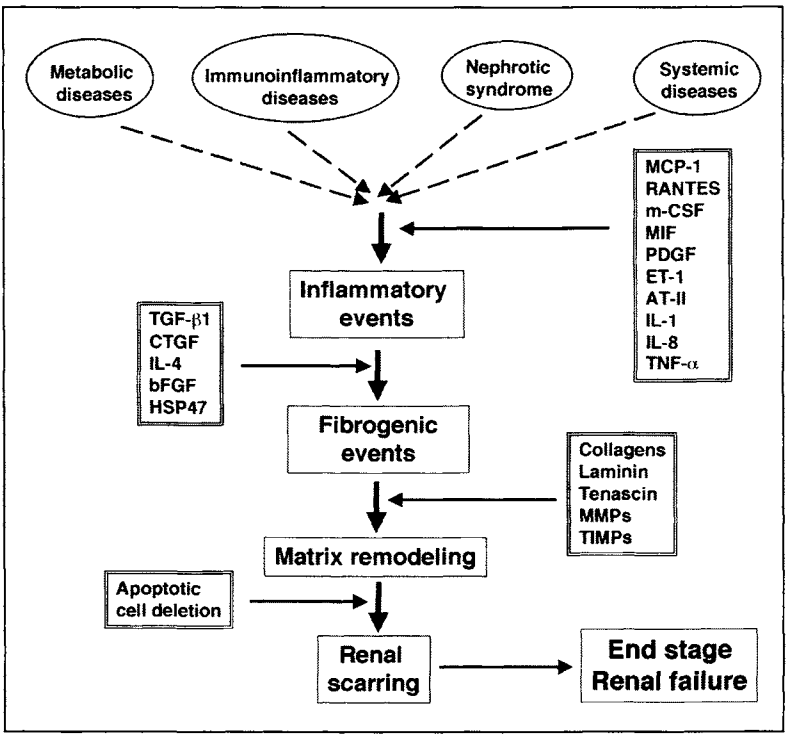

Figure 3. Schematic diagram of molecules involved in the multistep and multifactorial renal diseases that eventually lead to end stage renal failure. Not all molecules involved are included in this figure, in order to keep the diagram simple. [IL-1: Interleukin-1, IL-4: Interleukin-4, IL-8: Interleukin-8, TNF-α: Tumor necrosis factor-α, MCP-1: Monocyte chemoattractant protein, RANTES: Regulated upon activation, normal T cell expressed and secreted, m-CSF: Macrophage colony-stimulating factor, MIF: Macrophage migration inhibitory factor, PDGF: Platelet-derived growth factor, ET-1: Endothelin 1, ATII: Angiotensin II, TGF-β1: Transforming growth factor beta1, CTGF: Connective tissue growth factor, bFGF: Basic fibroblast growth factor, HSP47: Heat shock protein 47, MMP: Matrix metalloproteinase, TIMP: Tissue inhibitor of metalloproteinase].

role for chemokines in distinct steps of leukocyte extravasation has been demonstrated. Growth-related oncogene (GRO)/CXCL1 and fractalkine/CX3CL1 are thought to mediate the initial firm adhesion, whereas the chemokine MCP-1 is required for the later steps of leukocyte spreading and diapedesis.[35,36] Thus, these studies emphasize the significance of the interaction of endothelial cells with leukocytes in ischemia-reperfusion injury.

Various experimental models of ischemia-reperfusion injury have been reported (Table 1). Using a renal ischemia-reperfusion model, it was recently demonstrated that p38 mitogen-activated protein kinase (MAPK) plays a key role in cell infiltration and tubular necrosis by regulating the expression of IL-1, TNF-α, MCP-1 and RANTES.[37] In addition, glucocorticoids reduced ischemia-reperfusion injury in the kidneys by inhibiting the expression of JE/MCP-1.[38] Osteopontin not only promoted the accumulation of macrophages, but also exerted renoprotective effects in renal ischemia-reperfusion injury. Osteopontin inhibited the induction of inducible nitric oxide synthase and suppressed the synthesis of nitric oxide, resulting reduced peroxide levels in the cells, thus promoting the survival of cells exposed to hypoxia.[39] It has been demonstrated that the inhibition of neutrophil infiltration into ischemic kidneys during reperfusion by neutralizing the effects of chemokines (GRO and MIP-2)

