Chemokines and chemokine receptors in arthritis

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1. ABSTRACT

Chemokines are involved in leukocyte recruitment to inflammatory sites, such as the synovial tissue in rheumatoid arthritis (RA). There is a structural and a functional classification of chemokines. The former includes four groups: CXC, CC, C and CX_3C chemokines. Chemokines may also be either inflammatory or homeostatic, however, these functions often overlap. Anti-chemokine and anti-chemokine receptor targeting may be therapeutically used in the future biological therapy of arthritis. Most data in this field have been obtained from animal models of arthritis as only very few human RA trials have been completed. However, it is very likely that various specific chemokine and chemokine receptor antagonists will be developed and administered to RA patients.

2. INTRODUCTION

In arthritis, leukocytes extravasate through the vascular endothelium into the synovial tissue. Numerous synovial chemotactic mediators termed chemokines and their receptors are involved in this process (1-10). Currently, there are more than 50 known chemokines and 19 chemokine receptors (2). Some of these chemokines and chemokine receptors are also involved in intense synovial angiogenesis, the formation of new capillaries from preexisting vessels (5,7,11). In rheumatoid arthritis (RA), pro-inflammatory chemokines overrule anti-inflammatory chemokines resulting in accelerated inflammation in the synovial tissue (1-11). Thus, non-specific or specific blockade of chemokines may attenuate synovitis (1-12).

Table 1. Chemokines and chemokine receptors relevant for inflammatory synovitis[1]

Chemokine receptor	Chemokine ligand
CXC chemokine receptors	
CXCR1 (A)	IL-8/CXCL8 (A,H), GCP-2/CXCL6
CXCR2 (A)	IL-8/CXCL8 (A,H), ENA-78/CXCL5 (A), gro-alpha/CXCL1 (A), CTAP-III/CXCL7, GCP-2/CXCL6
CXCR3 (A)	IP-10/CXCL10, PF4/CXCL4, Mig/CXCL9
CXCR4 (A)	SDF-1/CXCL12
CXCR5	BCA-1/CXCL13
CXCR6	CXCL16 (A)
CXCR7	I-TAC/CXCL11, SDF-1/CXCL12
C-C chemokine receptors	
CCR1 (A,H)	MIP-1-alpha/CCL3 (A), RANTES/CCL5 (A), MCP-3/CCL7, HCC-1/CCL14, HCC-2/CCL15, HCC-4/CCL16
CCR2 (A)	MCP-1/CCL2 (A,H), MCP-3/CCL7, HCC-4/CCL16
CCR3	RANTES/CCL5, MCP-2/CCL8, MCP-3/CCL7, HCC-2/CCL15
CCR4	TARC/CCL17, CKLF1
CCR5 (A,H)	MIP-1-alpha/CCL3 (A), RANTES/CCL5 (A), MCP-2/CCL8, HCC-1/CCL14
CCR6	MIP-3-alpha/CCL20
CCR7	SLC/CCL21
C chemokine receptors	
XCR1	Lymphotactin/XCL1
C-X3-C chemokine receptors	
CX3CR1	Fractalkine/CX$_3$CL1 (A)

In this chapter, we will briefly review the role of chemokines and chemokine receptors in the pathogenesis of arthritis. We will also summarize recent studies on either non-specific or specific chemokine and chemokine receptor targeting.

3. CHEMOKINES AND CHEMOKINE RECEPTORS IN ARTHRITIS

Chemokines have been classified into the CXC, CC, C and CX$_3$C supergene families. The receptors for these chemokines have been termed accordingly as CXCR, CCR, CR and CX$_3$CR (2,5,6,13-16). Although each chemokine has its own traditional name, they are also considered as CXCL, CCL, XCL and CX$_3$CL chemokine ligands (2,5,6,10) (Table 1). Apart from this structural classification, as some chemokines are primarily involved in the development of lymphoid tissues and lymphoid neogenesis, while others rather play a role in inflammation, chemokines have also been functionally classified into homeostatic and inflammatory subclasses (10).

3.1. CXC chemokines in arthritis

In these chemokines, there are two conserved C residues separated by one unconserved amino acid (2,15). CXC chemokines chemoattract neutrophils, lymphocytes and monocytes into the synovium (10,16). These mediators are also involved in cell adhesion, leukocyte integrin expression and L-selectin shedding, cytoskeletal reorganization, neutrophil degranulation and phagocytosis, as well as the production of proteases, prostanoids and platelet-activating factor (5,15,17).

