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Chemokines in lupus nephritis

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1. ABSTRACT

Lupus nephritis is a common solid organ manifestation of systemic lupus erythematosus (SLE). The disease is tightly linked to the production of autoantibodies and circulating immune complexes, i.e. immune complex glomerulonephritis. In this process chemokines mediate multiple biological effects, e.g. orchestrating proinflammatory microenvironments, the recruitment of immune cell subsets into the kidney, as well as the local activation of such immune effector cells. Autoimmune mice with targeted deletions of certain single chemokines or chemokine receptors are protected from renal autoimmune tissue injury. Interventional studies with specific antagonists against certain chemokines and chemokine receptors further support these findings. In this review we summarise the available experimental and human data on the expression and functional role of chemokines and chemokine receptors in lupus nephritis.

2. INTRODUCTION TO LUPUS NEPHRITIS

Systemic lupus erythematosus (SLE) is a paradigmatic disease characterized by systemic autoimmunity against multiple ubiquitous autoantigens (1). Systemic autoimmunity, identified by and the presence of autoantibodies against lupus autoantigens, is a rather common phenomenon while solid organ autoimmune tissue injury affects only a small percentage of individuals with autoimmunity (1). For the understanding of lupus manifestations it is helpful to distinguish between the evolution of autoimmunity, i.e. loss of tolerance against distinct autoantigens, and the mechanisms of autoimmune tissue injury. In fact, many data suggest that clinical lupus is often a combination of immune dysregulation at multiple levels. While data on the role of chemokines for the phase of induction of autoimmunity are mostly lacking, chemokines appear to be of major importance for the initiation and progression of autoimmune tissue injury, i.e. tissue inflammation (2).

Table 1. Classification of lupus nephritis

I	Minimal mesangial lupus nephritis	Normal glomeruli (light microscopy), mesangial immune deposits (immunofluorescence) mesangial immune deposits (immunofluorescence or electron microscopy)
II	Mesangial proliferative lupus nephritis	Mesangial hypercellularity or mesangial matrix expansion (light microscopy), with
III	Focal lupus nephritis	Endo- or extracapillary immune complex glomerulonephritis (<50% of glomeruli) (A) active lesions (proliferation), (C) chronic inactive lesions with glomerular scars (A/C) active and chronic lesions (proliferation and sclerosis)
IV	Diffuse lupus nephritis	Endo- or extracapillary glomerulonephritis (>50% of glomeruli) S (A) segmental proliferative, G (A) global proliferative lupus nephritis S (A/C) active and chronic lesions S (C) segmental inactive lesions with scars, G (C) global inactive lesions with scars
V	Membranous lupus nephritis	Linear subepithelial immune complexes, may occur in combination with class III or IV
VI	Advanced sclerosis lupus nephritis	>90% of glomeruli globally sclerosed without residual activity

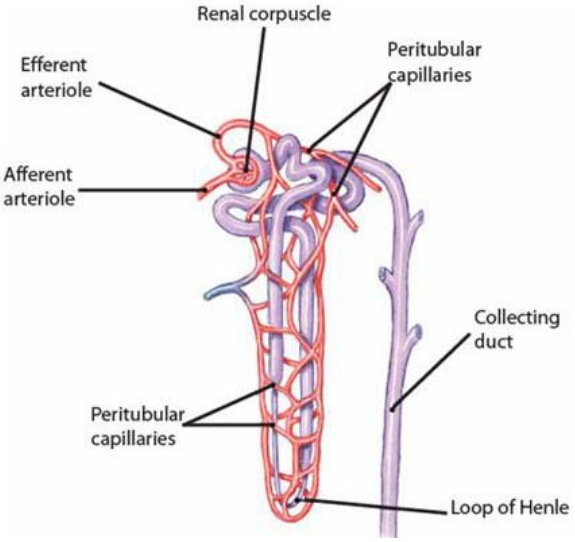

Figure 1. Compartments and Capillary network of Kidney. It can be divided as high shear-stress and high permeability glomerular capillaries (renal corpuscle) and the low shear-stress peritubular microcirculation.

