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The chemokine network in systemic lupus erythematous nephritis

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TABLE OF CONTENTS

1. ABSTRACT

In response to renal immune complex accumulation in systemic lupus erythematosus (SLE), monocytes, T lymphocytes, and neutrophils infiltrate the kidney and mediate tissue injury and renal dysfunction. Chemotactic factors induced by immune complexes are responsible for recruiting these inflammatory cells to the kidney. Considerable attention has focused on the role of the chemokine network in regulating renal leukocyte recruitment in autoimmune glomerular diseases. In animal models of SLE nephritis, intervention studies directed at chemokines or chemokine receptors have provided definitive proof that specific chemokines are involved in the pathogenesis of renal inflammation. These same chemokines and chemokine receptors are expressed in the kidney during human SLE nephritis, and correlate with markers of renal injury and inflammation. This review will describe and integrate the animal and human data to build a case for targeting the chemokine network as a novel approach to the treatment of SLE nephritis. Anti-chemokine therapies hold the promise of efficacy with fewer adverse side-effects than the non-specific immunosuppression regimens currently in use.

2. INTRODUCTION

Inflammation is a characteristic finding in organs affected by systemic lupus erythematosus (SLE), and seems to be particularly important for the pathogenesis of kidney injury in patients with lupus nephritis (1-10). Monocytes, macrophages, and T lymphocytes are the most conspicuous inflammatory cells to enter the kidney during SLE nephritis (Figure 1), although neutrophils and B lymphocytes can also be found. These infiltrating white blood cells injure the kidney through a variety of mediators, including cytokines, eicosanoids, proteolytic enzymes, and reactive oxygen species (9, 11-23). In SLE nephritis, leukocytes are recruited to the kidney by soluble chemotactic factors that are generated or expressed in response to renal immune complex accumulation, and include complement activation products and chemokines (24-27).

An overview of chemokines and their receptors is found elsewhere in this issue of *Frontiers in Bioscience*. Briefly, the chemokine network is comprised of at least 50 ligands and 20 G-protein coupled receptors, and may be broadly divided into inducible chemokines that are upregulated during tissue injury, and constitutively-

Table 1. Renal chemokine/chemokine receptor expression in murine SLE nephritis

MRL-*Fas*^{lpr}	NZB/NZW	MRL-*Fas*^{lpr} mesangial cells treated with anti-DS DNA antibodies
MCP-1/CCL2	MCP-1/CCL2	IL-8/CXCL8
RANTES/CCL5	RANTES/CCL5	Fractalkine/CX3CL1
MIP-1 beta/CCL4	Mig/CXCL9	
IP-10/CXCL10	SDF-1/CXCL12	
CCL9	BLC/CXCL13	
CCR1		
CCR2		
CCR5		

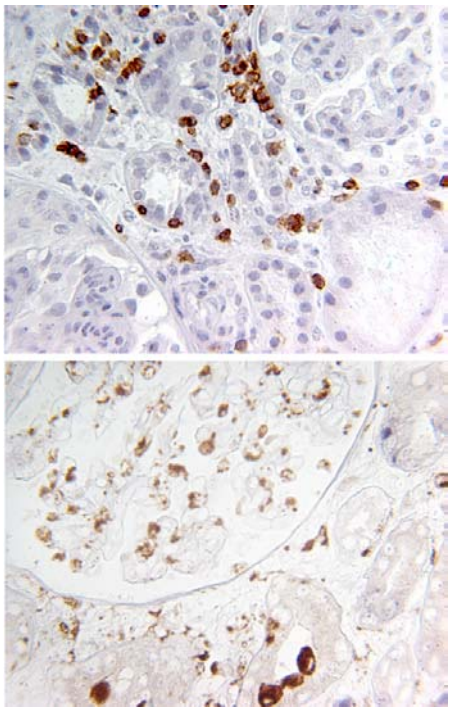

Figure 1. Leukocyte infiltration into the kidney during SLE nephritis. These sections are from a patient with WHO class IV lupus nephritis. The upper panel is stained for CD3+ T lymphocytes and the bottom panel is stained for CD68+ monocytes/macrophages. Typically, CD68+ cells are found within glomeruli and the tubulointerstitial space, whereas CD3+ cells are mainly found in the tubulointerstitial space and the periglomerular area.

expressed chemokines that regulate normal lymphocyte trafficking to, and the architecture of lymphoid organs (28). The inducible chemokines have received the most attention with respect to inflammatory diseases of the kidney because they recruit monocytes, neutrophils, and lymphocytes to tissues undergoing pathological change, and activate leukocyte proinflammatory programs. However certain members of the constitutive chemokine subgroup have recently been implicated in SLE nephritis.

Interfering with the chemokine network represents a novel approach for the treatment of inflammatory kidney injury. Studies in experimental lupus nephritis have shown that blocking specific chemokines or their receptors can significantly reduce renal inflammation. Studies in human lupus nephritis have shown a compelling association of specific chemokines with disease activity. This review will integrate these studies to make the case for targeting the chemokine system to treat human SLE nephritis.

3. ESTABLISHING A ROLE FOR SPECIFIC CHEMOKINES IN SLE NEPHRITIS: INSIGHTS FROM ANIMAL STUDIES

As the complexity of the chemokine network became clear it was realized that several chemokines could bind to a single leukocyte chemokine receptor, and that individual chemokines could bind to several receptors. Thus in principle, multiple chemokines can recruit and activate similar leukocyte subsets. This apparent functional redundancy suggested that manipulating single chemokines or chemokine receptors would have little therapeutic impact in inflammatory diseases. Studies in animal models of SLE nephritis proved this concept to be incorrect.

3.1. Intrarenal chemokine expression in murine models of SLE nephritis

Table 1 summarizes the results from several studies of chemokine expression in various murine models of lupus nephritis. Using the MRL-*Fas*^{lpr} murine model of lupus nephritis, it was shown that MRL-*Fas*^{lpr} kidneys only expressed the chemokines RANTES/CCL5, MIP-1 beta/CCL4, IP-10/CXCL10, and MCP-1/CCL2 out of a panel of 9 tested, and MCP-1/CCL2 and RANTES/CCL5 transcripts were the most abundant (29). Similarly, chemokine receptor expression in the MRL-*Fas*^{lpr} kidney was restricted to CCR1, CCR2, and CCR5, which bind RANTES/CCL5 (CCR1,5), MCP-1/CCL2 (CCR2) and MIP-1 beta/CCL4 (CCR1) (29). A more extensive examination of kidney gene expression during the evolution of nephritis in the MRL-*Fas*^{lpr} mouse was undertaken using cDNA microarray technology (30). Although this approach is expected to afford the most comprehensive picture of chemokine gene expression in murine lupus nephritis, only IP-10/CXCL10, CCL9, and CCR2 were found to be upregulated. The reason for these limited results is not clear. Kidneys from New Zealand Black/New Zealand White (NZB/W) mice, another murine model of lupus nephritis, expressed RANTES/CCL5 and monokine induced by interferon-gamma (Mig/CXCL9) (31), and MCP-1/CCL2 (32). In an *in vitro* approach, mesangial cells from MRL-*Fas*^{lpr} mice were treated with a number of pathogenic anti-double stranded DNA antibodies and gene expression assessed with microarray assays (33). These studies showed that the chemokines interleukin-8 (IL-8/CXCL1) and fractalkine/CX3CL1 were upregulated. Although the involvement of other members of the chemokine network in SLE nephritis cannot be completely excluded by these studies, and despite some inconsistencies between investigations that may have been technique dependent, the apparent activation of a limited repertoire of chemokines and chemokine receptors is encouraging from a therapeutic point of view, and suggests at least a moderate degree of chemokine specificity for lupus.