Interleukin-8 (IL-8)/CXCL8, epithelial-neutrophil activating protein 78 (ENA-78)/CXCL5 and growth-related oncogene alpha (gro-alpha)/CXCL1 are considered as the most important inflammatory chemokines associated with arthritis. These chemokines are abundantly expressed in the sera, synovial fluids and synovial tissues of RA patients (18-23). Synovial macrophages are major producers of IL-8/CXCL8, ENA-78/CXC5 and gro-alpha/CXCL1 (19-22,24), however, synovial lining cells,

fibroblasts and endothelial cells may also release these chemokines (19-22,24,25). There is a relationship between the genetic code and function of these chemokines, as genes coding these chemokines are clustered on chromosome 4q12-13 and all three chemokines chemoattract primarily neutrophils (16). The regulation of IL-8/CXCL8 production by synovial fibroblasts is controlled by NF-kappa-B (26). As an IL-8/CXCL8 binding site was discovered on endothelial syndecan-3, this suggests a role of chemokine-syndecan interactions during leukocyte trafficking into the arthritic synovial tissue (27). An intraarticular injection of IL-8/CXCL8 induced synovial inflammation in rabbit knee joints (28). In the rat adjuvant-induced arthritis (AIA) model for RA, the development of arthritis was associated with abundant ENA-78/CXCL5 production in the sera and, later, in the joints of rats (29). Gro-alpha/CXCL1 also enhances collagen deposition by RA fibroblasts and thus synovial fibrosis (30).

Connective tissue activating protein III (CTAP-III)/CXCL7 is produced by platelets and it has been detected in RA sera and synovial tissue samples (31). This inflammatory chemokine stimulates the proliferation of synovial fibroblasts, extracellular matrix deposition and thus synovial fibrosis (2,31,32). Cytokines and growth factors including IL-1, fibroblast growth factors and epidermal growth factor act in concert with CTAP-III/CXCL7 during proteoglycan synthesis (31,32). This chemokine also induces angiogenesis (2,31,32).

There is also abundant production of granulocyte chemotactic protein 2 (GCP-2)/CXCL6 in RA (33). GCP-2/CXCL6 expression is up-regulated on RA synovial fibroblasts via Toll-like receptor 2 (TLR2) signaling pathways (33).

Interferon-gamma-inducible protein 10 (IP-10)/CXCL10, monokine induced by interferon-gamma (Mig)/CXCL9 and platelet factor 4 (PF4)/CXCL4 exert pro-inflammatory, but anti-angiogenic effects in RA (2,17,34-36). These chemokines have been detected in the sera. Synovial macrophages and fibroblasts release these

chemokines (34-36). In contrast to other CXC chemokines described above, the genes of PF4/CXCL4 and IP-10/CXCL10 are located on different chromosomes, and these chemokines recruit lymphocytes and monocytes rather than neutrophils (15,16). The induction of IP-10/CXCL10 on synovial fibroblasts requires intercellular adhesion molecule 1 (ICAM-1) and beta$_2$ integrins (35).

While other CXC chemokines described above have common receptors, stromal cell-derived factor 1 (SDF-1)/CXCL12 is a specific ligand for CXCR4. SDF-1/CXCL12 is primarily a homeostatic chemokine involved in lymphoid organization, however, it has also been implicated in synovial inflammation and synovial lymphoid neogenesis (37-39). SDF-1/CXCL12 is expressed by synovial endothelial cells and this chemokine induces strong integrin-mediated adhesion of T cells to ICAM-1 (40). T cells are also able to migrate beneath cultured RA synovial fibroblasts. This process is termed pseudoemperipolesis. SDF-1/CXCL12 has also been implicated in this process (37). In a SCID mouse model, this chemokine stimulated monocyte recruitment into human synovial tissue engrafted onto the mice (34). Synovial T cell adhesion to fibroblasts upregulate SDF-1/CXCL12 production. This process involves IL-17- and CD40-CD40 ligand-dependent mechanisms (41). SDF-1/CXCL12 binds to endothelial proteoglycans and thus it mediates integrin-dependent leukocyte transendothelial migration, osteoclastogenesis, the development of bone erosions and thus radiographic progression in RA (39,42-44).

