The Role of chemokines and chemokine receptors in diabetic nephropathy

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1. ABSTRACT

Diabetic nephropathy is increasingly considered as an inflammatory disease characterized by leukocyte infiltration at every stage of renal involvement. Chemokines are important participants in the recruitment of specific subpopulations of inflammatory cells into renal compartments. MCP-1/CCL2 has been identified as having a key role in monocyte/macrophage recruitment in animal models of diabetic nephropathy, as well as in renal biopsies from patients with type 1 and 2 diabetes. Various factors of the diabetic milieu can induce renal expression of MCP-1/CCL2 and cell adhesion molecules, and thereby mediate the macrophage responses that ultimately cause renal injury. Possibly fractalkine/CX3CL1 functions as an arrest chemokine in monocyte/macrophage adhesion before migration into the kidney. T lymphocyte recruitment is influenced by up-regulation of RANTES/CCL5 throughout glomerular as well as tubulointerstitial structures as well as IP-10/CXCL10 mainly in the tubulointerstitium. Improved knowledge of gene polymorphisms of chemokines and their receptors could be useful to predict onset of diabetic nephropathy and define its progression. Blockade of the renin-angiotensin-aldosterone system is currently the only clinically used strategy to treat the inflammatory process in diabetic nephropathy. Newer strategies point to chemokine receptor antagonists and even to immunosuppressive therapy, but still remain in the experimental stage.

2. INTRODUCTION

Beyond hemodynamic and metabolic abnormalities, inflammatory processes and immune cells are involved in the development and progression of diabetic nephropathy. Increased glomerular and interstitial infiltration of monocytes/macrophages (M/M) has been observed both in human biopsies and in animal models (1-4). Activated T lymphocytes have also been found in connection with diabetic nephropathy (5,6). Moreover, patients with diabetes exhibit increased serum levels of acute phase proteins (7,8) and elevated blood neutrophils (9,10), suggesting an inflammatory state. However, the molecular and cellular mechanisms modulating intrarenal inflammation in diabetic nephropathy remain poorly understood. Chemokines and their receptors are key elements involved in inflammatory cell interactions and recruitment of inflammatory cells. Thus, a better understanding of chemokine expression and the pathways of chemokines and their receptors in diabetic nephropathy can be a helpful step in understanding the inflammatory component of this disease. In the present review, the original chemokine names are used together with the new nomenclature.

3. DIABETIC NEPHROPATHY AND M/M RECRUITMENT

M/M are central mediators of renal vascular inflammation, and their accumulation within the kidney is a
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Table 1. Potential role of chemokines in the pathogenesis of diabetic nephropathy

<table>
<thead>
<tr>
<th>Monocyte/Macrophage Recruitment</th>
<th>Pathophysiological relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP1/CCL2</td>
<td>• Proteinuria ↑</td>
</tr>
<tr>
<td></td>
<td>• Mesangial proliferation ↑</td>
</tr>
<tr>
<td></td>
<td>• Tubulointerstitial lesions ↑</td>
</tr>
<tr>
<td></td>
<td>• Collagen deposition ↑</td>
</tr>
<tr>
<td>Fractalkine/CX3CL1</td>
<td>• Arrest of M/M in the kidney</td>
</tr>
<tr>
<td>Lymphocyte Recruitment</td>
<td>Pathophysiological relevance</td>
</tr>
<tr>
<td>RANTES/CCL5</td>
<td>• Involvement in T lymphocyte recruitment</td>
</tr>
<tr>
<td></td>
<td>• Accelerated chronic inflammation</td>
</tr>
<tr>
<td>IP10/CXCL10</td>
<td>• Involvement in infiltration of T cells into the tubulointerstitium</td>
</tr>
</tbody>
</table>

characteristic feature in diabetic nephropathy (2,11). The precise molecular mechanisms behind M/M migration into the kidney remain unclear, but chemokines and their receptors are involved in this process (see Table 1). The monocyte chemoattractant protein-1 (MCP-1/CCL2) and fractalkine/CX3CL1 play a major role in M/M recruitment. Although in vitro studies have provided evidence that inflammatory stimuli can induce the production of a broad spectrum of chemokines in resident cells of the kidney, including interleukin 8 (IL-8/CXCL8), the interferon-gamma inducible protein (IP-10/ CXCL10) or the macrophage inflammatory protein alpha (MIP-1α/CXCL3), their impact on the migration of leukocytes into the kidney during diabetic nephropathy is unclear (12-14).