Table 2. Effect of anti-chemokine interventions on kidney inflammation in lupus-prone mice

Intervention (reference)	Glomerular Macrophages	Glomerular T Cells	Interstitial Macrophages	Interstitial Cells	Perivascular Macrophages	Perivascular T Cells
MCP-1/CCL2 Knockout (34)	34% ↓	No change	50-72% ↓	50-72% ↓	No change	No change
CCR2 Antagonist (37)	54% ↓	Not done	"large" ↓	Not done	No change	No change
CCR2 Antagonist (36)	33% ↓	55% ↓	80% ↓	75% ↓	65% ↓	71% ↓
CCR2 Knockout (38)	50% ↓	44% ↓	55% ↓	42% ↓	Not done	Not done
CCR1 Antagonist (39)	No change	No change	87% ↓	51% ↓	Not done	Not done
CX3CR1 Antagonist (40)	78% ↓	No change	56% ↓	50% ↓	53% ↓	No change
CCR4 Antagonist (36)	No change	No change	No change	No change	No change	No change

Consistent with this specificity, chemokine expression in murine lupus nephritis showed a specific temporal relationship to the evolution of kidney injury. MCP-1/CCL2 and RANTES/CCL5 were upregulated *prior* to leukocyte infiltration of MRL-*Fas*^{lpr} kidneys, and preceded intrarenal chemokine receptor expression and increases in nephritogenic cytokines such as IL-1 beta, TNF-alpha, and IFN-gamma (29, 34). In contrast, MIP-1 beta/CCL4 and IP-10/CXCL10 expression coincided with developing renal lesions and proteinuria.

3.2. The outcome of manipulating the chemokine network in murine SLE nephritis

The most compelling evidence against functional redundancy as a limiting factor in therapeutically targeting the chemokine network in SLE nephritis comes from interfering with specific chemokines or chemokine receptors in the MRL-*Fas*^{lpr} mouse. Most studies focused on MCP-1/CCL2 and it receptor CCR2. When MCP-1/CCL2 knockout mice were cross-bred with the lupus-prone mice, the MCP-1/CCL2 deficient MRL-*Fas*^{lpr} mice showed prolonged survival and preserved renal function compared to wild-type mice, and had a significant decrease in renal inflammation (34). The reduction of infiltrating macrophages and T cells was most profound in the interstitial compartment, followed by macrophage depletion from glomeruli (Table 2). Interestingly, there was no effect on interstitial perivascular inflammatory cells, consistent with weak MCP-1/CCL2 expression by blood vessels (34). Similarly, blocking the interaction between MCP-1/CCL2 and CCR2 attenuated glomerular and interstitial inflammation and kidney damage in murine SLE (35-37). The attenuation of inflammation in MRL-*Fas*^{lpr} kidneys after blocking CCR2 was similar to that observed with MCP-1/CCL2 deficiency (Table 2), however an improvement in vasculitis was also demonstrated in one investigation (36). In these studies CCR2 was blocked before the development of renal lesions, early in the course of renal injury, and after severe glomerulonephritis had been established. Antagonizing CCR2 was effective in reducing renal inflammation at each of these time points (36, 37), although when started after severe glomerulonephritis no reduction in proteinuria was observed (37). Finally, CCR2 deficient mice cross-bred with MRL-*Fas*^{lpr} mice showed a similar degree of protection from glomerulonephritis as blocking CCR2 or MCP-1/CCL2 deficiency (38).

The role of a few other chemokine-receptor pairs has been tested in lupus-prone mice. Renal function improved in MRL-*Fas*^{lpr} mice with established glomerulonephritis given a CCR1 antagonist (39). These mice showed a decrease in interstitial fibrosis and inflammation, but had no reduction of glomerular inflammatory infiltrates or proteinuria. Glomerular inflammation and pathology (crescents, glomerulosclerosis), and interstitial vasculitis improved in MRL-*Fas*^{lpr} mice treated before or early in the course of nephritis with a CX3CR1 antagonist to block its interaction with the chemoattractant/adhesion factor fractalkine/CX3CL1 (40). This pattern of protection is likely due to the fact that fractalkine was expressed mainly by glomerular endothelial cells and the interstitial microvasculature. Not every chemokine or chemokine receptor has a role in lupus nephritis. For example, an antagonist of the chemokine TARC/CCL17 (receptor CCR4) had no effect on murine SLE nephritis (36).

Two groups looked at the effect of trans-retinoic acid on the course of murine SLE nephritis. In the MRL-*Fas*^{lpr} model, retinoic acid significantly decreased glomerular endocapillary proliferation, kidney damage, and albuminuria (41). Infiltrating glomerular macrophages and T lymphocytes were reduced by 86% and 66% respectively, and interstitial lymphocytes and macrophages were reduced by 75% and 66% respectively (41). Treatment with retinoic acid also attenuated kidney expression of pro-inflammatory cytokines like interleukin-1, and several chemokines, including MCP-1/CCL2, RANTES/CCL5, and MIP-1 alpha, beta/CCL3/CCL4. A similar improvement in kidney damage and reduction in renal inflammation was observed in NZB/W mice treated with trans-retinoic acid, along with almost complete suppression of intrarenal MCP-1/CCL2 mRNA (32). In both studies it was postulated that the improvement in kidney inflammation was due to inhibition of chemokine expression, however time course studies to show that the decline in chemokine expression preceded the reduction in leukocyte infiltration were not done.

With the exception of the CCR2 knockout model, none of the interventions used to antagonize the chemokine network in the MRL-*Fas*^{lpr} mouse affected renal immune complex or complement deposition, the amount or distribution of circulating immunoglobulin isotypes, or anti-double stranded DNA antibody titers (34, 36-40). Additionally, blocking CCR2 with a truncated form of MCP-1/CCL2 did not influence systemic helper T cell polarization, a component of autoimmunity (42). In contrast, CCR2-deficient MRL-*Fas*^{lpr} mice had similar levels of serum immunoglobulins and renal immune complex and complement deposition as wild-type mice, but had lower anti-double-stranded DNA antibody titers, and fewer CD4 and CD8 T cells (38). Thus, autoimmunity is not primarily affected by antagonizing these inducible

chemokines, so it is unlikely that chemokines predispose to SLE, but are more important in mediating the renal injury of SLE. Absence of CCR2 during the development of the immune system may affect the subsequent development of autoimmunity, but achieving the therapeutic equivalent of a CCR2 knockout in human lupus is unlikely. In the NZB/W model retinoic acid treatment in combination with steroids did attenuate anti-DNA production, but retinoic acid and steroids are not specific for chemokines, and affect other components of the immune system (32).

It is important to note that in some models of glomerulonephritis, such as the immune complex-mediated nephrotoxic serum nephritis, genetic deficiency of the chemokine receptors CCR1 and CCR2 actually resulted in more severe renal injury compared to the wild-type (43, 44). There are several possible reasons for this unexpected outcome. Maturation of the immune system in the absence of CCR1 and CCR2 may predispose to aberrant immune responses (43, 45, 46), including a shift in the relative importance of other chemokine ligand-receptor pairs in mediating renal injury. Alternatively, CCR1 and CCR2 may have ligands that down-regulate inflammation and are thus protective. These would have no effect in the setting of absolute (genetic) receptor deficiency, but may still provide some protection during treatment with receptor blockers, because pharmacologic receptor blockade would probably not be absolute. Although the results of these chemokine receptor knock-outs are not consistent with the observed effects of CCR1 and CCR2 antagonists in murine lupus nephritis, these data should be considered as chemokine receptor antagonists are developed and tested in human SLE nephritis.