The crucial role of B cells in the pathogenesis of RA has been acknowledged in recent years (45-47). Among homeostatic chemokines involved in B cell migration and lymphoid tissue organization, B-cell activating chemokine-1 (BCA-1)/CXCL13, the specific ligand for CXCR5, is also expressed by synovial fibroblasts, endothelial cells and follicular dendritic cells within the RA synovium (48).

CXCL16, the specific ligand for CXCR6, primarily mediates lymphocyte recruitment and lymph node organization. Yet, large amounts of CXCL16 were detected in RA synovia (49,50). Both synovial macrophages and fibroblasts secrete CXCL16 (49,50). Monocytes begin to express CXCL16 upon differentiation into macrophages (51). In the SCID mouse chimera model, CXCL16 recruited human mononuclear cells to the engrafted human RA synovial tissues (50). CXCL16-mediated leukocyte extravasation into the synovial tissue involved MAP kinase (MAPK) pathways (50).

3.2. CC chemokines
Monocyte chemoattractant protein 1 (MCP-1)/CCL2, macrophage inflammatory protein 1-alpha (MIP-1-alpha)/CCL3 and Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES)/CCL5 exert chemotactic activity towards T cells, monocytes and natural killer (NK) cells (6,52-54). All these chemokines have been detected in RA sera and synovia (19,35,52-54). The synovial release of MCP-1/CCL2 and MIP-1-alpha/CCL3

may be further augmented by pro-inflammatory cytokines, such as TNF-alpha or IL-1 (19,53,55). Among other triggers, IL-18 also induces MCP-1/CCL2 production by macrophages (56). Hypoxia decreases (57), while TLR2 ligands stimulate MCP-1/CCL2 expression by synovial fibroblasts (33). The injection of MCP-1/CCL2 into rabbit knees induced arthritis (58). MCP-1/CCL2 has been implicated in TNF-mediated osteoclast differentiation of peripheral blood monocytes. Thus, this chemokine, similarly to SDF-1/CXCL12, is involved in periarticular bone resorption in arthritis (59). MIP-1-alpha/CCL3 production is augmented by TNF-alpha, IL-1 and IL-15 (60,61). A single nucleotide polymorphism (SNP) within the RANTES promoter gene promotes susceptibility to RA in Chinese patients (62).

MIP-3-alpha/CCL20, the specific ligand for CCR6, is chemotactic for monocytes and lymphocytes (2,63). RA synovial fibroblasts produce this chemokine in response to TNF-alpha, IL-1, IL-17 and IL-18 (63-66). This chemokine has been implicated in the recruitment of IL-17-producing CCR6^{+} Th17 cells into the synovium (67). MIP-3-alpha/CCL2 induces both osteoblast proliferation and osteoclast differentiation. Furthermore, increased expression of this chemokine was detected in the subchondral bone of RA patients. MIP-3-alpha/CCL20 may collaborate with the RANK ligand system in the uncoupling between new bone formation and bone resorption in RA (68).

CCL18 facilitates T cell attraction by antigen-presenting cells. Serum CCL18 levels is increased in RA patients and correlate with disease activity in RA (69). Synovial fluid neutrophils release CCL18 during their recruitment into the joints (70).

MCP-4/CCL13 is expressed in the cartilage of the RA joint. The combination of IFN-gamma, TNF-alpha and IL-1 stimulate the release of MCP-4/CCL13 from arthritic chondrocytes. This chemokine stimulates synovial fibroblast proliferation (71).

Among primarily homeostatic CC chemokines, Epstein-Barr virus-induced gene 1 ligand chemokine (ELC)/CCL19 has also been detected in RA synovial tissues (40). Secondary lymphoid tissue chemokine (SLC)/CCL21 has been implicated in lymphoid neogenesis within the arthritic synovial tissue (48,72). Thymus and Activation Regulated Chemokine (TARC)/CCL17 and Pulmonary and Activation regulated Chemokine (PARC)/CCL18 also mediate T cell recruitment into the RA synovium (73-75).

In a single recent study, MCP-2/CCL8, MCP-3/CCL7, hemofiltrate CC chemokine 1 (HCC-1)/CCL14, HCC-2/CCL15 and HCC-4/CCL16 have been detected in the RA synovium (76). The function of these chemokines in RA has not been fully elucidated. Chemokine-like factor 1 (CKLF1) is a functional ligand of CCR4. Its expression is up-regulated on activated CD4^{+} and CD8^{+} T cells in RA (77).