3.1. Monocyte chemoattractant protein-1 (MCP-1/CCL2)

MCP-1/CCL2 is believed to play a key role in mediating M/M into renal tissue. It is secreted by mononuclear and various non-leukocytic cells including renal resident cells (13-15). Infiltrated M/M release various substances including lysosomal enzymes, nitric oxide, reactive oxygen intermediates or TGF-beta which are essential mediators of renal damage (16,17). In adoptive transfer studies it was shown that M/M can induce proteinuria and mesangial proliferation using an experimental glomerulonephritis model (18). A role of MCP-1/CCL2 has been found in experimental glomerulonephritis models (19-21) and human nephritis (22-24), where it mediates crescent formation and progressive tubulointerstitial lesions via M/M recruitment and activation.

Urinary MCP-1/CCL2 levels were found to be significantly increased in patients with diabetic nephropathy with nephrotic syndrome and advanced tubulointerstitial lesions, and were correlated with the number of CD68-positive infiltrating M/M in the interstitium (25). In addition, both immunohistochemical and in situ hybridization analyses revealed MCP-1/CCL2 positive cells within the tubulointerstitial lesions (25). Tashiro et al. showed in patients with type 2 diabetes and overt nephropathy gradually increasing urinary MCP-1/CCL2 levels according to the clinical stage of the disease (26). Furthermore, urinary MCP-1/CCL2 excretion was positively correlated with the tubular damage marker N-acetylglucosaminidase and albuminuria in Japanese patients with type 2 diabetes, indicating that increased tubular MCP-1/CCL2 expression contributes to renal damage (27). Therefore, the authors suggest that strongly increased levels of proteinuria itself can accelerate the progression of tubulointerstitial lesions by increasing the MCP-1/CCL2 expression in renal tubules, irrespective of the underlying primary renal disease (27). Another study by this group in which enhanced levels of urinary MCP-1/CCL2 excretion in patients with IgA nephropathy and macroalbuminuria comparable to those with diabetic nephropathy were detected, seems to confirm this hypothesis (28). A recent study of MCP-1/CCL2 deficient mice with streptozotocin-induced diabetes demonstrated attenuated diabetic nephropathy, with marked reductions in glomerular and interstitial macrophage accumulation, histological damage, and renal fibrosis in diabetic MCP-1/CCL2 -/- animals compared with the wild-type (29). In db/db mice, a model of type 2 diabetes, MCP-1/CCL2 deficiency did not influence the development of obesity, insulin resistance or type 2 diabetes, but reduced renal M/M accumulation and the progression of diabetic renal injury (30).

High glucose stimulates the expression of MCP-1/CCL2 in cultured human mesangial cells (31).The transcription of the MCP-1/CCL2 gene is activated by the transcriptional factor NF-kappaB (31) when high levels of glucose lead to sustained activation of NF-kappaB (32). In renal biopsies of patients with type 2 diabetes and overt nephropathy, a strong up-regulation of MCP-1/CCL2 mainly in the tubular cells was positively correlated with NF-kappaB activation in the same cells (33). In cultured mouse mesangial cells, Ha et al. identified high glucose mediated stimulation of protein kinase C (PKC) resulting in the generation of reactive oxygen species (ROS) that activate in turn NF-kappaB and stimulate MCP-1/CCL2 expression (34). The stimulatory role for NF-kappaB activation, in particular the p65 subunit in the transcription of MCP-1/CCL2 and renal M/M infiltration, was confirmed in streptozotocin-induced diabetes in rats (35,36). The formation and accumulation of “advanced glycation end products” (AGEs) are known to progress at an extremely accelerated rate in diabetes mellitus. AGEs have been implicated in the pathogenesis of diabetic nephropathy, mediating progressive alteration of the renal architecture and loss of renal function (37-40). In cultured human mesangial cells, AGE-treatment led to enhanced apoptotic cell death and concomitant increased expression of MCP-1/CCL2 (41). To study the role of the “receptor for advanced glycation end products” (RAGE), Gu et al. showed a suppression of AGE-mediated induction of MCP-1/CCL2 using a blocking RAGE antibody in differentiated mouse podocytes (42). These results suggest that AGE-induced MCP-1/CCL2 expression is connected with RAGE activation in podocytes (42). In contrast, in galecin/AGE
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Glomerular hypertension in diabetic nephropathy causes mechanical stretch and promotes glomerular injury by stimulating overproduction of extracellular matrix proteins and cytokines (44-46). Mechanical stretching of human mesangial cells stimulates expression of MCP-1/CCL2 via NF-kappaB (47). This response was accelerated in a high glucose medium, suggesting additive effects of hemodynamic and metabolic factors of diabetic nephropathy (47).