Experiments in which chemokine expression is enhanced in lupus-prone mice also support a pathogenic role for the chemokine system in SLE nephritis. This is best illustrated by the delivery of RANTES/CCL5 directly into MRL-*Fas*^{lpr} kidneys through a gene transfer technique before the onset of nephritis (47). The over-production of RANTES/CCL5 greatly accelerated the development of interstitial inflammation, resulting in a predominantly CD4+ T lymphocyte infiltrate (47). Other studies provide less direct evidence because chemokines were upregulated along with other cytokines in the context of a systemic perturbation. For example, activation of Toll-like receptors 3, 7, and 9 by injection of their specific ligands into MRL-*Fas*^{lpr} mice greatly worsened kidney pathology, increased glomerular and/or interstitial macrophages and T cells, and enhanced intrarenal expression of MCP-1/CCL2 and RANTES/CCL5 (48-50). It was postulated that these chemokines contributed to the increased inflammatory infiltrates. In another model, MRL-*Fas*^{lpr} mice deficient in P-selectin or its ligand were unexpectedly found to have a phenotype of decreased survival, accelerated glomerulonephritis, and a 2.5-fold increase in renal MCP-1/CCL2 expression (51). The role of enhanced MCP-1/CCL2 in this model is however unclear, because its increase did not precede the worsening of glomerular pathology, and neutrophils rather than monocytes or T lymphocytes were the dominant infiltrating cells. Interestingly, the murine neutrophil chemokine KC (an IL-8/CXCL8 analog) was not increased in the P-selectin deficient mice (51).

3.3. A role for constitutive/homeostatic chemokines in murine SLE nephritis

A very interesting report examined the role of the constitutive chemokine stromal cell-derived factor 1 (SDF-1/CXCL12; receptor CXCR4) in SLE nephritis (52). Using NZB/W lupus-prone mice, it was shown that their peritoneal B1a lymphocytes were highly sensitive to the chemotactic effects of SDF-1/CXCL12, and proliferated and had increased survival in the presence of SDF-1/CXCL12. B1a lymphocytes may be autoreactive, and have been considered to play an important role in pathogenic autoantibody production during autoimmunity (53). Although SDF-1/CXCL12 has been considered a constitutive chemokine, this investigation demonstrated induction of SDF-1/CXCL12 expression by glomerular podocytes during the development of lupus nephritis in NZB/W mice (52). Most importantly, when NZB/W mice were treated with anti-SDF-1/CXCL12 antibodies prior to the development of nephritis, the appearance of anti-double stranded DNA antibodies, proteinuria, and death were prevented for the duration of treatment (52). Furthermore, when anti-SDF-1/CXCL12 antibodies were given to NZB/W mice with established nephritis a marked decrease in proteinuria and glomerular pathology was observed. The treated mice demonstrated mainly WHO class II-type lesions, in contrast to WHO class IV lesions in untreated animals, consistent with the observed reduction of immunoglobulin deposits in the glomerular capillary subendothelial space. With respect to indicators of autoimmunity, anti-SDF-1/CXCL12-treated mice had fewer activated CD4 lymphocytes in the spleen and lymph nodes, lower levels of anti-double stranded DNA antibodies despite similar levels of total immunoglobulins, and fewer B1a lymphocytes.

Other investigators showed that the constitutive B lymphocyte chemokine (BLC/CXCL13; receptor CXCR5) was induced in NZB/W kidneys during the development of nephritis (31). The origin of BLC/CXCL13 appeared to be from infiltrating mononuclear, possibly myeloid dendritic cells. Interestingly, B1 lymphocytes were more sensitive to chemotactic effects of BLC/CXCL13 than other types of B cells, and examination of the kidneys of NZB/W mice showed a significant B lymphocyte infiltrate with a relatively large proportion of B1 cells (31, 53). It was speculated that aberrant expression of BLC/CXCL13 in the kidneys of lupus-prone mice may serve to recruit B1 cells to the kidney to establish a lymphoid environment that predisposes to the development of organ-specific autoimmunity.

The role of SDF-1/CXCL12 and BLC/CXCL13 in other animal models of lupus nephritis has not been established. It is possible that the genetic background of the SLE strains affects the repertoire of intrarenal chemokine expression. The relevance to human lupus is also not yet clear, but there is some evidence suggesting a role of these chemokines. Data were recently presented showing that

Table 3. Intrarenal chemokine expression in human SLE nephritis

Chemokine (reference)	Glomerular Compartment Protein	Glomerular Compartment mRNA	Interstitial Compartment Protein	Interstitial Compartment mRNA
MCP-1/CCL2 (67)	Present	NT[1]	NT	NT
MCP-1/CCL2 (56)	ND[2]	ND	Present	Present
MCP-1/CCL2 (65)	Present	NT	NT	NT
MCP-1/CCL2 (57)	ND	ND	Present	Present
MIP-1 alpha/CCL3 (67)	Present	NT	NT	NT
MIP-1 alpha/CCL3 (56)	Present	Present	Present	Present
MIP-1 beta/CCL4 (67)	Present	NT	NT	NT
IL-8/CXCL8 (58)	Present	Present	Present	Present
IL-8/CXCL8 (66)	Present	NT	NT	NT
IL-8/CXCL8 (63)	NT	Present	NT	Present
IP-10/CXCL10 (61)	NT	ND	NT	Present
CXCL9 (61)	NT	ND	NT	Present
CXCL9 (61)	NT	ND	NT	Present

NT = not tested; [2]ND = none detected

patients with SLE nephritis have significant renal B-cell infiltrates, with some developing T and B cell aggregates, and a few with germinal centers (Guttikonda, et. al., American College of Rheumatology Meeting, 2006). Furthermore, dendritic cells infiltrate the glomeruli of patients with active lupus nephritis, although these are mainly plasmacytoid rather than the myeloid dendritic cells thought to produce BLC/CXCL13 (54).

4. EVIDENCE LINKING THE CHEMOKINE NETWORK TO HUMAN SLE NEPHRITIS

In contrast to animal studies, a pathogenic role of chemokines in human SLE nephritis cannot be established until chemokine antagonists are available for clinical use. Nonetheless, several approaches have shown a relationship of the chemokine system to human lupus nephritis. These studies are compelling and are summarized in the following sections.

4.1. Intrarenal chemokine expression in human SLE nephritis

The initial clue that chemokines participate in human SLE nephritis came from several investigations that demonstrated the presence of chemokines within the kidney during active SLE nephritis (Table 3). These investigations were not exhaustive in terms of the number of chemokines examined, and focused mainly on MCP-1/CCL2, MIP-1 alpha/CCL3, MIP-1 beta/CCL4, interleukin-8 (IL-8/CXCL8), and IP-10/CXCL10, chemokines shown to be relevant in murine models of SLE nephritis. Another study also looked at RANTES/CCL5, but included only two patients with SLE nephritis (55). Renal chemokine expression was shown by immunohistochemistry and *in situ* hybridization, demonstrating chemokines could be synthesized locally, and that their appearance in the kidney or the urine did not necessarily imply filtration from the circulation. Chemokine transcripts were found in infiltrating mononuclear leukocytes, as well as resident renal cells (glomerular endothelial cells, mesangial cells, podocytes, renal tubular epithelial cells, and peritubular capillary endothelial cells), indicating that intrinsic kidney cells can produce chemokines during immune complex disease (55-58).