3.3. C and CX$_3$C chemokines in RA

The C chemokine family contains two members, lymphotactin/XCL1 and single C motif 1-beta (SCM-1-beta)/XCL2 (5,6). Lymphotactin/XCL1 is involved in T cell chemotaxis and it has been detected on CD8$^+$ and CD4$^+$/CD28$^-$ T cells in RA (78). This chemokine stimulates T cell accumulation into the RA joint and down-regulates matrix metalloproteinase 2 (MMP-2) production by RA synovial fibroblasts (79).

The single member of the CX$_3$C family is fractalkine/CX$_3$CL1, which is chemotactic for monocytes, lymphocytes and it also serves as a CD4$^+$ T cell adhesion molecule (80-83). Fractalkine/CX$_3$CL1 enhances the adhesion of senescent T cells to synovial fibroblasts. In addition, this chemokine provides survival signals for and costimulates the production of pro-inflammatory cytokines by these T cells (83). Fractalkine/CX$_3$CL1 regulates the cytoskeletal structure, proliferation and migration of synovial fibroblasts (84,85). The activity of this chemokine involves JNK, ERK-1/2 and Akt (85). RA synovial macrophages, fibroblasts, endothelial and dendritic cells produce fractalkine/CX$_3$CL1 (81,83). Fractalkine/CX$_3$CL1 has been associated with disease activity in rheumatoid vasculitis (86), as well as with accelerated atherosclerosis and increased cardiovascular morbidity in RA (87-89).

3.4. Chemokine receptors in arthritis

Chemokine receptors are 7-transmembrane domain receptors expressed on the target cells. Some chemokine receptors, such as CXCR2, CCR1 or CCR3 have multiple ligands, while others including CXCR4, CXCR5, CXCR6, CCR8 or CCR9 are specific receptors for one single ligand (2,6,16) (Table 1).

Generally all CXCRs have been associated with the pathogenesis of arthritis. CXCR1 and CXCR2 exert abundant expression in the RA synovium. These chemokine receptors recognize the most relevant inflammatory and angiogenic CXC chemokines described above (2,6). CXCR3 may be the most important receptor in leukocyte homing into the RA synovium (81,90,91). Most T cells in the RA synovial fluid express this chemokine receptor (92). The high expression of CXCR3 on synovial T cells has been associated with a high IFN-gamma/IL-4 ratio, suggesting a preferential Th1 over Th2 phenotype of these T cells (93). CXCR3 is also expressed on RA synovial endothelial and dendritic cells (90,94). CXCR4 is involved in SDF-1/CXCL12-dependent ingress of lymphocytes into the RA synovial tissue (39). CXCR5 is expressed by T, B cells, macrophages and endothelial cells (93) and it is involved in synovial lymphoid neogenesis underlying arthritis (95). CXCR6 mediates CXCL16-induced synovitis (50). CXCR4, CXCR5 and CXCR6 bind their respective homeostatic chemokine ligands, SDF-1/CXCL12, BCA-1/CXCL13 and CXCL16. Thus, these CXC chemokine receptors are involved in both homeostatic and inflammatory processes (2,10,39,50,96).

Among CC chemokine receptors, CCR1 and CCR5 are abundantly expressed in the RA synovium (76,81,91,97). These CCRs, as well as CCR2 and CCR3 are also present on articular chondrocytes (98). CCR4 has also been implicated in leukocyte ingress into the RA joint (94). In some studies, a SNP leading to the production of the truncated delta-32-CCR5 non-functional receptor allele was found to be protective against RA (99). However, this protective role could not be confirmed in other national cohorts (100,101). CCR6, the single receptor for MIP-3-alpha/CCL20 has also been detected on RA synovial leukocytes (63). CCR6 is involved in the ingress of Th17 arthritogenic lymphocytes into the joint (67). CCR7 has been associated with synovial lymphoid neogenesis in mice (95). A putative chemokine receptor, CCR-like receptor 2 (CCRL2) has been identified on RA synovial fluid neutrophils and macrophages (102). In comparative study on CCRs, peripheral blood monocytes mainly expressed CCR1 and CCR2 suggesting that these receptors were involved in monocyte recruitment from the circulation. In contrast, CCR3 and CCR5 expression were up-regulated in RA SF indicating that these CCRs were important in monocyte retention in the joint (97).