Lupus nephritis (LN) affects 30% of all SLE patients. LN presents in different shapes which are distinguished by defined histopathological criteria of glomerular pathology (Table 1) (3). Particularly, diffuse proliferative LN and membranous LN represent major complications of SLE which, if not aggressively treated, remain associated with significant morbidity and mortality. Although the classification of LN is defined by the glomerular pathology, LN is not restricted to the glomerular renal compartment and progression to end-stage kidney disease is always associated with significant tubulointerstitial damage and fibrosis. Tubulointerstitial injury LN often develops secondary to glomerular immune complex deposition but immune complex deposits are mostly also found in peritubular capillaries. However, in LN glomerular pathology is always present, hence, as markers of damage to the glomerular filtration barrier, proteinuria and hematuria are important diagnostic signal of LN and are regularly checked in SLE patients. At the time when proteinuria and hematuria develop as a clinical sign of LN, antinuclear antibodies and autoantibodies against dsDNA or other nucleoproteins are usually present. Histologically, the recruitment of macrophages, T cells, and B cells becomes a major feature of proliferative LN, supporting the concept that renal leukocyte recruitment is of major importance for the persistence and progression of renal pathology and dysfunction.

3. CHEMOKINE EXPRESSION IN LUPUS NEPHRITIS

In the kidney, all types of glomerular cells, i.e. endothelial cells, podocytes, and mesangial cells or cells of the tubulointerstitial compartment, i.e. the different types of tubular epithelial cells or interstitial fibroblasts, can produce inflammatory chemokines (4). Immune complexes, complement activation, reactive oxygen species, cytokines, angiotensin II, and pathogen-associated molecules such as lipopolysaccharide are common triggers for the production of proinflammatory chemokines in renal cells (5). The functional importance of local chemokine release for compartment-specific(Figure-1) tissue damage became evident from animal studies with predominant glomerular or tubulointerstitial pathology.

3.1. Observations from animal studies

CCL2/MCP-1 and CCL5/RANTES are exclusively produced within glomeruli in acute glomerulonephritis (5). By contrast, their expression is confined to tubular epithelial cells and interstitial leukocyte infiltrates in tubulointerstitial disease secondary to obstructive nephropathy (6). As mentioned above, in advanced LN usually both compartments are affected by autoimmune tissue inflammation, hence, proinflammatory chemokines are produced in both diseased compartments (7). Generally, the spatial expression of chemokines correlates with a local accumulation of chemokine receptor-positive leukocytes (5-7). Chemokines are involved in the initiation as well as the progression of LN (8). Chemokine expression usually precedes the infiltration of leukocytes and renal damage (5-7). Attenuation of the renal chemokine production precedes the resolution of the inflammatory process (5). However, when local chemokine expression is maintained or enhanced by additional inflammatory stimuli, e.g. by ligating Toll-like receptors with microbial products, additional recruitment and activation of leukocytes can cause an accelerated progression of the preexisting renal disease (9-12) (Figure-2).

Mouse strains that spontaneously develop lupus-like autoimmune disease are mostly used to study LN. These include MRL/MpJ-*fas*^{l}(MRL/lpr) mice and NZB mice crossed with NZW mice (NZB/NZW) (13). Both of these mouse strains are characterized by the production of