Intra-renal chemokine receptor expression on infiltrating inflammatory cells provides indirect evidence that chemokines are involved in recruiting these leukocytes to the kidney during glomerulonephritis. Receptor expression studies also showed that certain receptors were restricted to specific leukocyte subsets or renal compartments. For example, in SLE nephritis, CCR1 and CCR5 were observed mainly on interstitial CD68+ monocytes/macrophages and CD3+ T lymphocytes, and had relatively low expression within glomeruli (59, 60). The majority of CCR5-positive cells were T lymphocytes, while monocytes/macrophages and T cells were CCR1 positive (59, 60). Similarly, CXCR3 was shown to be expressed mainly in the interstitium by infiltrating T cells (61). While no studies have looked at CCR2 with immunohistochemistry in SLE, one investigation used *in situ* hybridization to characterize its distribution in crescentic (otherwise unspecified) glomerulonephritis (62). CCR2 mRNA was expressed by infiltrating glomerular monocytes/macrophages and some interstitial T lymphocytes. As expected, CXCR1-positive cells in SLE nephritis were thought to be neutrophils, and were located in and around glomeruli (63). Interestingly, CX3CR1demonstrated the least restricted distribution pattern and was found on both macrophages and T lymphocytes, and in glomeruli and the interstitial space, suggesting the possibility that its ligand, fractalkine/CX3CL1 functions mainly as an adhesion molecule (64). Excluding CX3CR1, each of these receptors can bind multiple ligands, so receptor expression is not necessarily indicative of the role of a specific chemokine. Furthermore, ligand-receptor binding often causes receptor internalization, thus immunohistochemical studies must be interpreted cautiously.

Because chemokines are not found, or only minimally expressed in normal kidney tissue (kidneys not suitable for transplantation, pre-transplant biopsies, non-involved areas of nephrectomies for cancer), or glomerular disease controls (thin glomerular basement membrane disease, minimal change disease, focal segmental glomerulosclerosis, mild IgA nephropathy), their appearance in SLE nephritis has been taken as evidence for involvement in renal inflammatory injury (61, 63, 65-67). Although limited, correlations of intrarenal chemokine expression to kidney pathology and function also support this involvement. For example, the expression of MCP-1/CCL2, MIP-1 alpha/CCL3 and beta/CCL4 was higher in cellular crescents than fibrocellular crescents, and was not detected in fibrous crescents (67). MIP-1 alpha/CCL3 and

MCP-1/CCL2 expression was significantly correlated with the number of CD68-positive macrophages in glomerular crescents, and was higher in glomeruli showing rupture of Bowman's capsule, but not in glomeruli showing necrosis of capillary loops (67). Similarly, IL-8/CXCL8 expression was associated with renal dysfunction (58).

4.2. Surveys of chemokine expression in human SLE nephritis

Because of the possibility of functional redundancy within the chemokine network, it is important to understand whether chemokine expression in human lupus nephritis is restricted to a specific subset of chemokines. Although no studies have completely addressed this question, some information is available. Using a proteomic approach, serum cytokine levels were measured in patients with SLE (68). Out of 160 cytokines, 23 were upregulated in lupus, including 12 chemokines (CXCL11, CXCL2, BLC/CXCL13, IL-8/CXCL8, CXCL9, IP-10/CXCL10, CCL7, MIP-1 alpha/CCL3, TARC/CCL17, CCL19, CCL8, MCP-1/CCL2). One chemokine (CCL20) was down-regulated. The protein microarrays used in these experiments included 31 different chemokines, suggesting some degree of specificity of chemokine expression in SLE. A few of these upregulated chemokines were verified in independent investigations, including MCP-1/CCL2 and IL-8/CXCL8 (see Section 4.3), IP-10/CXCL10 (69, 70), and TARC/CCL17 (71). Although serum levels do not reflect intrarenal chemokine expression, CXCL11, BLC/CXCL13, IP-10/CXCL10, and MIP-1 alpha/CCL3 were significantly higher in patients with active renal lupus, and CCL8, MCP-1/CCL2, and CXCL2 showed a trend toward significance. TARC/CCL17 levels were highest in patients with class I and II SLE nephritis, and decreased in the more severe classes (III and IV) of nephritis (71). Interestingly, among the chemokines not shown to be differentially expressed in this study, RANTES/CCL5, MIP-1 beta/CCL4, and fractalkine/CX3CL1 have been found in the kidneys in human and murine SLE nephritis. This demonstrates the importance of assessing the pattern of chemokine expression within specific target organs. Accordingly, global gene regulation in laser-captured glomeruli from patients with active class III and IV SLE nephritis was measured using cDNA microarrays (72). Unexpectedly, only two chemokines were found to be upregulated. These were MCP-1/CCL2 and MIP-1 alpha /CCL3. While this finding is consistent with activation of only a subset of chemokines in human SLE nephritis, it is likely that additional chemokines important for kidney injury were missed because the contribution of the renal tubulointerstitial compartment was not assessed. Furthermore, gene expression was examined only at a single point in a disease that evolves over time.

4.3. Urine expression of immunoreactive chemokines in human SLE nephritis

The search for biomarkers of lupus nephritis led to the discovery that chemokines are found in the urine of patients with SLE nephritis, and can be measured by ELISA. Correlation of urine chemokines with disease activity, renal function, and renal injury also provided important indirect evidence supporting the involvement of the chemokine network in the pathogenesis of SLE nephritis. Most investigations of urine chemokines have focused on MCP-1/CCL2 and IL-8/CXCL8 (57, 66, 73-76).

In a prospective study we examined urine MCP-1/CCL2 (uMCP-1) and urine IL-8/CXCL8 (uIL-8) in serial samples obtained from lupus patients before, during, and after renal and nonrenal flares (73). The mean uMCP-1 at renal flare was significantly greater than that of healthy control subjects, SLE patients with chronic, stable kidney disease (disease controls), and SLE patients with nonrenal SLE. Despite some overlap between control and flare levels, 73% of uMCP-1 values at flare were above the 95^{TH} percentile of uMCP-1 values from disease controls, indicating that uMCP-1 is a sensitive marker for renal flare. Additionally, at nonrenal flare uMCP-1 expression was not different than that of healthy controls. Thus, uMCP-1 is also a specific marker for SLE nephritis in a lupus population, and is not confounded by systemic, nonrenal SLE activity. These findings are consistent with other reports of significant increases in uMCP-1 during active SLE nephritis (56, 57, 74).

It is likely that uMCP-1 is derived, at least in part, from intrarenal synthesis rather than simply filtration through glomeruli injured during SLE nephritis. Evidence in favor of intrarenal synthesis include a poor correlation between serum and urine levels of MCP-1/CCL2 (57, 74, 77), no relationship between the amount of MCP-1/CCL2 in the urine at flare and the degree of proteinuria (73, 78), and no correlation between uMCP-1 and uIL-8 (57, 73). IL-8/CXCL8 is a good "filtration" control for MCP-1/CCL2 as it is of similar molecular mass and charge (79). There is however a correlation between uMCP-1 and urine levels of TWEAK (r^2=0.25, P<0.001), a ~27kDa TNF superfamily cytokine that induces MCP-1/CCL2 production by glomerular cells and is increased in SLE nephritis (80). Like uMCP-1, uTWEAK did not correlate with the magnitude of proteinuria (r^2=0.005, P>0.50) and was felt to be produced in the kidneys. TWEAK may be a component of an intrarenal cytokine network that regulates chemokine expression during SLE nephritis (80).