Regarding the C and CX$_3$C chemokine receptors, XCR1 is expressed on RA synovial lymphocytes, macrophages and fibroblasts (2,6), while CX$_3$CR1 has been detected on macrophages and dendritic cells (82). As described above, the fractalkine/CX$_3$CL1-CX$_3$CR1 system has been implicated in the pathogenesis of RA-associated atherosclerosis (87-89) (see later).

4. FUNCTIONAL ASPECTS OF CHEMOKINES AND CHEMOKINE RECEPTORS IN SYNOVIAL INFLAMMATION

4.1. Inflammatory and homeostatic chemokines in RA

As described above, chemokines have been functionally classified into homeostatic and inflammatory subgroups, however, these functions often overlap (10). Homeostatic chemokines are constitutively produced in lymphoid or non-lymphoid tissues. Lymphoid neogenesis has been associated with arthritis leading to lymphoid aggregates and germinal center-like structures within the inflamed synovial tissue. The synovium, in many ways, is similar to the skin, as well as to other mucosa-associated lymphoid tissues (MALT) (10,48,96). Some primarily homeostatic chemokines including SDF-1/CXCL12, BCA-1/CXCL13, CXCL16, TARC/CCL17, PARC/CCL18, ELC/CCL19 and SLC/CCL21 may also be involved in synovial inflammation (10,39,40,48,50,96,103,104).

On the other hand, most CXC and CC chemokines, C and CX$_3$C chemokines, as well as their respective receptors are primarily inflammatory chemokines (2,6,96). As described above, IL-8/CXCL8, ENA-78/CXCL5, gro-alpha/CXCL1, CTAP-III/CXCL7, IP-10/CXCL10, Mig/CXCL9, PF4/CXCL4, GCP-2/CXCL6, MCP-1/CCL2, MIP-1-alpha/CCL3, MIP-3-alpha/CCL20, RANTES/CCL5, lymphotactin/XCL1 and fractalkine/CX$_3$CL1 are involved in leukocyte migration into the synovium (2,5,6,9,48,77).

4.2. The functional role of chemokine receptor expression patterns in inflammation

Certain chemokine receptor expression patterns have been associated with different types of chronic inflammation. For example, Th0-Th1 type inflammation observed in RA has been primarily associated with the abundant synovial expression of CXCR3 and CCR5. In contrast, asthma, a known Th2 type disease, rather involves CCR3, CCR4, CCR8 and their ligands (16,81,91,105).

4.3. Chemokines and chemokine receptors in synovial angiogenesis and RA-related atherosclerosis

RA has been associated with the perpetuation of synovial neovascularization dependent upon the imbalance between angiogenic and angiostatic mediators (1,3,5,8). Some chemokines and chemokine receptors may also promote or suppress synovial angiogenesis (3,5,8).

In general, CXC chemokines containing the ELR (Glu-Leu-Arg) amino acid motif are angiogenic, while those, lacking this sequence are rather angiostatic (5,17). As one exception to this rule, SDF-1/CXCL12 is ELR$^-$, nevertheless it still stimulates neovascularization (5,17). Among ELR$^+$ CXC chemokines, IL-8/CXCL8, ENA-78/CXCL5, CTAP-III/CXCL7 and gro-alpha/CXCL1 are chemotactic for endothelial cells and they stimulate synovial angiogenesis (1,5,15,17,31,106). SDF-1/CXCL12 cooperates with the hypoxia-hypoxia-inducible factor (HIF)-vascular endothelial growth factor (VEGF) pathway, which plays a central role in the regulation of angiogenesis (103,107,108). SDF-1/CXCL12 expression has also been associated with tumor angiogenesis and its expression may serve as a prognostic marker in gliomas (109). The ELR$^-$ IP-10/CXCL10, Mig/CXCL9 and PF4/CXCL4 are angiostatic (5,15,17,110-112). IP-10/CXCL10 inhibits VEGF-dependent angiogenesis, in turn, VEGF induces endothelial expression of IP-10/CXCL10 (5,17,110,111). Thus, IP-10/CXCL10 may be an important regulator of VEGF-dependent synovial neovascularization (110,111).

Much less information has become available regarding the role of CC chemokines in synovial angiogenesis. For example, MCP-1/CCL2 induces endothelial cell chemotaxis and capillary formation via the CCR2 endothelial receptor (113,114). These effects involve the Ets-1 transcription factor, as well as integrins and ERK-1/2 (114). Myeloid progenitor inhibitory factor 1 (MPIF-1)/CCL23 has also been implicated in endothelial cell migration and angiogenesis (115). In contrast, the homeostatic chemokine SLC/CCL21 inhibits tumor progression and angiogenesis (116).