The renal renin angiotensin system (RAS) is activated in diabetes mellitus. Clinically, strategies to inhibit the RAS are the major therapeutic cornerstones to inhibit the RAS are the major therapeutic cornerstones to prevent development and progression of diabetic nephropathy (48). In vitro and in vivo data provide evidence that angiotensin II (ANG II) directly induces the expression of MCP-1/CCL2. Treatment with the ACE-inhibitor enalapril and the AT1-receptor antagonist candesartan dramatically suppressed renal MCP-1/CCL2 expression in streptozotocin treated rats (49). This was associated with a marked reduction in renal M/M infiltration and proteinuria. Janiak and colleagues described an increased survival of obese Zucker rats (a model of type 2 diabetes) treated with irbesartan that was accompanied by a reduction of the extent of glomerular and tubulointerstitial lesions together with a reduction of urinary MCP-1/CCL2 excretion (50). A similar reduction in glomerular and tubular MCP-1/CCL2 expression and amelioration of renal damage with reduced M/M infiltration was found in Zucker rats treated with olmesartan (51). Additionally, incubation of tubular cells with albumin was performed in this study and resulted in an elevated MCP-1/CCL2 release (51). These results suggest that protein leakage through the altered glomerular ultrafiltration barrier in diabetic nephropathy stimulates MCP-1/CCL2 production in tubular cells and that MCP-1/CCL2 released into the interstitial space induces M/M infiltration. In patients with type 1 and 2 diabetes, treatment with ACE inhibitors or AT1-receptor blockers led to a reduction of urinary MCP-1/CCL2 excretion, improvement of renal function, and reduction of oxidative stress (52,53). In renal biopsies from patients with type 2 diabetes, MCP-1/CCL2 and activated NF-kappaB were increased in tubular and interstitial cells in close spatial association to increased ANG II levels (54).

Growth factors such as TGF-beta and the hepatocyte growth factor (HGF) increased MCP-1/CCL2 expression in diabetic rats (55). Moreover, in cultured macrophages, MCP-1/CCL2 raised the secretion of TGF-beta1, which in turn increased the expression of collagen type I and III as well as fibronectin in renal interstitial myofibroblasts (55). Therefore, the authors postulated that apical signals of an enhanced glomerular filtration of growth factors in diabetic nephropathy might be translated into tubulointerstitial events which are recognized by cells in the interstitium, where they stimulate formation of interstitial myofibroblasts through M/M recruitment. Furthermore, MCP-1/CCL2 also mediates collagen deposition in experimental glomerulonephritis by TGF-beta independently of M/M infiltration (57).

3.2. Fractalkine (CX3CL1)

Fractalkine/CX3CL1 exists in membrane-bound as well as in soluble form, and therefore acts as a chemoattractant and adhesion molecule (58). In diabetes mellitus, fractalkine/CX3CL1 expression is upregulated in human coronary arteries with atherosclerosis (59) and kidneys along the glomerular and peritubular capillaries (60). The corresponding receptor for fractalkine, CX3CR1, is expressed on monocytes (61). In the diabetic rat kidney mRNA expression of fractalkine/CX3CL1 and CX3CR1 is increased and some CX3CR1 positive cells are M/M (60). Similar to other chemokines, up-regulation of fractalkine/CX3CL1 is induced in proximal tubular cells by protein overload through NF-kappaB and p38 mitogen-activated protein kinase-dependent pathways (62). Moreover, AGEs (63) and TNF-alpha (64) also induce fractalkine/CX3CL1 in the kidney.