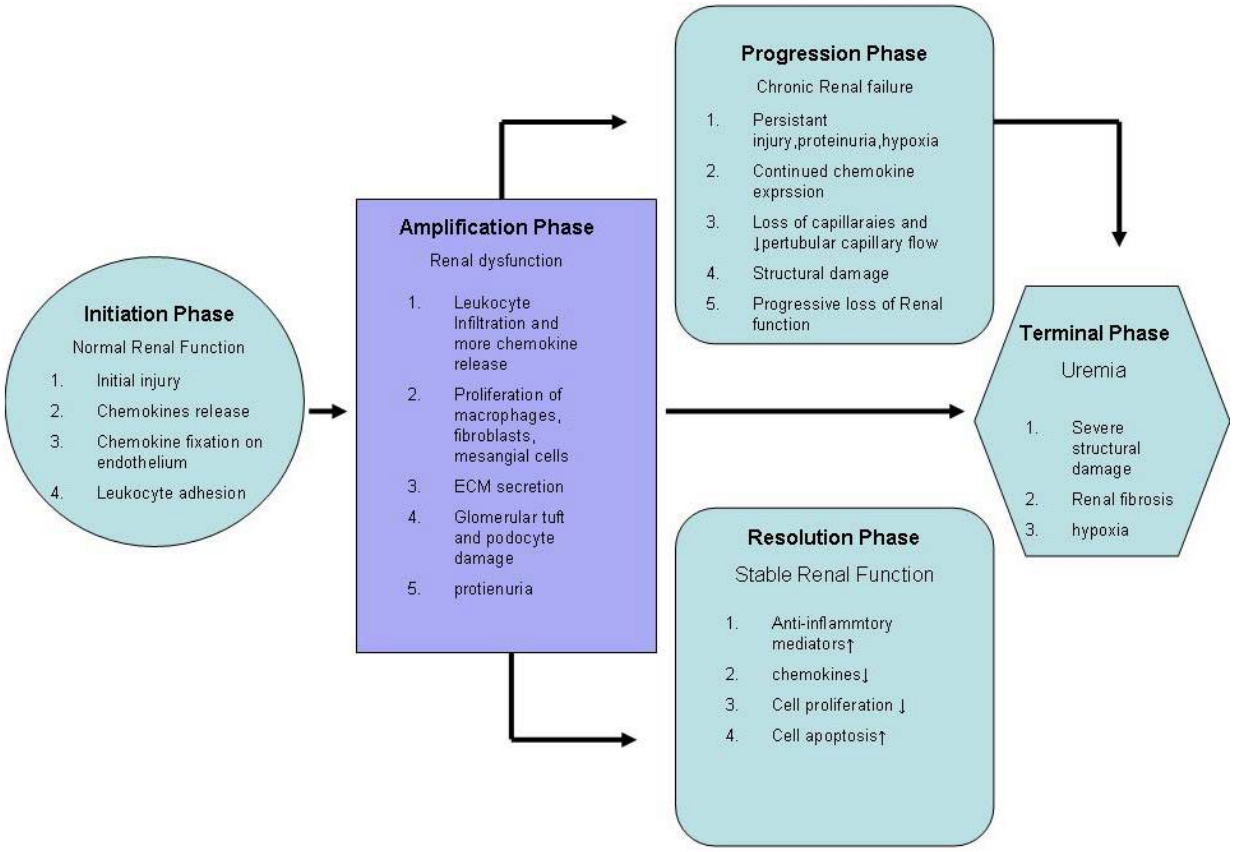

Figure 2. Proposed model of chemokine involvement in progressive renal disease and fibrosis. Initiation phase: Intrinsic renal cells secrete chemokines upon immunologic, toxic, ischemic or mechanical injuries. Adhesion molecules and chemokines on endothelial cells of glomerular or peritubular capillaries supports leukocyte arrest and transmigration either into the mesangium or the interstitial space. At this stage rennal function parameters may still be normal. Amplification phase: Infiltrating leukocytes release lipid mediators, cytokines, and chemokines causing glomerular and/or tubulointerstitial inflammation which results in hematuria, leukocyturia, and proteinuria. Proinflammatory and profibrotic cytokines stimulate the proliferation of mesangial cells in the glomerulus and of interstitial fibroblasts in the interstitium. Upon stimulation activated mesangial cells and interstitial fibroblasts increase the synthesis of extracellular (EC) matrix components. Leukocyte infiltration, fibroblast proliferation, matrix deposition as well as edema will increase the interstitial volume. In this phase renal dysfunction is almost always overt and may cause clinical symtpoms and laboratory abnormalities. Progression phase: Although the initial stimulus may have already subsided the structural damage of acute inflammation may have become irreversible. Focal glomerulosclerosis with misdirected filtration and proteinuria maintains a persistent signal for tubular epithelial cells to release chemokines into the interstitium. Overspill of locally secreted cytokines and chemokines also supports downstream inflammation of the renal interstitium. Massive increase of the interstitial volume and destruction of perutubular capillaries supports renal ischemia leading to tubular atrophy, secondary glomerulosclerosis, and progressive renal dysfunction. In this phase a progressive decline of renal function is evident and may cause multiple problems to the patient. End stage renal disease: Continuous destruction of the peritubular capillary network and tubular segments further support renal ischemia which is a strong stimulus for fibroblast proliferation and matrix synthesis via autocrine mechanisms. Myofibroblasts support tissue contraction up to the ultimate stage, the end-stage shrunken kidney. Uremia will ultimately cause death unless renal replacement therapy is initiated.

autoantibodies against nuclear autoantigens, glomerular immune complex deposition, local complement activation and subsequent renal leukocyte recruitment. Renal pathology in these mice progresses to end-stage renal disease within 6-10 months of age(14).