Chemokine receptors recognizing the most relevant angiogenic chemokine ligands described above exert inflammatory and angiogenic properties in RA. CXCR2 may be the most important chemokine receptor implicated in synovial angiogenesis as CXCR2 is a receptor for angiogenic, ELR$^+$ CXC chemokines described above (5,98,113). CXCR4 is involved in SDF-1/CXCL12-mediated synovial neovascularization (39,117). Hypoxia induces CXCR4 expression via the stimulation of HIF-1 and VEGF production (118). CXCR7 recognizing I-

TAC/CXCL11 and SDF-1/CXCL12 may also be involved in synovial angiogenesis (119). CCR2 is a receptor for the angiogenic MCP-1/CCL2 (5,113). In a murine model of skeletal muscle injury, CCR2-deficient animals exerted delayed muscular angiogenesis and decreased VEGF production (120). In contrast to these angiogenic chemokine receptors, CXCR3, which binds the angiostatic chemokines IP-10/CXCL10 and Mig/CXCL9, may rather be involved in chemokine-mediated angiostasis (2,5,6,16,17).

Fractalkine/CX$_3$CL1 and CX$_3$CR1 have been implicated in arthritis-related angiogenesis, as well as atherosclerosis (82,87,89,121). Indeed, CX$_3$CR1 expression on atherogenic CD4$^+$/CD28$^-$ T cells correlated with vascular damage in RA (88). Moreover, CX$_3$CR1-deficient mice develop lesser degree of atherosclerosis than do wild type animals (121). The M280/I249 SNP in the CX$_3$CR1 gene has been associated with decreased cardiovascular risk in humans (87).

4.4. Regulation of chemokine production during leukocyte recruitment

There may be a temporal regulation of chemokine and chemokine receptor production in the inflamed synovium. When the temporal expression of CXC and CC chemokines was assessed in sera and joint homogenates of rats with AIA, the production of ENA-78/CXCL5 and MIP-1-alpha/CCL3 showed a very early increase, preceding clinical symptoms. The release of these "early" chemokines occurred parallel with neutrophil recruitment and the production of acute-phase reactants. In contrast, MCP-1/CCL2 was rather involved in the later phase of AIA (122). In rat AIA, CCR1 exerted high constitutive expression on macrophages throughout the disease course. CCR5 expression was up-regulated on synovial macrophages. CCR2 expression on endothelial cells was down-regulated during the progression of the disease. CCR3 expression on macrophages also decreased during the course of AIA. These results suggest that CCR2 and CCR5 may sustain inflammatory changes, while CCR2 and CCR3 may play a role in initial recruitment of leukocytes into the synovial tissue (123).

A regulatory network of pro-inflammatory cytokines and chemokines exists in the arthritic synovium (2,5,6,124,125). As discussed above, some cytokines including TNF-alpha, IL-1, IL-6, IL-15, IL-18 and others may enhance, while others rather suppress chemokine production (2,5,21,53,125). For example, IL-8/CXCL8 secretion by RA synovial fibroblasts is stimulated by IL-4 but inhibited by IFN-gamma. In contrast, RANTES/CCL5 production is suppressed by IL-4 but augmented by IFN-gamma (55). On the other hand, some chemokines may also influence cytokine production (2,5,6,29,126). For example, MIP-1-alpha/CCL3 stimulates the synthesis of TNF-alpha, IL-1 and IL-6 by synovial macrophages (5,126).

As described above, TLRs may also be involved in the regulation of chemokine function. TLR2 ligands activate synovial fibroblasts. Peptidoglycan, a TLR2

ligand, stimulated, among others, IL-8/CXCL8, Gro-alpha/CXCL1, MCP-1/CCL2, MIP-1-alpha/CCL3 and RANTES/CCL5 mRNA expression by these fibroblasts (33).

5. TARGETING OF CHEMOKINES AND CHEMOKINE RECEPTORS

Chemokines and chemokine receptors may be targeted by non-specific, as well as by chemokine-specific approaches. These strategies have been tried in animal models of arthritis, *in vitro* cultures of human RA synovial cells and tissues, as well as in a very limited number of human RA clinical trials (2,5,6,9,127) (Table 1).