As opposed to other investigations (57, 74), most patients in our cohort were on chronic immunosuppressive therapy (e.g. steroids and mycophenolate mofetil), but there was no relationship between the cumulative amount of therapy received during the 30 days preceding flare and uMCP-1 levels (73). Similarly treatment with renoprotective agents such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers did not influence uMCP-1 levels at flare. These findings suggest that current therapies for SLE nephritis are inadequate to suppress pathogenic cytokine production. Furthermore, uMCP-1 appears to be a robust marker of SLE nephritis activity even in patients with chronic disease on maintenance therapy who intermittently flare. These patients comprise the largest and most diagnostically challenging SLE population.

In contrast to uMCP-1 expression, uIL-8 levels in our patient cohort were not increased at renal flare relative to

disease controls, and were only mildly elevated compared to healthy subjects (73). This finding was unexpected based on previous reports of significantly increased uIL-8 during active SLE nephritis (66, 75, 76), but may be due, in part, to the fact that untreated patients were studied in several of these investigations. Thus, compared to uMCP-1, uIL-8 appears to be a less useful marker for following patients with established lupus nephritis on maintenance therapy.

Time course analysis of urine chemokine expression during the lupus renal flare cycle showed that uMCP-1 appeared to increase as early as 2-4 months before flare, suggesting that serial measurement of uMCP-1 in a renal lupus population may predict flare onset (73). Successful treatment of SLE nephritis was associated with a decline in uMCP-1 levels (56, 57, 74), however resolution to control values often took several months (73), a further indication that available treatments are not particularly effective at attenuating chemokine expression. Patients who did not respond to treatment had persistently high uMCP-1 levels (73). Interestingly, a small subgroup of patients improved clinically following flare, but continued to show elevated uMCP-1 (73). Although this finding needs to be confirmed, it raises the intriguing possibility that persistently high uMCP-1 in this group is a marker of ongoing subclinical inflammation.

In those studies that demonstrated high uIL-8 levels at renal flare, treatment-induced resolution of SLE nephritis was accompanied by a decline in uIL-8 (66, 76). After steroid and/or cytotoxic (cyclophosphamide) therapy the length of time needed for a response in uIL-8 was highly variable, and appeared to be anywhere from 4-24 weeks (66, 76). One study showed no definite effect after 4 weeks (75).

As discussed in Section 4.2, a proteomic survey of circulating, systemic cytokine expression in SLE demonstrated increased MCP-1/CCL2 and IL-8/CXCL8 levels (68). More focused investigations of MCP-1/CCL2 in the serum or plasma of SLE patients have generally found increased levels compared to normal serum, but this was seen in both active and inactive disease, and there was no correlation with uMCP-1 (57, 69, 70, 74, 77). Furthermore, treatment did not necessarily cause a fall in serum levels (57). With respect to IL-8/CXCL8 plasma expression in SLE, data are conflicting. Two investigations did not detect IL-8/CXCL8 in the plasma of SLE nephritis patients or healthy controls (57, 66), one study found no difference between plasma levels in SLE nephritis and healthy controls (75), and one study found serum IL-8/CXCL8 to be significantly higher in SLE, and within the SLE group, to be higher in patients with kidney involvement (81). These findings suggest that for SLE nephritis, urine chemokines are more relevant biomarkers than serum chemokines.

In addition to the strong association of uMCP-1 with clinical activity in SLE nephritis, other correlations with kidney function and kidney histology support a pathogenic role of MCP-1 in lupus nephritis. We showed that: 1) uMCP-1 was 3.4-fold higher in patients with impaired renal function at flare than patients with normal renal function at flare; 2) uMCP-1 levels in patients with severe renal flare were higher than patients with mild renal flare; 3) Patients with a diagnosis of class III or IV lupus nephritis compared to class V had 3.5-fold higher uMCP-1 levels; and 4) persistent renal functional impairment correlated with a persistent elevation of uMCP-1 post-renal flare (73).

A handful of studies have examined the relationship of uMCP-1 to renal pathology in human SLE nephritis. The results are conflicting, and thus difficult to synthesize into a definitive description. Several studies showed that the highest levels of uMCP-1 were found in patients with severe crescentic or necrotizing class IV SLE nephritis, while patients with class V nephritis had normal to modestly elevated levels (57, 73, 74). In contrast, one report observed similar uMCP-1 levels in class IV and V nephritis, but did not examine urine samples that were coincident with the biopsies (82). Elevated uMCP-1 levels are also found in the absence of acute/active glomerular lesions. We and others observed moderately high uMCP-1 in patients with lesions such as glomerulosclerosis, fibrocellular/fibrous crescents, and interstitial inflammation and fibrosis (56, 73), raising the possibility that, in addition to acute inflammatory injury, MCP-1/CCL2 may facilitate renal fibrosis (72). However when interstitial fibrosis was analyzed as a function of uMCP-1, there was no correlation (56, 83). Finally, in addition to these traditional histologic evaluations, a correlation between uMCP-1 and renal monocyte infiltration, especially in the interstitial compartment, has been described (56, 74), although even this is not a consistent finding (57). Considering all of these data together, uMCP-1 does appear to reflect glomerular and interstitial inflammatory injury. Furthermore, uMCP-1 seems to correlate better with the types of pathologic processes present in the kidney as opposed to the class of glomerulonephritis. The question of MCP-1 involvement in renal fibrosis remains open (see 4.6).

Less information is known regarding the association of uIL-8 and kidney injury. However, uIL-8 expression was exclusively found in inflammatory lupus glomerulonephritis (class III and IV) as opposed to non-inflammatory class V glomerulonephritis (57, 66). Urine IL-8 also appeared to correlate with glomerular leukocyte (type not specified) infiltration (66).

For completeness, it should be mentioned that MIP-1 alpha/CCL3 has also been measured in the urine of patients with lupus nephritis (56). Two of 20 patients had increased levels of uMIP-1 alpha, and these were both class IV glomerulonephritis. This study looked at uMIP-1 alpha in assorted types of crescentic glomerulonephritis, and found that uMIP-1 alpha correlated with cellular crescents and glomerular monocytes, but not interstitial lesions.

4.4. Urine expression of chemokine mRNA in human SLE nephritis

In a complementary approach to measuring immunoreactive chemokines in the urine of lupus patients, several groups examined chemokine mRNA levels in the

urine sediment of patients with SLE nephritis (83-86). For MCP-1/CCL2 these data are, in general, consistent with the urine chemokine protein data. The mRNA studies also showed that RANTES/CCL5 and IP-10/CXCL10, chemokines that are highly relevant to murine lupus (see Section 3), may also be involved in human lupus nephritis.

Patients with active SLE nephritis showed significantly greater uMCP-1 and uRANTES mRNA levels than patients with inactive nephritis, patients with inactive nonrenal SLE, and healthy controls (83, 84). Interestingly, chemokine mRNA levels in the urine of renal SLE patients in remission were higher than that of nonrenal SLE patients. Following steroid treatment with or without cytotoxic agents, uMCP-1 mRNA fell by weeks 12-24, and paralleled the decline in nephritis activity (85). Urine MCP-1 and uRANTES mRNA correlated with the renal SLE disease activity index (SLEDAI), proteinuria, and inversely with estimated glomerular filtration rate (a modest association at best). A correlation of uMCP-1 mRNA and histologic activity was noted, but there was no relationship between uMCP-1 mRNA and crescents, leukocyte infiltration, interstitial inflammation, or renal scarring (83). Urine RANTES mRNA did not correlate with any histologic measurements or renal scarring (84). When uRANTES mRNA was measured prospectively, receiver-operating characteristic (ROC) analysis found it to be a poor predictor of renal flare. Although the exact cellular source of chemokine RNA in the urine sediment is not known, most of the cells in sediment are renal tubular epithelial cells, with leukocytes making up only 27% of the sediment (84). The majority of the leukocytes were T lymphocytes; macrophages were about 10-fold less.