In an in vitro study fractalkine/CX3CL1 mediated arrest and migration of CD16+ monocytes, suggesting that fractalkine might function as an arrest chemokine in the pathway of M/M adhesion before migration into the diabetic kidney (65). However the extent to which fractalkine/CX3CL1 is involved in recruitment of T lymphocytes remains controversial. The expression of CX3CR1 in T lymphocytes has been reported recently (66,67). Cockwell et al. demonstrated that cytokine-activated proximal tubular epithelial cells selectively attracted activated T cells through the generating of chemokines (68). Fractalkine/CX3CL1, RANTES/CCL5...
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and gamma-interferon-inducible-protein (IP-10/CXCL10) have been identified as responsible chemokines for mediating attraction of T cells.

4. DIABETIC NEPHROPATHY AND LYMPHOCYTE RECRUITMENT

Naive as well as effector T cells express the lymphocyte function-associated antigen-1 (LFA-1). ICAM-1 expression is found on renal endothelial, epithelial, and mesangial cells (69-71). Therefore it is likely that ICAM-1 interacts with T cells and stimulates migration into the kidney. Homing of CD4+ cells into glomeruli of diabetic kidneys was decreased in ICAM-1-deficient-db/db mice compared with ICAM-1 intact db/db mice (72). The role of chemokines in lymphocyte recruitment in diabetic nephropathy is summarized in Table 1.

4.1. Regulated upon activation, normal T cell expressed and secreted (RANTES/CCL5)

Another important CC-chemokine in diabetic nephropathy, RANTES/CCL5, is a potent chemoattractant for M/M and granulocytes, but also for T cells, and is involved in enhanced chronic inflammation. RANTES/CCL5 is expressed by various cell types including lymphocytes, fibroblasts, mesangial cells and renal tubular epithelial cells (73-75). Molecular studies have identified NF-kappaB binding sites within the promoter region of the RANTES/CCL5 gene (76). In the kidney, up-regulation of RANTES/CCL5 is induced by similar effectors as described for MCP-1/CCL2. For example, marked induction of RANTES/CCL5 predominantly in mesangial and tubular cells was found in connection with NF-kappaB dependent pathways (77,78), protein overload (77), activation of the RAS (79), enhanced glomerular filtration of growth factors such as TGF-beta or HGF (80), and cytokines such as TNF-alpha (81). In human renal biopsies, CCR5 (the chemokine receptor for RANTES/CCL5), is mainly expressed by infiltrating T cells in the interstitium, but was not detected on intrinsic cells of glomerular, tubular, or vascular structures (85). A human renal biopsy study of patients with various renal diseases showed that glomerular CCR5-positive cells were closely correlated with extracapillary lesions and urinary MIP-1-alpha/CCL3 levels, while interstitial CCR5-positive cells, mainly CD3-positive T cells, were correlated with interstitial lesions and urinary RANTES/CCL5 levels (86).

Expression of CCR2, the receptor for MCP-1/CCL2, is mainly represented by the distribution of M/M in renal tissue (87). Inhibition of CCR2 by receptor antagonists as well as a CCR2 knockout model are characterized by a reduced degree of M/M infiltration and abolished renal fibrosis (88). Similar effects could be shown by the delivery of a mutant of the MCP-1/CCL2 gene into mice (89). In CCR2 deficient mice tubular necrosis and the number of infiltrating M/M were significantly lowered after transient renal ischemia (90).