MRL/lpr mice up-regulate a limited number of chemokines and chemokine receptors during progressive LN. CCL2/MCP-1, CCL4/MIP-10, CCL5/RANTES and CXCL10/IP-10 were induced amongst nine proinflammatory chemokines (7). Immunostaining and *in situ* hybridization localized CCL2/MCP-1 and CCL5/RANTES to glomeruli, tubular epithelial cells and interstitial mononuclear cell infiltrates in kidneys of MRL/lpr mice (7, 15). This was consistent with an increased expression of CCL2/MCP-1 in intrinsic glomerular cells, tubular epithelium and infiltrating mononuclear in NZB/NZW mice (16). The expression pattern of chemokine receptors was consistent with this pattern of chemokines. In MRL/lpr mice the expression of CCL2/MCP-1, CCL4/MIP-10, and CCL5/RANTES were associated with their respective chemokine receptors

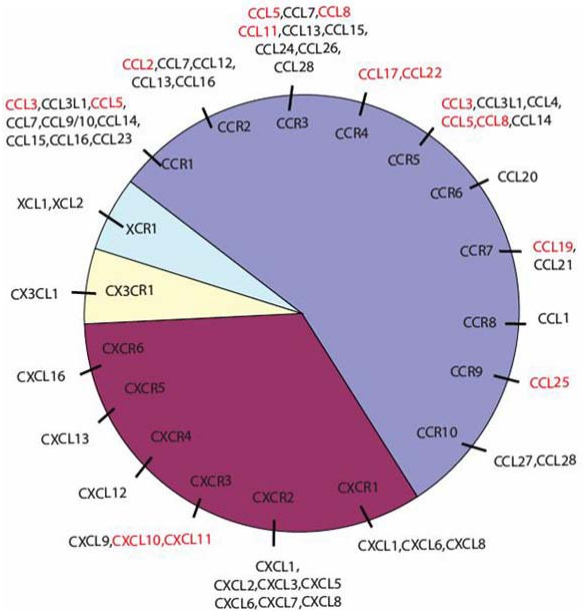

Figure 3. Classification of chemokines. depending on the relative position of the first two cysteines, chemokines are divided into CC, CXC, C, and CX3C subfamilies, and their receptors as CCR,CXCR,CR.and CX3CR respectively.

CCR1, CCR2, and CCR5 on infiltrating mononuclear leukocytes, and could not be detected in intrinsic renal cells (7, 17, 18). Regarding the temporal expression the chemokines antedated the expression of their receptors consistent with the hypothesis that local chemokine expression represents an early signal which is followed by the spatial recruitment of leukocytes. In fact, chemokine receptor positive leukocytes co-localized with sites of chemokine expression and tissue damage (7). Additional triggers of intrarenal chemokine production such as local activation of toll-like receptors is associated with increased leukocyte recruitment and an accelerated progression of LN (9-12). Thus, chemokines do not only mediate the initiation of LN, but also the progression of renal damage including disease exacerbations triggered by ligands to Toll-like receptors of viral or bacterial origin.

A pathogenetic role for chemokines in lupus is also supported by a genome-wide mRNA expression analysis in spleens and kidneys of lupus-prone MRL/lpr mice. The CXCR3 ligands, CXCL9/MIG and CXCL10/IP-10, were induced early in the spleens, and CXCL10/IP-10 in nephritic kidneys (19). Interestingly, both chemokine genes are located at known lupus susceptibility loci of MRL/lpr mice (19). In addition to their role in leukoycte recruitment CXCL9/MIG and CXCL10/IP-10 can trigger Th1 responses, a characteristic feature of LN. Furthermore CXCL10/IP-10 may also have non-inflammatory functions in mediating glomerular injury.

3.2. Observations From Human Studies:

Human mesangial cells proliferate in response to CXCL10/IP-10 and express a CXCR3-related receptor (20,21), indicating a role for this chemokine in mediating mesangioproliferative glomerular lesions. Human renal biopsy studies confirm the expression of chemokines and chemokine receptors in LN (21-26). Laser-capture microscopy allows to perform transcriptional phenotyping of glomerular isolates from such biopsies. Using this technology the inflammatory chemokines CCL2/MCP-1 and CCL3/MIP-10 were found to be abundantly expressed in nephritic glomeruli (27). In addition, levels of chemokines like CCL2/MCP-1, CCL3/MIP-10, CCL5/RANTES, CXCL10/IP-10, and CXCL12/SDF1 are elevated in the serum and urine of patients with active disease (26,28-30). Generally, SLE patients show increased expression of CCR1 and CXCR2 on T cells but patients with renal involvement show also increased surface expression of CCR3 and CXCR3 (31).