A very interesting study examined uIP-10 mRNA and mRNA for its receptor CXCR3 as potential biomarkers to non-invasively differentiate between class IV SLE nephritis and all other classes of glomerulonephritis (86). Urine IP-10 and CXCR3 mRNA was found to be higher two weeks before renal biopsy in patients with class IV nephritis compared to patients with class II, III, and V nephritis. Healthy controls did not have measurable amounts of uIP-10 or uCXCR3 mRNA. At the time of urine collection for chemokine measurement, patients had been on moderate doses of steroids for at least one month. Patients with class IV nephritis were then treated with steroids plus a cytotoxic agents (cyclophosphamide or MMF), and uIP-10 and uCXCR3 mRNA was measured prospectively every month for 5 months. Ten responders showed a steady decline in the mRNA levels, while 4 non-responders showed a tendency for the urine chemokine mRNA levels to increase over time. Each non-responder was re-biopsied, confirming a worsening of the glomerulonephritis.

ROC analysis was used to calculate the sensitivity and specificity of uIP-10 and uCXCR3 mRNA to distinguish class IV from other lupus nephritis classes. The optimal mRNA level cut points were associated with sensitivities/specificities for uIP-10 and uCXCR3 of 73%/94% and 65%/83%, respectively (86). These values were far better than those of other potential markers, including proteinuria, hematuria, leukocyturia, SLEDAI, and creatinine clearance.

4.5. Chemokine genetics in human SLE nephritis

An individual's genetic background may influence the severity of their inflammatory response to the accumulation of immune complexes in the kidney. Chemokine gene polymorphisms may contribute to an inflammatory genotype that, along with other pro-inflammatory cytokine polymorphisms, determines lupus nephritis phenotype. We identified an *MCP-1/CCL2* distal regulatory region single nucleotide polymorphism (SNP, A-2518G) that affects gene transcription and MCP-1/CCL2 protein levels (87). The G allele was associated with higher cytokine-induced MCP-1/CCL2 production by normal peripheral blood mononuclear cells (PBMC) *in vitro* (87), and spontaneous or lipopolysaccharide-induced MCP-1/CCL2 production by PBMC from SLE patients (82).

The A-2518G *MCP-1/CCL2* SNP has been evaluated as a susceptibility factor for SLE nephritis with conflicting results. One investigation found that the G allele frequency was significantly higher in SLE patients compared to healthy individuals (32 vs. 17%), and that among SLE patients, the frequency of the G allele (48 vs. 23%) was higher in those with lupus nephritis (82). These patients were mainly European American or African American. In contrast, there was no difference in genotype distribution between controls and SLE patients of Asian origin, with or without SLE nephritis (88). Similarly, *MCP-1/CCL2* genotype was not found to be associated with lupus or lupus nephritis in Spanish SLE patients (89, 90).

Other chemokine variants have shown similar conflicting results when analyzed as risk factors for SLE nephritis. For example, two promoter polymorphisms in the *RANTES/CCL5* gene (C-28G, G-403A) that affect RANTES/CCL5 expression were examined. One study found no association of either SNP with SLE nephritis in 46 Chinese lupus patients, 26 of whom had nephritis (88), while a second study showed that the frequency of -403G was significantly higher (by 14%) in 34 patients with renal lupus out of a cohort of 146 total patients (91). This was not an expected result, given the observation that -403A has been associated with increased *RANTES/CCL5* promoter activity (92). In contrast, no association of *RANTES/CCL5* -403G or A and nephritis was found in a Spanish cohort of 500 SLE patients, of whom 37% had renal involvement (93). Polymorphisms in the chemokine receptors CCR2 and CCR5 were not found to contribute to SLE susceptibility in a Spanish cohort, but a 32 base-pair deletion variant of CCR5 was found more frequently in patients with biopsy-proven nephritis compared to patients without renal SLE (93). Again, this is not an expected result, as the CCR5 deletion variant has been shown to be protective against acute allograft rejection and to enhance allograft survival in kidney transplant recipients (94, 95).

The discrepant outcomes of all of these studies may be attributed to small sample sizes for genetic analyses, ethnic differences, or other unknown population stratification effects. However, it is not necessarily

surprising that genetic variants of inducible chemokines do not influence overall risk for SLE nephritis, because these chemokines are probably not involved in the development of autoimmunity per se (see Section 3.2). It is more likely that chemokine variants will affect the severity of kidney inflammation in patients with SLE and renal involvement. The studies that examined genotype as a risk factor for SLE nephritis did not use kidney histology to stratify patients by the level of inflammation. To address this question the *in vivo* effects of *MCP-1/CCL2* -2518G on renal leukocyte infiltration were examined in patients with class IV SLE nephritis. CD68+ monocytes/macrophages and CD3+ T lymphocytes were counted in kidney biopsies from patient segregated by their *MCP-1/CCL2* genotype (96). There was a significant increase in CD68+ interstitial cells in patients (n=10) who had at least one G allele at position -2518 compared to patients (n=12) who were AA homozygotes (9.2±3 vs. 1.3±1.1 cells/high power field, $P<0.015$), and a trend toward more glomerular CD68+ cells (11.1±3 vs. 5.8±2.6 cells/glomerulus). There were no differences in CD3+ cells between genotypes. Interestingly, uMCP-1 levels were significantly higher in patients with a G allele than AA homozygotes (82). Furthermore, a SNP in the *IL-8/CXCL8* gene regulatory region (T-845C) was highly correlated with severe (class IV) SLE nephritis in African American lupus patients (97). The odds of having *IL-8/CXCL8* -845C were approximately ninefold higher in patients with class IV nephritis than in patients with non-class IV nephritis (97). These data suggest that the most promising use of chemokine genotyping may be to predict the degree of kidney inflammation that can be expected during renal flare, and who may benefit most from anti-chemokine therapies as they are developed.

4.6. Non-inflammatory actions of chemokines

Chemokines appear to have effects besides recruitment of leukocytes to the kidney, some of which may contribute to renal injury, while some may be beneficial. As discussed in 4.3, MCP-1/CCL2 may be involved in promoting renal fibrosis. While this may be a consequence of MCP-1/CCL2-induced inflammation, *in vitro* studies showed that MCP-1/CCL2 upregulated pro-collagen expression by cultured fibroblasts and CD14+ monocytes, presumably through the induction of transforming growth factor-beta 1 (98, 99). In contrast, the ligand-receptor pair IP-10/CXCL10 and CXCR3 appear to attenuate fibrosis, at least in pulmonary and cardiac tissue (100, 101).

IP-10/CXCL10 and CXCR3 may also regulate intrinsic kidney cell proliferation in autoimmune disease. Human mesangial cells proliferate in response to IP-10/CXCL10 *in vitro*, and in IgA nephropathy, an immune complex glomerulonephritis that targets the mesangium, CXCR3 was strongly expressed by mesangial cells (102). The consequences of chemokine-induced proliferation remain to be determined. A limited increase in mesangial proliferation could enhance immune complex clearance from the glomerulus, however a sustained increase in glomerular cellularity seems to impair glomerular function (103, 104)

5. ENDOGENOUS REGULATION OF THE CHEMOKINE NETWORK IN SLE NEPHRITIS

To prevent uncontrolled inflammation, the chemokine network is almost certainly regulated by endogenous anti-inflammatory systems. To date, such regulatory systems have received little attention, especially in the context of SLE nephritis. If chemokine activity is attenuated by endogenous anti-inflammatory networks, defects in these networks could lead to unchecked kidney inflammation in response to immune complex deposition. The following sections summarize our initial efforts at identifying endogenous regulators of chemokine activity.