Table 1. Chemokines/chemokine receptors as molecular targets in therapy

Targets	Models	Tools	Effects	Refs.
Chemokines				
1) MCP-1				
	Ischemia-reperfusion	7ND	Prevention	50
	Crescentic glomerulonephritis	Neutralizing antibodies	Prevention	20, 54-56
		Gene targeting mice	Prevention	58
		Cyclooxygenase inhibitor	Worse	69
	Immune complex glomerulonephritis	Angiotensin converting enzyme inhibitor	Prevention	73
	Anti-Thy-1 nephritis	Neutralizing antibodies	Prevention	66
		Angiotensin receptor 1 antagonist	Prevention	94
		Prostaglandin E1	Prevention	93
		Pentoxifylline	Prevention	68
		Cyclooxygenase inhibitor	Worse	69
	Lupus nephritis	Gene targeting mice	Prevention	75
		Bindarit	Prevention	79
	Unilateral ureteral obstruction	Angiotensin receptor 1 antagonist	Prevention	86
		Angiotensin converting enzyme inhibitor		
		Y-27632	Prevention	87
	Diabetic nephropathy	Angiotensin converting enzyme inhibitor	Prevention	81
2) MIP-1α				
	Crescentic glomerulonephritis	Neutralizing antibodies	Prevention	57
3) RANTES				
	Transplantation	Met-RANTES	Prevention	43, 48
	Anti-Thy-1 nephritis	AOP-RANTES	Prevention	67
4) IL-8				
	Immune complex glomerulonephritis	Neutralizing antibodies	Prevention	19
5) MIP-2				
	Ischemia-reperfusion	Neutralizing antibodies	Prevention	40
	Crescentic glomerulonephritis	Neutralizing antibodies	Prevention	60
6) GRO				
	Ischemia-reperfusion	Neutralizing antibodies	Prevention	40
7) CINC				
	Crescentic glomerulonephritis	Neutralizing antibodies	Prevention	57
Chemokine receptor				
1) CCR1				
	Transplantation	BX471	Prevention	49
		FTY720	Prevention	50
	Crescentic glomerulonephritis	Gene targeting mice	Worse	59
	Unilateral ureteral obstruction	BX471	Prevention	88

resulted in attenuation of the renal injuries.[40] Importantly, disruption of MCP-1/CCR2 signaling in CCR2 null mice could effectively attenuate renal ischemia reperfusion injury. Ongoing studies, using propagermanium, a selective inhibitor of MCP-1/CCR2 signaling, have shown relatively less inflammatory cell infiltration, and tubular necrosis in kidneys in the ischemia-reperfusion model (unpublished data). Using a gene therapy approach, expression of an amino-terminal deletion mutant of MCP-1 to inhibit MCP-1/CCR2 signaling resulted in decreased acute tubular necrosis and less infiltration of macrophages.[41]

Transplant Nephropathy

Renal transplantation is one of the most important clinical situations with exposure to ischemia-reperfusion injury. Recently, early nonspecific ischemic injury has been related to subsequent immunologic injuries in renal transplant rejection.[42] Rat models of transplantation have facilitated a functional study of the role of cytokines/chemokines in acute and chronic renal rejection.[43,44] In a rat model of acute renal transplant rejection, the expression of RANTES was upregulated, at the mRNA level, by as early as 6 hours, and this upregulation was again noted on day 3 to day 6.[45] Increased expression of RANTES in the early hours of engraftment may be related to ischemic injury, and could, in part, induce subsequent immunologic responses. In addition, macrophages and their secreted products play important roles in the eventual immune-mediated rejection process. Moreover, increased production of certain cytokines (IL-8, -10, -15), chemokines (RANTES, MIP-1, MCP-1) and hepatocyte growth factor (HGF) by infiltrating leukocytes, tubular epithelial cells, and endothelium may have a determinant role in renal transplant rejection.[44,46,47]

Recent studies have documented beneficial effects of blocking the bioactivities of certain chemokines in renal transplant rejection. For example, Met-RANTES, a chemokine receptor antagonist, not only reduced vascular and tubular damage in acute renal transplant rejection,[43] but also protected renal allografts from long-term deterioration.[48] In addition, a CCR1-specific nonpeptide antagonist, BX471, exhibited efficacy in a rabbit allograft rejection model.[49] FTY720 is a novel immunomodulator that acts by chemokine-dependent lymphocyte homing into secondary lymphoid organs leading to profound lymphocyte depletion in the blood.[50] Oral administration of FTY720 to cynomolgus monkeys with renal allotransplantation has been shown to prevent acute allograft rejection, with resultant rejection-free allograft survival.[50] The expression of MCP-1 in acute renal transplant rejection correlated with the number of infiltrating macrophages,[51] and elevated urinary MCP-1 excretion during rejection episodes, which diminished after successful treatment. However, the inhibitory impacts of MCP-1/CCR2 on allograft rejection need further comprehensive studies.