4. CHEMOKINE-MEDIATED RENAL PATHOLOGY IN LUPUS NEPHRITIS

The functional significance of proinflammatory chemokines for the pathogenesis of kidney disease have been identified by blocking chemokine activity with neutralizing antibodies, chemokine receptor antagonists, and targeted disruption of chemokine and chemokine receptor genes in experimental models of glomerulonephritis (32,33).

4.1. Observations from animal studies

The proinflammatory CC chemokine CCL2/MCP-1, a major monocyte/macrophage chemoattractant, and its receptor CCR2 were identified as important mediators of glomerular leukocyte infiltration and injury in experimental glomerulonephritis (34-38). Furthermore, two CCL5/RANTES antagonists, amino-(AOP)-RANTES and Met-RANTES, both blocking the binding of CCL5/RANTES to its macrophage- and T-cell-expressed receptors CCR1, CCR3 and CCR5, have been demonstrated to reduce glomerular macrophage recruitment in rodent studies (38,39). The proinflammatory CC chemokines are not exclusive in mediating glomerular leukocyte recruitment. Additional experimental evidence suggests that CXC chemokines, including CXCL1/MIP-2, the CXC chemokine receptor CXCR2, the CX_3CL1/fractalkine receptor CX_3CR1, and the CC chemokine CCL22/MDC are relevant mediators of glomerular leukocyte accumulation and injury in glomerulonephritis (40-46). Blocking chemokines or their chemokine receptors(Figure.3) is not always associated with improved outcomes. In fact, blocking chemokines can also exacerbate glomerulonephritis. For example, when mice lacking CCR2 were subjected to nephrotoxic serum nephritis, proteinuria and glomerular pathology became worse, despite reduced glomerular macrophage infiltration (47). From these data is was suggested that targeting CCL2/MCP-1 and CCR2 in acute glomerulonephritis may not only interfere with the recruitment and activation of leukocytes, but may fundamentally alter the systemic immune response and subsequent glomerular injury, for example by altering balances in Th1 and Th2 effector mechanisms. Indeed, CCL2/MCP-1 deficient mice were reported to have diminished cellular and humoral Th2 responses (48), whereas CCR2 deficiency appears to decrease Th1 effectors (49). Interestingly, CCR1-deficient mice developed more severe glomerular pathology, greater

proteinuria and an increased renal infiltration of macrophages and T cells during nephrotoxic serum nephritis (50). Enhanced Th1-responses were noted in these mice, again suggesting an altered systemic immune response in the effector phase as a potential mechanism of exacerbation (50). Recently, we showed that the CCL5/RANTES antagonists Met-RANTES and AOP-RANTES both aggravated glomerular damage and proteinuria in murine immune-complex glomerulonephritis, despite effectively blocking glomerular leukocyte recruitment. This was associated with an altered, more inflammatory phenotype of the resident glomerular macrophages which may be attributable to partial agonistic effects of the modified chemokines which were used as antagonists (51).

Evidence for the pathogenic role of single chemokines and chemokine receptors in LN comes from studies with autoimmune mice with targeted deletion of chemokines or chemokine receptors. CCL2/MCP-1-deficient MRL/lpr mice show prolonged survival and infiltration of glomerular macrophages, and accumulation of interstitial macrophages and T cells were reduced in CCL2/MCP-1- deficient mice (15). Perivascular T cell infiltrates were not affected by the lack of CCL2/MCP-1 consistent with the low expression of CCL2/MCP-1 in the perivascular area (15). Obviously, the recruitment of T cells into the perivascular area is mediated by other chemokines like CCL5/RANTES (43). CCL2/MCP-1 also mediates arthritis in lupus. MRL/lpr mice treated with a CCL2/MCP-1 antagonist prevented the onset of arthritis (55).