5.1. Cyclopentenone prostaglandins and the Nrf2 pathway

The effect of J-series cyclopentenone prostaglandins on MCP-1/CCL2 production by human kidney mesangial cells was investigated. J-series prostaglandins are derived from prostaglandin D_2 (PGD2) through a series of dehydration steps that eventually lead to 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15dPGJ2) (105). J-series prostaglandins were studied because there is evidence they are made in the kidney (106, 107), they were shown to block induction of the pro-inflammatory transcription factor nuclear factor-kappa B (NF-κB), which has been implicated in chemokine gene activation (108-110), and they are natural agonists of peroxisome proliferator-activated receptor-gamma, a nuclear hormone receptor that has significant anti-inflammatory activities (111-115). A link between J-series prostaglandins and SLE nephritis was suggested by a study that showed MRL-*Fas*^{lpr} mesangial cells did not appropriately increase production of PGJ2 in the presence of IL-1β (106), indicating a possible defect in SLE that favors a dysregulated inflammatory response. We, and subsequently others found PGJ2 and 15dPGJ2 were potent inhibitors of IL-1β-induced MCP-1/CCL2 expression (116, 117). In contrast to its effects on MCP-1, 15dPGJ2 induced IL-8/CXCL8 production in various cell types (117-119), an observation that on the surface appears to be inconsistent with a strictly anti-inflammatory role for 15dPGJ2, but may be reconcilable (see below). The *in vivo* role of 15dPGJ2 remains elusive because it is difficult to measure. Nonetheless, a PGJ2 metabolite has been identified in the urine of normal individuals, but women produce less than men, a particularly intriguing finding in light of the higher incidence of SLE in women (107).

Further evaluation of the effects of 15dPGJ2 on mesangial biology identified a pathway with significant relevance to SLE. Briefly, we found that 15dPGJ2 induced heme oxygenase-1 (HO-1) in human mesangial cells by activating the transcription factor Nrf2 (120). Nrf2 responds to environmental stress by initiating a cell-defense gene program (121). Genes known to be Nrf2-dependent typically contain a *cis*-acting DNA regulatory sequence called the antioxidant response element (122-124), and include glutathione-S-transferase, gamma-glutamylcysteine synthase, HO-1, glutathione peroxidase and thioredoxin (121). Besides controlling genes that defend cells against chemical and oxidant damage, emerging evidence suggests that the Nrf2 pathway mitigates inflammation and

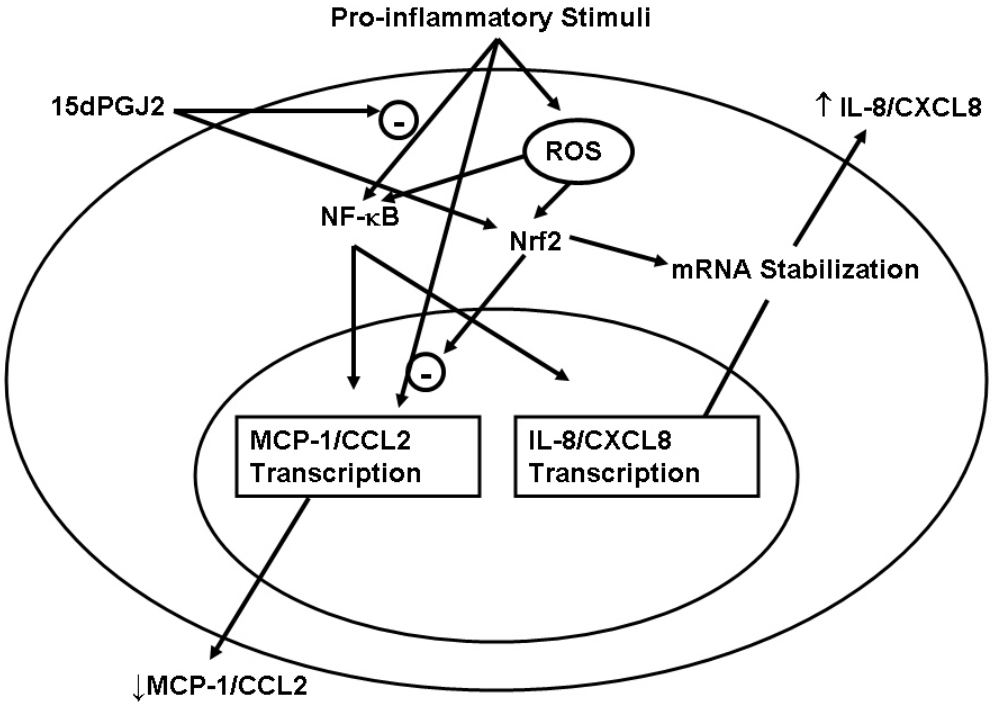

Figure 2. Interactions between cyclopentenone prostaglandins, the Nrf2 pathway, and chemokines. Pro-inflammatory stimuli activate the transcription factor NF-κB which can induce MCP-1/CCL2 and IL-8/CXCL8 gene transcription. NF-κB activation can be blocked by cyclopentenone prostaglandins such as PGJ2 and 15dPGJ2. Pro-inflammatory stimuli can activate the transcription factor Nrf2 by inducing oxidative stress (ROS; reactive oxygen species), and 15dPGJ2 can activate Nrf2 by modifying intracellular thiols. Nrf2 blocks MCP-1/CCL2 gene transcription through an unknown mechanism, but increases IL-8/CXCL8 levels by stabilizing its mRNA. The implications of this discordant chemokine response are discussed in the text.

maintains immune tolerance. Nrf2 deficient mice had significantly more pulmonary inflammation after hyperoxic and bleomycin-induced lung injury than wild-type animals (125, 126), and demonstrated prolonged inflammation during cutaneous wound healing (127) and carrageenan-induced pleurisy. Most important for SLE and SLE nephritis, aged Nrf2-deficient female mice developed an SLE-like autoimmune disease, characterized by circulating anti-nuclear and anti-double stranded DNA antibodies and severe glomerulonephritis (128, 129).

Because disruption of the Nrf2 pathway impaired the resolution of inflammation, and given the central role of chemokines in mediating inflammation, the possibility that Nrf2 could attenuate chemokine expression was investigated. Activation of the Nrf2 pathway in human mesangial cells, microvascular endothelial cells, and various cell lines did not affect baseline MCP-1/CCL2 production, but blocked cytokine-induced MCP-1/CCL2 production (130). Unexpectedly, Nrf2 activation significantly enhanced IL-8/CXCL8 mRNA expression and protein production (131). These interactions are summarized in Figure 2. An increase in IL-8/CXCL8 expression is not consistent with an anti-inflammatory role for Nrf2, if IL-8/CXCL8 is considered as only a pro-inflammatory mediator. However, there are data that challenge this conventional wisdom. For example, IL-8/CXCL8 can suppress neutrophil adhesion to activated endothelium (132, 133), and block neutrophil emigration to sites of inflammation (133-135). Additionally, the endothelial isoform of IL-8/CXCL8 appears to have tissue-protective effects, such as mediating normal wound healing, decreasing scar formation, promoting tissue remodeling through endothelial proliferation, protecting myocardium during ischemia-reperfusion injury, and maintaining normal glomerular architecture (58, 136-138). Interestingly, although neutrophils are not a major source of IL-8/CXCL8 (139), neutrophils from patients with active SLE demonstrate a defect in IL-8/CXCL8 production (140). These findings suggest the role of IL-8/CXCL8 in lupus renal flare is more complex than simply promoting inflammation.