Crescentic Glomerulonephritis

Rapidly progressive crescentic glomerulonephritis is usually associated with clinical features of anemia and morphological features of tubulointerstitial nephritis that eventually lead to renal insufficiency. To monitor clinical symptoms, and to understand the disease activity of crescentic glomerulonephritis, it is essential to determine specific molecule(s) involved in the disease process. Increased urinary levels of MIP-1α have been selectively detected in patients with crescentic glomerulonephritis; MIP-1α was mostly undetectable in urine samples collected from healthy control subjects and in patients with renal diseases lacking crescent formation.[52] Urinary MIP-1α 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] Moreover, elevated urinary levels of MIP-1α and the number of CCR5-positive cells dramatically decreased during glucocorticoid therapy-induced convalescence. MIP-1α-positive cells were mainly detected in crescentic lesions. CCR1, and CCR5-positive cells, preferentially expressed on Th1 T cells,[53] were detected in diseased glomeruli and interstitium.[23] It is likely that MIP-1α plays a significant role in crescentic glomerulonephritis, by recruiting and activating macrophages and T cells. Measurement of urinary levels of MIP-1α appears to be clinically useful as its level correlates with disease activity of human crescentic glomerulonephritis.

Recent studies have documented the beneficial effects of neutralizing antibodies and specific chemokine/chemokine receptor antagonists in crescentic glomerulonephritis. Anti-MCP-1 or anti- MIP-1α antibodies or MCP-1 deficiency resulted in less glomerular accumulation of macrophages, reduced crescent formation, decreased interstitial damage, and most importantly, less proteinuria.[20,54-58] In contrast, aggravated renal dysfunction and increased proteinuria have been detected in CCR1-disrupted mice, compared to wild-type mice.[59]

The beneficial effects of blocking the bioactivities of CXC chemokines have been reported in crescentic glomerulonephritis. Neutralizing antibodies against cytokine-induced neutrophil chemoattractant (CINC) ameliorated the cell infiltration, including neutrophils, and reduced urinary protein excretion.[57] Similarly, a single dose of anti-MIP-2 antibody resulted in reduced neutrophil influx (40% at 4 hours) and periodic acid-Schiff-containing fibrin deposition (54% at 24 hours). These results suggest the crucial role of MIP-2 in recruiting neutrophils during glomerular inflammation.[60] However, the combination of anti-CINC and anti-MIP-1α antibodies did not show any additional beneficial effects.[57]

The viral macrophage inflammatory protein-II (vMIP-II) encoded by Kaposi's sarcoma-associated herpes virus is unique among all known chemokines in that vMIP-II shows a broad-spectrum interaction with both CC and CXC chemokine receptors, including CCR5 and CXCR4. vMIP-II patently inhibited MCP-1-, MIP-1α-, RANTES-, and fractalkine-induced chemotaxis of activated leukocytes isolated from nephritic glomeruli; it also reduced glomerular infiltration of leukocytes, and markedly attenuated proteinuria in the rat model of glomerulonephritis.[61]

Recently, modulation of the p38 MAPK pathway by using specific inhibitors was shown to have beneficial effects on the progression of crescentic glomerulonephritis. The MAPK signal transduction pathway is thought to be involved in the regulation of cell proliferation and apoptotic cell deletion in inflammatory diseases.[62] The activation of MAPK isoform p38, detected in mesangial cells, is closely associated with apoptosis, stress responses and acute and/or chronic inflammation.[62] Moreover, phosphorylation of p38 MAPK contributes to the activation of nuclear factor (NF)-κB and activating protein (AP)-1, which are essentially involved in inflammatory processes. FR167653 is a specific p38 MAPK pathway inhibitor. FR167653 markedly decreased IL-1β-induced phosphorylation of p38 MAPK in cultured rat mesangial cells.[63] In vivo administration of FR167653 reduced glomerular damage, including crescentic formation, proteinuria, and glomerulosclerosis in an experimental model of crescentic glomerulonephritis.[63,64] In addition, FR167653 markedly decreased renal expression of certain cytokines and chemokines. Hence, p38 MAPK might be a potential target for developing future therapeutic strategies against crescentic glomerulonephritis.