CX3CR1, the receptor for fractalkine, was found on infiltrating M/M, and on T cells in different renal compartments. In glomerular disease with prominent M/M infiltration, the distribution of M/M matched the distribution of CX3CR1 and in interstitial infiltrates the distribution of CX3CR1 corresponded to the distribution of both T cells and M/M (91). The pattern of CX3CR1 expressing cells was consistent with its ligand fractalkine. The colocalization of CX3CR1 and fractalkine argues for the hypothesis that the CX3CR1/fractalkine complex mediates adhesion in the early extravasation cascade, whereas the ligands of CCR2 and CCR5 might guide inflammatory cells to more specific renal compartments (91). In a model of streptozotocin-treated rats, CX3CR1 was found upregulated in diabetic nephropathy (60).
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Table 2. Therapeutic strategies to interfere with chemokines in animal models

<table>
<thead>
<tr>
<th>Experimental Treatment</th>
<th>Target</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressive therapy (e.g. Methotrexate, Mycophenolate mofetil, Mizoribine)</td>
<td>MCP-1/CCL2 ↓ TGF-beta ↓</td>
<td>Albuminuria ↓ Glomerulosclerosis ↓</td>
</tr>
<tr>
<td>Protein kinase C inhibitor</td>
<td>MCP-1/CCL2 ↓ TGF-beta ↓</td>
<td>Inhibition of increased renal M/M recruitment</td>
</tr>
<tr>
<td>Eicosapentaenoic acid</td>
<td>MCP-1/CCL2 ↓</td>
<td>Amelioration of diabetic nephropathy</td>
</tr>
<tr>
<td>Brevicsapine</td>
<td>MCP-1/CCL2 ↓ TGF-beta ↓</td>
<td>M/M recruitment ↓</td>
</tr>
<tr>
<td>ACE-inhibitors, AT1-receptor blocker</td>
<td>MCP-1/CCL2 ↓ RANTES/CCL5 ↓ TGF-beta ↓</td>
<td>Amelioration of diabetic nephropathy M/M infiltration ↓</td>
</tr>
<tr>
<td>Spirinolactone</td>
<td>MCP-1/CCL2 ↓ RANTES/CCL5 ↓</td>
<td>M/M infiltration ↓</td>
</tr>
<tr>
<td>Penicillin</td>
<td>MCP-1/CCL2 ↓ RANTES/CCL5 ↓ TNF-alpha ↓ ICAM-1 ↓</td>
<td>M/M and T cell infiltration ↓ Proinflammatory ↓</td>
</tr>
<tr>
<td>CCR1 antagonists</td>
<td>CCR1 ↓ CCR2 ↓ CCR5 ↓ MCP-1/CCL2 ↓</td>
<td>Interstitial M/M infiltration ↓ Tubular atrophy ↓ Interstitial fibrosis ↓ Proliferation of epithelial and interstitial cells ↓</td>
</tr>
<tr>
<td>CCR2 antagonists</td>
<td>CCR2</td>
<td>M/M infiltration ↓ Renal fibrosis ↓</td>
</tr>
<tr>
<td>IP-10/CXCL10 antibody</td>
<td>IP-10/CXCL10 ↓</td>
<td>Infiltrating tubulo-interstitial T cells ↓ Renal function ↑</td>
</tr>
</tbody>
</table>

CCR1 has been identified recently as playing a critical role in the recruitment of renal interstitial M/M (92). Ninichuk et al. used a CCR1 antagonist to block interstitial M/M recruitment in uninephrectomized db/db mice, an accelerated model for advanced nephropathy of type 2 diabetes (92). CCR1 blockade reduced interstitial M/M infiltration, most likely by interfering with M/M adhesion to activated endothelial cells of peritubular capillaries in the renal interstitium (92). Furthermore, a reduction of proliferating tubular epithelial and interstitial cells, tubular atrophy, and interstitial fibrosis was observed (92).