The Nrf2 pathway may thus have dual roles in SLE. By preventing oxidative damage to DNA and other cellular antigens, Nrf2-dependent genes may contribute to the maintenance of tolerance (129). In the setting of clinical autoimmunity, the Nrf2 pathway may down-regulate the (renal) inflammatory response to immune complex deposition, in part because Nrf2 activation blocks the expression of chemokines such as MCP-1/CCL2, and possibly other pro-inflammatory factors. The induction of IL-8/CXCL8 by Nrf2 is paradoxical in this model, and requires either a paradigm shift away from a strictly proinflammatory role for IL-8 in SLE nephritis, or indicates that other, presently unknown gene products activated by Nrf2 antagonize the actions of IL-8.

5.2. Adiponectin

Adiponectin, a 30 kDa adipocyte-derived cytokine, was identified as one of the most highly expressed cytokines in the urine of patients with active SLE nephritis during a survey of the urine proteome with an immobilized antibody array (141). Adiponectin was evaluated as a potential biomarker for renal SLE. Urine levels varied with the renal flare cycle, and plasma levels were higher in patients with renal SLE than healthy individuals or patients with nonrenal SLE (141). Among lupus nephritis patients, mean plasma levels at renal flare were highest in those with class III and IV nephritis, as opposed to those with non-inflammatory, class V disease. Adiponectin is associated mainly with metabolic disorders such as obesity and diabetes mellitus (142-145), although an emerging literature suggests that adiponectin has anti-inflammatory and vasoprotective properties (143, 146-149). We thus postulated that adiponectin may be an endogenous regulator of chemokine expression. To the contrary, we found that full-length human recombinant adiponectin actually increased IL-8/CXCL8 and MCP-1/CCL2 production by microvascular endothelial cells and PBMC (150). Other investigators showed a similar induction of chemokines and pro-inflammatory cytokines by adiponectin in various tissue (151-155). Furthermore, urine adiponectin levels significantly correlated with uMCP-1 levels during lupus renal flare (150). The observation that adiponectin has pro- and anti-inflammatory effects may be reconciled by the finding that high molecular weight isoforms of adiponectin appear to be pro-inflammatory, whereas low molecular weight isoforms appear to be anti-inflammatory (155-157). The exact role of adiponectin in lupus nephritis remains to be worked out. However, the presence of both low and high molecular weight isoforms in the kidney, along with the expression of specific adiponectin receptors by glomerular epithelial cells ((141), Rovin, et. al., American Society of Nephrology Meeting, 2006), suggests that the intra-renal balance of high and low molecular weight adiponectin could modulate chemokine expression during SLE nephritis.

6. SUMMARY AND PERSPECTIVE

In summary, murine models suggest that only a subset of chemokines and chemokine receptors are expressed in the kidney during SLE nephritis. Blocking the activity of specific chemokines, or interfering with receptor-ligand interactions in these models provides proof that individual chemokines and chemokine receptors are involved in the pathogenesis of glomerular and interstitial inflammation and renal dysfunction during lupus. The finding that antagonizing the chemokine network is effective even after experimental lupus nephritis is established supports the premise that chemokine-directed therapies will be clinically effective in treating human SLE nephritis. These intervention studies also show that inhibiting a single chemokine or receptor does not completely abrogate renal injury (Table 2). It is conceivable that blocking more than one chemokine or receptor will increase efficacy, especially since the murine data indicate that individual chemokines may target specific intrarenal compartments. Finally, manipulating the inducible chemokine system does not appear to shut down autoimmunity or the initiation of immune complex renal injury. It is thus likely that chemokine-based therapies will have a role in treating renal inflammation and attenuating progressive renal injury, but will need to be used in conjunction with therapies that cause remission of SLE. A caveat is the possibility that inhibition of certain constitutive chemokines, which may actually be inducible in the context of SLE, can cause remission of autoimmunity.

Considering human lupus nephritis, there is ample circumstantial evidence that the chemokine network is involved in disease pathogenesis. Association studies place specific chemokines and chemokine receptors in the kidney during active inflammation, and show that chemokine levels or expression parallel disease activity and reflect renal injury. The subset of chemokines and chemokine receptors found in human SLE overlaps with the subset found in murine models, and shows a similar tendency toward compartmentalization of expression. Despite an absence of chemokine-directed intervention studies in clinical lupus, the similarities between human and experimental lupus nephritis with respect to the chemokine network provide further reassurance that the network does play a pathogenic role in human SLE. Measurement of urine chemokines appears to represent intra-renal events better than serum measurements, and urine chemokine levels may be useful biomarkers for following the clinical course of SLE nephritis, and predicting disease flares and outcomes. Urine chemokines may be especially useful as biomarkers for deciding who to treat with chemokine/chemokine receptor antagonists, and monitoring the efficacy of this treatment.

The challenge in targeting the human chemokine system therapeutically in lupus nephritis will be to choose which chemokines and chemokine receptors to antagonize, and how to time chemokine-directed interventions to the state of the disease. For example, certain chemokine or chemokine receptor antagonists may be more effective during acute severe inflammatory injury resulting in crescentic glomerulonephritis, while others may be more important in treating progressive kidney disease due to chronic interstitial (and possibly glomerular) inflammation. Antagonizing MCP-1/CCL2 or it receptor CCR2 is an obvious choice given all the information available on this receptor-ligand pair. Other high-yield targets in terms of therapeutic potential include MIP-1 alpha/CCL3, MIP-1 beta/CCL4, RANTES/CCL5, IP-10/CXCL10, and their receptors. Antagonists of these chemokines and receptors may be used most effectively in conjunction with an antagonist of the MCP-1/CCL2-CCR receptor-ligand pair, to more thoroughly cover the interstitial as well as glomerular compartment, and more effectively block T lymphocyte infiltration. Blocking fractalkine/CX3CL1 or CX3CR1 should also be considered given its effectiveness in murine lupus, the fact that fractalkine/CX3CL1 may function as a general leukocyte adhesion molecule, and the promiscuous expression of CX3CR1 on macrophages and T cells throughout the kidney. Chemokine blockade is expected to result in less generalized immunosuppression

than standard therapies because only specific leukocyte subsets will be targeted, and because local, intrarenal chemokine expression may be more relevant than systemic expression.

Other considerations must be taken into account when working with the chemokine network. First, some of the non-inflammatory actions of chemokines may be beneficial, such as the potential attenuation of fibrosis by IP-10/CXCL10. Therefore, while an IP-10/CXCL10 antagonist may be useful early in active lupus nephritis, prolonged use may be undesirable, especially in chronic, progressive disease. Additionally, antagonism of the chemokine network may be achievable by manipulating endogenous chemokine regulatory pathways. This may provide therapeutic benefit with less overall immunosuppression. Finally, the role of constitutive chemokines in human lupus nephritis deserves further investigation given the possibility that these chemokines may affect not only inflammation, but also autoimmunity.

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Abbreviations: SLE : systemic lupus erythematosus ; NZB/W : New Zealand Black/New Zealand White ; IL-1 : interleukin-1 ; TNF : Tumor necrosis factor ; IFN : interferon ; MCP-1: monocyte chemoattractant protein-1; IL-8: interleukin-8; uMCP-1: urine MCP-1; uIL-8: urine IL-8; SNP: single nucleotide polymorphism; PGD2: prostaglandin D_2; 15dPGJ2: 15-deoxy-$\Delta^{12,14}$-PGJ_2 ; HO-1: Heme oxygenase-1

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