Acute/Experimental Nephritis

The acute phase of glomerulonephritis is morphologically characterized by infiltration of inflammatory cells into glomeruli and proliferation of mesangial cells. Renal parenchymal cells express chemokine receptors as well as their ligands in such conditions.[2] In vitro studies have demonstrated that proinflammatory stimuli, such as IL-1β, TNF-α, and IFN-γ, immune complexes, and certain growth factors, including PDGF and basic fibroblast growth factor

(bFGF), are able to induce IL-8, MCP-1, IP-10, MIP-1α and RANTES from resident renal cells.[2] In turn, these stimuli induce the expression of CCR1 and CXCR3 on resident renal cells, especially mesangial cells.[18,65] These observations are suggestive of a positive feedback loop through cytokines/chemokines, which results in renal inflammation. Indeed, the CXC chemokines, MIP-2 and keratinocyte-derived cytokine (KC) are able to induce MCP-1 and RANTES expression in mesangial cells.[30] Autoinduction of MIP-2 and KC mRNA was also detected. This chemokine amplification mechanism is thought to contribute to the maintenance and chronic course of glomerular inflammation.

Anti-Thy1 antibody-induced nephritis is a well-studied rat model of mesangial proliferative glomerulonephritis, characterized by complement-dependent mesangiolysis, inflammatory reactions, and subsequent glomerulosclerosis. MCP-1 mediated infiltration of monocytes is suggested to play an important role in the progression of glomerular lesions in Thy-1 nephritis, and blocking the bioactivity of MCP-1 has been shown to reduce renal injury in this model of nephritis.[66] Similarly, a CCR5 chemokine receptor antagonist, AOP-RANTES, ameliorated monocyte/macrophage infiltration and improved glomerular pathology in an experimental model of nephritis.[67] It was concluded that the use of chemokine receptor antagonists might offer a new therapeutic option in treating inflammatory renal diseases. In addition, treatment with a clinically available nonselective inhibitor of cyclic 3',5'-nucleotide phosphodiesterase, pentoxifylline, resulted in reduced accumulation and proliferation of glomerular macrophages, suppression of activation and proliferation of mesangial cells, and proteinuria; all the above-mentioned changes were associated with decreased glomerular expression of MCP-1 and intercellular adhesion molecule-1 (ICAM-1) in the experimental model of nephritis at 2 hours and on day 1 of the study.[68] In contrast, the effect of cyclooxygenase (COX) inhibitors was evaluated in an anti-thymocyte antibody model and an anti-GBM model of glomerulonephritis.[69] These studies have suggested that COX products might serve as endogenous repressors of MCP-1 formation in the studied models of experimental nephritis. COX-1 and COX-2 products may regulate differently as selective COX-2 inhibitors exert less influence on chemokine expression.

It has been well documented that angiotensin II regulates the synthesis of certain proinflammatory cytokines and chemokines in the kidney. Angiotensin II plays an active role in inflammatory responses in renal diseases in concert with chemokine/cytokine expression, possibly by activating NF-κB.[70] Rats with experimental immune complex nephritis, treated with the angiotensin converting enzyme (ACE) inhibitor quinapril,[71] exhibited reduced expression of MCP-1.

NF-κB stays inactive in the cytoplasm, however upon activation by a wide range of factors, it translocates into the nucleus and regulates the expression of genes encoding cytokines, growth factors, oncogenes, transcription factors, and receptors involved in various pathological processes, including immunoinflammatory disorders. Activation of NF-κB leads to transcription of such genes as IL-1 and TNF-α, ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1), MCP-1, m-CSF, inducible nitric oxide synthase (iNOS) and tissue factor. All these above-mentioned molecules have been shown to play important roles in the induction and propagation of various renal diseases.[72,73]