5.1. Non-specific agents

Some non-steroidal anti-inflammatory drugs, corticosteroids, traditional disease-modifying antirheumatic drugs (DMARD) and anti-TNF biologics exert multiple anti-inflammatory properties including chemokine inhibition. For example, diclofenac and meloxicam attenuated IL-8/CXCL8 production in the rat antigen-induced arthritis (AgIA) model (128). Dexamethasone, inhibited IL-8/CXCL8 and MCP-1/CCL2 release in RA patients (129). Among DMARDs, sulfasalazine inhibited the production of IL-8/CXCL8, MCP-1/CCL2 and gro-alpha/CXCL1 in cultured RA synovial tissue explants (130). Sulfapyridine inhibited the expression of IL-8/CXCL8 and MCP-1/CCL2 on cytokine-treated EC (131). In contrast, gold salts hardly had any effects on IL-8/CXCL8 or MCP-1/CCL2 synthesis (129). Methotrexate in combination with leflunomide suppressed MCP-1/CCL2 expression within the RA synovium (132). Methotrexate also suppressed the expression of CCR2 on RA peripheral blood monocytes. This effect correlated with lower disease activity (133). There have been increasing number of studies with anti-TNF agents. Infliximab suppressec IL-8/CXCL8, gro-alpha/CXCL1, CXCL16, MCP-1/CCL2 and RANTES/CCL5 production in RA (51,134-137). Infliximab also reduced CCR3 and CCR5 expression on T cells in RA patients. The expression of these chemokine receptors was higher on non-responders than on responders (138). Treatment of RA patients with either infliximab or etanercept resulted in the clearance of CXCR3$^+$ T cells from the synovium (139). Chemokine inhibition may have relevance for safety of anti-TNF therapy: infliximab reduced the secretion of IL-8/CXCL8, MIP-1-alpha/CCL3 and MCP-1/CCL2 in response to Mycobacteria. These authors suggest that the increased incidence of tuberculosis in infliximab-treated RA patients may be related, in part, to the inhibition of TNF-dependent chemokine gradients and impaired leukocyte migration (140).

Among other non-specific small molecule compounds, antioxidants including N-acetyl-L-cysteine and 2-oxothiazolidine-4-carboxylate, inhibited the expression of IL-8/CXCL8 and MCP-1/CCL2 mRNA by activated human synovial fibroblasts (141). Simvastatin inhibited IL-8/CXCL8 production by TNF-alpha-stimulated RA synovial fibroblasts (142). Triptolide, a diterpenoid triepoxide with potent anti-inflammatory effects, inhibited MCP-1/CCL2, MIP-1-alpha/CCL3 and RANTES/CCL5

production in the rat AIA model (143). Epigallocatechin-3-gallate (EGCG), a compound derived from green tea, suppressed ENA-78/CXCL5, gro-alpha/CXCL1 and RANTES/CCL5 production by IL-1-stimulated RA synovial fibroblasts (144). A recently developed dual cyclooxygenase-lipoxygenase inhibitor, ML3000, downregulated Mig/CXCL9, IP-10/CXCL10 and I-TAC/CXCL11 expression on RA synovial fibroblasts (145). Activation of peroxisome proliferator-activated receptor gamma (PPAR-gamma) suppresses MCP-1/CCL2 expression in monocytes (59). Thus, PPAR-gamma agonists, such as glitazones, may inhibit chemokine production.

5.2. Specific chemokine and chemokine receptor targeting

Neutralizing antibodies to IL-8/CXCL8 prevented arthritis in rabbits (146). In the rat AIA model, a neutralizing polyclonal anti-ENA-78/CXCL5 antibody administered intravenously prevented the onset of the disease, however, it failed to inhibit the progression of synovitis when administered therapeutically (29). The preventative administration of an anti-gro-alpha/CXCL1 antibody delayed the onset and severity of collagen-induced arthritis (CIA) in mice (147). A synthetic peptide derived from PF4/CXCL4 inhibited the development of murine CIA (104). An antibody to CXCL16 suppressed synovitis and joint destruction in murine CIA (49). Passive immunization of mice with anti-MIP-1-alpha/CCL3 decreased the severity of murine CIA (147). A monoclonal antibody to MCP-1/CCL2 reduced synovitis in rat CIA (148). An anti-MCP-1/CCL2 antibody also prevented the recruitment of ^{111}In-labeled T cells into the synovium in the rat model of streptococcal cell wall antigen (SCW)-induced arthritis (149). A novel inhibitor of endogenous MCP-1/CCL2, p8A-MCP-1, suppressed cytokine expression, synovial leukocyte infiltration, joint erosion and improved clinical signs of rat AIA (150). Another peptide inhibitor of MCP-1/CCL2 suppressed the development of arthritis in MRL-lpr mice (151). An anti-RANTES/CCL5 antibody inhibited the progression of murine CIA (152). KE-298, a combined MCP-1/CCL2 and RANTES/CCL5 inhibitor, attenuated the severity of rat AIA (153). A monoclonal antibody to fractalkine/CX$_3$CL1 inhibited synovitis and joint destruction in murine CIA (154).