Evidence for the role of the CCL2/MCP-1 – CCR2 axis in LN also comes from the analysis of CCR2-deficient MRL/lpr mice. CCR2-deficient animals showed prolonged survival just as CCL2/MCP-1-deficient MRL/lpr mice (56). Lack of CCR2 reduced lymphadenopathy, proteinuria, and renal lesion scores. This was associated with reduced infiltration of T cells and macrophages into the glomerular and tubulointerstitial compartment. CCL2 and CCR2 do not seem to regulate immune complex disease in MRL/lpr mice. Levels of circulating immunoglobulin isotypes and immune complex deposition in glomeruli were comparable in CCR2- or CCL2-deficient and -intact mice(15,56).

Chemokine function in the effector phase of the renal immune response can also be studied by delivering chemokines locally into the adult kidney. For example, when CCL5/RANTES was transfected by gene transfer into the kidneys of MRL/lpr mice in advance of nephritis, it fostered the local recruitment of macrophages and T cells associated with the onset of LN (57). Thus, it is likely that early expression of CCL5/RANTES in MRL/lpr kidneys is important for initiating renal disease.

4.2. Observations from human studies

Together, experimental data support a functional role of single chemokines and their receptors in regulating the kidney's response to injury. Are these data relevant to human glomerulonephritis? The answer may be yes. Human biopsy studies have mostly demonstrated similar spatial and temporal expression patterns of these proinflammatory chemokines and chemokine receptors in association with compartment-specific renal leukocyte infiltration and tissue damage (20-25,52-54).The pathogenic role of chemokines in LN is supported by epidemiological studies on genetic polymorphisms of chemokine or chemokine receptor genes. The CCL2/MCP-1 gene often carries an (A/G) polymorphism at position -2518 upstream from the transcription site which was reported to be associated with lower circulating CCL2 levels (58). The A/A genotype was reported to be is less frequent in SLE patients than in controls in some but not all studies (58-60). Different ethnical backgrounds and in insufficient statistical power may explain this discrepancy. In one study the A/A genotype was observed in only 23% of the LN patients compared to 58% of SLE patients without LN (61). This would argue for the concept that a CCL2 -2518 A/G or G/G genotype may predispose to the development of SLE, and SLE patients with these genotypes may be at higher risk for LN, because increased CCL2/MCP-1 secretion promotes autoimmune tissue injury. In fact, patients with LN heterozygous or homozygous for the -2518 G allele show larger monocyte infiltrates the renal interstitial compartment (62). Chinese children with or without SLE have identical frequencies of the –2518 (A/G) CCL2/MCP-1 and the –403 (G/A) CCL5/RANTES gene polymorphisms (63). However, the distribution of the –28 (C/G) CCL5/RANTES gene polymorphism, which leads to increased CCL5/RANTES expression is more frequent in SLE patients and significantly associated with higher levels of antinuclear antibodies, lower levels of complement C3, and a higher incidence of neuropsychiatric manifestations of lupus (63). Another study proposed an association between the (G/A) polymorphism at the CCL5/RANTES -403 locus with LN (64). The Δ32 deletion of the CCR5 gene is more prevalent in patients with biopsy-proven LN, and a higher severity index was found among patients bearing this CCR5 allele (65). This is somehow contradictory to other studies that found an association between the Δ 32 mutation and improved renal outcomes, for example better long-term graft survival in renal transplant recipients, and an increased renal survival in patients with IgA nephropathy (66, 67). Nevertheless, these data not only point to a functional role of chemokines and receptors in human disease, but also underline that genetic variants may contribute to the various clinical patterns of disease manifestations in lupus.

5. CHEMOKINE AS THERAPEUTIC TARGET IN LUPUS NEPHRITIS

Conventional gene-deficient mice may not always reliably predict the outcome of therapeutic blockade due to the role of the lacking gene for the induction of the disease model. Thus, validating the therapeutic potential of chemokine or chemokine receptor blockade requires either conditional knock-out technologies or the use of specific antagonists. Only studies that block the target after the disease model has been established may predict a therapeutic outcome. Proinflammatory chemokines tend to ligate more than one chemokine receptor. Hence,