Lupus Nephritis

MCP-1 promotes autoimmune renal disease through the recruitment of macrophages and T cells, and the recruitment process is augmented by locally produced cytokines and/or chemokines in New Zealand Black x New Zealand White (NZB/W) F1 mice[74] and MRL-*Fas*^{lpr} mice.[75] In addition, modulation of the biological activities of MCP-1 dramatically reduced the recruitment of macrophages and T cells that not only reduced pathological alterations in the kidney, lung, skin, and lymph node, but also diminished proteinuria, and prolonged survival.[75]

Mononuclear cell infiltration has been demonstrated in the kidneys of MRL-*Fas*^{lpr} mice, by weeks 10 to 12. At week 12, the expression of certain chemokines, including CCR1, CCR2, and CCR5 was upregulated in the mice kidneys, associated with morphological features of renal injuries and proteinuria. These results are in accord with the notion that chemokine-mediated leukocyte infiltration precedes proteinuria and renal damage in MRL-*Fas*^{lpr} mice.[76] From the perspective of Th1/Th2 balance, CCR4$^+$, but not CCR5$^+$ T lymphocytes in peripheral blood, which represent Th2 cells, preferentially migrate into the kidneys of patients with lupus nephritis. It is likely that the disproportionate distribution of CCR4$^+$ T lymphocytes might play an important role in the development of subsequent renal injuries that are found in patients with lupus nephritis.[77] In addition, markedly enhanced expression of the B lymphocyte chemokine (BLC/CXCL13) has been detected in the thymus and kidneys of aged (NZB/W) F1 mice developing lupus nephritis. These observations suggest that myeloid dendritic cells in the target organs in aged (NZB/W) F1 mice may play a pivotal role in disrupting immune tolerance in the thymus and in recruiting autoantibody-producing B cells in the development of murine lupus.[78]

Recent studies have documented the beneficial effects of modulating cytokines/chemokines in lupus nephritis. Mice [(NZB/W) F1] treated with Bindarit (50 mg/kg/day, p.o.), a novel molecule devoid of immunosuppressive effects, resulted in a delayed onset of proteinuria and reduced impairment of renal function, and prolonged survival.[79] Similarly, daily oral administration of FR167653 (a selective inhibitor of p38 MAPK) decreased p38 MAPK phosphorylation in the kidneys, which resulted in reduced renal accumulation of macrophages and lymphocytes and an improvement of overall renal pathology, with prolonged survival; FR167653 treatment also reduced expression of MCP-1 and IgG production in MRL-*Fas*^{lpr} mice.[80]

Diabetic Nephropathy

In addition to the metabolic and hemodynamic abnormalities, infiltration of inflammatory cells, including macrophages, into diseased kidneys is an important histological feature that is associated with the progression of diabetic nephropathy.[32] Angiotensin II-dependent up-regulation of MCP-1 has been demonstrated to play a role in the genesis of glomerular and tubulointerstitial damage.[81] The glomerular recruitment of macrophages in streptozotocin-treated diabetic rats is regulated by angiotensin-stimulated MCP-1.[81] Therefore, activation of the renin-angiotensin system is an important determinant of the macrophage population in diabetic nephropathy, possibly by regulating certain chemokines. It is well accepted that in addition to their blood-pressurelowering effects, AT1 receptor antagonists are renoprotective in patients with type 2 diabetes mellitus with microalbuminuria.[82,83] More recently, combination treatment with an angiotensin-II receptor blocker and ACE inhibitor was found to be more effective in retarding the progression of nondiabetic renal diseases, in comparison with monotherapy.[84] Similarly, Utimura et al[85] reported the renoprotective effect of mycophenolate mofetil, which could have derived from its well-known anti-inflammatory properties that include restriction of lymphocyte and macrophage proliferation and modulation of the expression of adhesion molecules. These findings are consistent with the notion that inflammatory events are central to the pathogenesis of diabetic nephropathy.

Unilateral Ureteral Obstruction Model

A unilateral ureteral obstruction model is characterized by the interstitial infiltration of inflammatory cells, including macrophages, which gradually leads to the development of tubulointerstitial fibrosis, resulting in decreased renal function. Increased interstitial expression of