6. DIABETIC NEPHROPATHY AND GENE POLYMORPHISMS OF CHEMOKINES AND THEIR RECEPTORS

Polymorphisms of the promoter area of the CCR5 gene (59029G/A) and its agonist the RANTES/CCL5 gene (-28C/G) were associated with the development of nephropathy in Japanese patients with type 2 diabetes (93,94). In a retrospective study over 10 years, CCR5 (59029G/A) and RANTES/CCL5 (-28C/G) polymorphisms were compared in patients with type 2 diabetes without conversion to overt proteinuria with those developing nephropathy (95). The CCR5 59029G/A(+) genotype had a significantly higher frequency in the group that developed diabetic nephropathy, and in discriminate analysis an independent positive correlation with the onset of progression of nephropathy was found (95). The RANTES/CCL5 -28C/G genotype did not discriminate between the two groups and therefore appears not to be a predictor in the onset and progression of diabetic nephropathy (95). The data for CCR5 (59029G/A) polymorphisms in Japanese patients have been confirmed in a study with Asian patients (96). Interestingly, a study on Caucasian patients with type 1 diabetes identified two risk haplotypes in CCR5, carrying the 59029A allele with a 32-bp deletion and carrying the 59029G allele with a 32-bp insertion for the development of diabetic nephropathy in male patients (97). However, data on predictive genetic risk factors, as well as diabetic nephropathy and chemokines, are still preliminary; polymorphism studies are often problematic because of limited size and restriction to defined populations.

7. DIABETIC NEPHROPATHY AND THERAPEUTIC STRATEGIES INVOLVING CHEMOKINES

Experimental therapeutic strategies to interfere with chemokines and their receptors in diabetic nephropathy are shown in Table 2. Blockade of the RAS undoubtedly leads to complex protective mechanisms in progressive renal disease, including diabetic nephropathy. There is growing evidence that chemokines and their receptors are therapeutic targets of ACE inhibitors and AT1-receptor blockers. In animal models of diabetic nephropathy, blockade of the RAS led to suppression of MCP-1/CCL2 expression and was closely associated with effects on proteinuria and glomerular M/M number (98,99). Amann et al. could show that blockade of the RAS in type 2 diabetic patients with diabetic nephropathy reduces urinary MCP-1/CCL2 levels and improves renal function (52). Application of statins also reduced MCP-1/CCL2 expression and M/M infiltration in diabetic rats, as did AT1-receptor blockers (99,100). Addition of anti-TGF-beta antibody therapy to ACE inhibitor treatment resulted in the arrest of progressive diabetic nephropathy in animals and a decrease in the expression of MCP-1/CCL2, but this could not be achieved with the anti-TGF-beta antibody alone (98).

In experimental diabetes mellitus, there are an increasing number of studies in which immunosuppressive therapy with methotrexate, mycophenolate mofetil or irradiation has been shown to reduce urinary albumin excretion and glomerulosclerosis (101,102). Immunosuppressive therapy, e.g. with mycophenolate mofetil or mizoribine, led to reduced expression of MCP-1/CCL2 and TGF-beta in kidneys of diabetic rats.
expression of RANTES/CCL5, MCP-1/CCL2, TNF-alpha. Pentoxifylline is associated with a reduced mRNA 

of experimental glomerulonephritis with the phosphodiesterase inhibitor. Interestingly, the attenuation of experimental nephropathy, and reduced M/M infiltration and MCP-1/CCL2. Han et al. could show that treatment of type 2 diabetic rats with spironolactone ameliorated diabetic nephropathy and was accompanied by reduced MCP-1/CCL2 expression which might explain the beneficial effect (106). A Chinese group identified breviscapine, a flavonoid extracted from the Chinese herb Erigeron breviscapus, as suppressing M/M recruitment, and breeding studies in patients with diabetes mellitus. Caution is also advised in treatment with chemokine receptor antagonists because in corresponding knockout models acceleration of renal inflammation has been observed (113). This suggests that inhibition of chemokine processes must be timely and compartment-specific to provide measurable therapeutic benefit for renal structure and function. An overview of the described experimental therapeutic approaches is given in Table 1.

8. PERSPECTIVES

Chemokines and their receptors are clearly involved in the pathogenesis of diabetic nephropathy, especially in recruitment of M/M and T lymphocytes (Figure 2). Future therapeutic strategies could focus on diminishing T cell and M/M trafficking to reduce diabetic kidney damage. Selective therapies on the level of chemokine and the chemokine receptor might be a future tool to curb diabetic nephropathy. Despite the much improved understanding of chemokines in diabetic kidney disease gained principally by the studies using animal models, further investigation is needed to fully elucidate their role.

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