chemokine receptor blockade may be preferred to targeting a single chemokine. For example, using this approach the inflammatory chemokine receptor CCR1 was identified as a potential therapeutic target in LN. BX471, a small molecule antagonist with blocking activity for murine CCR1, was injected daily in female MRL/lpr mice from week 20 to 24 of age (17). As expected delayed onset of CCR1 blockade reduced the numbers of interstitial macrophages and T cells which was associated with reduced markers of renal fibrosis, i.e. smooth muscle actin-positive myofibroblasts, renal TGF-β mRNA expression, and interstitial collagen I deposits. The effect of CCR1 on these histopathological parameters was associated with improved renal excretory function (reduced blood urea nitrogen levels) in BX471-treated MRL/lpr mice. Consistent with the compartment-specific role of CCR1-dependent leukocyte recruitment the number of glomerular macrophages remained unaffected by BX471-treatment. In fact, glomerular pathology and proteinuria were not reduced by CCR1 blockade (17). Thus, CCR1 blockade can improve renal function and damage in MRL/lpr mice with advanced diffuse proliferative LN. In turn, CCR1-dependent interstitial leukocytic cell infiltrates contribute to the progression of renal failure in MRL/lpr mice with LN.

Targeting a chemokine or chemokine receptor that blocks both interstitial and glomerular leukocyte recruitment may be even more effective. The data from CCL2- and CCR2-deficient mice would argue for CCL2 or CCR2 being such candidates. A NH(2)-terminal-truncated CCL2 analog can act as a functional CCR2 antagonist which blocks glomerular as well as interstitial macrophage and T cell recruitment in MRL/lpr mice with LN (68). Giving the CCL2 analog from 7 or 12 weeks of age mimicked treatment in the pre-nephritic and early nephritic phase of LN and both resulted in a significant delay of LN. Subsequent studies confirmed these findings by using gene transfer of a plasmid transfection vector for the truncated CCL2 into skeletal muscles of 16 week old MRL/lpr mice (69,70). While these studies validate the CCL2-CCR2 axis for the treatment of LN, permanent gene transfer remains an unfeasible way of chemokine blockade in humans. We have developed an alternative approach by generating CCL2-specific Spiegelmers. Spiegelmers are oligonucleotides that bind to and neutralize the biological function of CCL2 just like neutralizing antibodies. Unlike aptamers, which consist out of natural D-oligonucleotides, Spiegelmers consist out of L-oligonucleotides which are nuclease-resistant and thus biostable without further modifications (71). Treating MRL/lpr mice with anti-CCL2 Spiegelmers prevented the onset of severe LN and other disease manifestations of SLE to the same extent as it was reported for the truncated CCL2 (72). These data provide a strong rationale for testing CCL2 (and most likely CCR2) antagonists in human LN.

CX_3CR1/fractalkine blockade was also evaluated by injecting a truncated CX_3CL1 analog into MRL/lpr mice (73). When the CX_3CL1/fractalkine analog was given to 8 week old MRL/lpr mice for another 8 weeks glomerular and tubulointerstitial damage improved which was associated with a reduced number of CX_3CR1 positive monocytes in the glomerular and interstitial compartment. Interestingly the beneficial effect of the CX_3CL1/fractalkine analog was restricted to autoimmune tissue injury in the kidney. Lung injury and sialdenitis remained unaffected by the treatment, which might relate to the organ-specific expression of CX_3CR1 (73).

Homeostatic chemokines have different functions and may not interfere with the recruitment of inflammatory cells to the nephritic kidney. However, blocking homeostatic chemokines may also have beneficial effects in LN. Blocking homeostatic chemokines might interfere with the spatial organization of leukocytes in secondary lymphoid organs which can be crucial for the activation of adaptive immune responses. For example, the administration of a CXCL12/SDF-1 antagonist to NZB/NZW mice with established lupus nephritis reduced DNA autoantibody production, glomerular immune complex deposits, proteinuria, and renal injury (74). The mechanisms of this observation remain to be determined because CXCL12/SDF-1 has additional functions for the homing of progenitor cells in the bone marrow (75) or the structural differentiation of podocytes. These two novel chemokine functions deserve further investigation as their role in LN is unknown to date. However, treatment studies with chemokine or chemokine antagonists in human LN have not yet been reported and remain a future challenge.

6. SUMMARY

A limited number of chemokines is up regulated in the initiation phase of LN which is followed by local infiltration of chemokine receptor positive inflammatory cells, proteinuria, and kidney damage. The spatial expression of chemokines matches with subsequent leukocyte recruitment. In the kidney compartment-specific functions of single chemokines and chemokine receptors have been identified which may relate to the different microvascular environments within the different kidney compartments. Sustained renal chemokine production by other triggers is associated with progression of LN. A small set of chemokines has been validated for therapy in appropriate animal models but evidence from human trials is still lacking.

7. ACKNOWLEDGEMENT

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