IL-1, TNF-α, MCP-1, TGF-β and type I collagen has been documented in this model.[86] Recently, the beneficial effects of Y-27632, a specific Rho-associated coiled-coil forming protein kinase (ROCK) inhibitor, were studied using the unilateral ureteral obstruction model.[87] In vivo studies have shown that Y-27632 treatment resulted in less alpha smooth muscle actin-positive cells, reduced numbers and expression of macrophages, MCP-1, TGF-β and α (I) collagen, and resulted in less interstitial fibrotic changes, in the unilateral ureteral obstruction model. It is therefore likely that the Rho-ROCK system may play an important role in fibrogenesis.[87] Similarly, blocking the chemokine receptor CCR1 using the nonpeptide antagonist BX471 resulted in reduced leukocyte infiltration, and subsequent improvement of renal fibrosis in unilateral ureteral obstruction.[88] Interestingly, BX471 was shown to be effective, even when it was used in the late stages of the disease, suggesting that CCR1 blockade may be useful in reducing early cellular infiltration and may modulate subsequent renal fibrosis, which is a major cause of end-stage renal failure.[88]

Effectiveness of Anti-Chemokine/Cytokine Therapy and Its Possible Therapeutic Implications in Renal Diseases

Agents that influence cAMP[89] or NF-κB, such as antioxidants, glucocorticoids and aspirin, can modulate the expression of chemokines/cytokines and improve renal pathology.[90] Clinically, during spontaneous or glucocorticoid therapy-induced convalescence in patients with inflammatory renal diseases, including acute glomerulonephritis, IgA nephropathy, lupus nephritis and crescentic glomerulonephritis, a reduced expression level of certain chemokines (IL-8, MCP-1, MIP-1α, fractalkine) and cytokines was detected.[2,91] In a separate study, Natori et al[92] assessed the pulse methylprednisolone (MP) dose required to exert these beneficial effects and its effect on the expression of cytokines/chemokines in an experimental model of crescentic glomerulonephritis. Numbers of glomerular and interstitial macrophages and T cells, as well as crescents, were reduced significantly by 5 mg/kg of MP, but a maximal effect was obtained by 30 mg/kg of MP. Urinary protein was reduced significantly in a 30 mg/kg group but not in other groups. The expression of chemokines was significantly inhibited by 5 mg/kg of MP. These results indicate that MP reduces the number of infiltrating mononuclear cells and formation of crescents in the rat model of crescentic nephritis in a dose-dependent fashion, despite the strong inhibition of chemokine expression at a lower dose. Therefore, the optimal dose of glucocorticoid remains to be determined clinically, although the expression of chemokines/chemokine receptors might be suppressed.

Furthermore, prostaglandin E1[93] and an AT1 receptor antagonist,[94] hydroxymethylglutaryl CoA reductase inhibitor[95] and ACE inhibitor[81] have been shown to inhibit the expression of certain chemokines/cytokines and to reduce the infiltration of inflammatory cells in experimental models of renal diseases.

Concluding Remarks

In this chapter, we have briefly summarized the current concept of renal inflammation that has resulted in a better conceptual understanding of the cellular and molecular basis of certain fibrotic renal diseases.[96-98] Based on in vitro and in vivo studies, it is likely that selective intervention of cytokines/chemokines, at the appropriate phase of a certain disease, may have the therapeutic potential for site- and phase-specific intervention into the progression of inflammatory renal diseases[99] (Tables 1, 2). Moreover, the development of humanized monoclonal antibodies, particular antagonists against cytokines/chemokines, or specific signal transduction pathways that can provide selective intrarenal blockage of bioactivities of involved

Table 2. Therapeutic strategy against cytokines/chemokines in renal diseases

1. Inhibition of gene expression of cytokines/chemokines
Interferon
Cyclosporin
Steroid
FK506
Mycophenolate mofetil
Vitamin D
Aspirin
HMG-CoA reductase inhibitors
Angiotensin converting enzyme inhibitors
Angiotensin receptor antagonists
All-trans-retinoic acid
Cannabinoid receptor agonists
Bindarit
2. Neutralization of cytokines/chemokines
Neutralizing antibodies
3. Inhibition of interaction between receptors and their ligands
Analogues (7ND)
Receptor antagonists
4. Inhibition of signal transduction
Kinase inhibitors

cytokines/chemokines, should have beneficial effects on modulation of renal inflammatory responses and subsequent progression of the disease process. It is apparent that various immunoinflammatory cytokines, chemokines, and adhesion molecules mediate the cell-cell and cell-matrix interactions to initiate and propagate various fibrotic renal diseases. Indeed, our understanding of the proinflammatory molecules involved in the pathogenesis of various renal diseases has provided new therapeutic choices, and led to the discovery of gene-based therapeutic options.

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