The efficacy of chemokine targeting may be increased by combining various specific strategies. For example, in murine AIA, a combination of MCP-1/CCL2 and gro-alpha/CXCL1 inhibition resulted in more pronounced effects than did MCP-1/CCL2 blockade alone (155). In the rabbit endotoxin-induced arthritis model, the combination of anti-IL-8/CXCL8 and anti-groα/CXCL1 antibodies inhibited knee arthritis better than did any of the two antibodies alone (156). Certainly, an increased toxicity using combined anti-chemokine strategies may be an important issue in the future (2).

Regarding chemokine receptor targeting, a nonpeptide oral antagonist of the CXCR2 receptor inhibited IL-8/CXCL-induced arthritis in rabbits (157). DF2162, an allosteric CXCR1/CXCR2 inhibitor diminished murine and

rat arthritis (158,159). In the AIA model, an anti-CXCR3 antibody inhibited T cell recruitment and disease progression (160). Some small molecule CXCR4 antagonists gave promising results in arthritis studies (161). For example, AMD3100 inhibited CIA in IFN-gamma-deficient mice (162), while T140 analogs ameliorated murine CIA (163). Numerous CCR1 and CCR2 antagonists have been developed in recent years (164-169). For example, J-113863, a small molecule CCR1 antagonist diminished synovitis and joint destruction in murine CIA (164). Met-RANTES, a dual CCR1/CCR5 antagonist, inhibited both murine CIA and rat AIA (170,171). Some anti-chemokine receptor effects may be dose-dependent. For example, while low doses of the MC-21 anti-CCR2 monoclonal antibody markedly improved murine CIA, high doses of this antibody rather had pro-inflammatory effects (172).

Adenoviral gene transfer may also be a useful method in chemokine targeting. The vaccinia virus expresses a 35 kDa soluble protein (35k), which inactivates a number of CC chemokines. A recombinant adenovirus containing 35k reduced migration of CCR5-transfected cells in response to RANTES/CCL5. This vector also suppressed chemotaxis of both CCR5-transfected cells and primary macrophages in mice (173).

There have been only limited number of published human anti-chemokine or anti-chemokine receptor trials. An anti-MCP-1/CCL2 antibody, ABN912, has been introduced to a randomized, controlled human RA trial. In this study, 33 patients received the active compound, while 12 received placebo. Serial arthroscopic biopsies were performed. ABN912 treatment was well tolerated, but there was no detectable clinical benefit or significant change in synovial biomarkers (174). A small molecule CCR1 antagonist has been tried in a two-week phase Ib study. This inhibitor decreased the number of synovial macrophages. About one-third of the patients also fulfilled the ACR20 criteria for clinical improvement (166). CP-481,715, another CCR1 antagonist inhibited monocyte chemotactic activity present in human RA synovial fluid samples (165). This compound has been evaluated in phase I for pharmacokinetics and safety (175). Some CCR2 inhibitors have also entered clinical trials (168). Among CCR5 inhibitors, maraviroc has been introduced to phase II-III trials in HIV infection and AIDS, as well as to phase II trial in RA (176).

6. SUMMARY

In this review, we have discussed the potential role of chemokines and chemokine receptors in the pathogenesis of arthritis. Numerous CXC, as well as some CC and CX_3C chemokines and their respective receptors have been implicated in leukocyte ingress into the inflamed synovium. Some chemokines and chemokine receptors are also involved in synovial angiogenesis. Anti-chemokine and anti-chemokine receptor targeting using either non-specific compounds or specific inhibitors may control synovial inflammation.

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Footnote: [1]Already targeted in animal models (A) or human (H) trials. See text for abbreviations

Abbreviations: AIA: adjuvant-induced arthritis, CIA: collagen-induced arthritis, DMARD: disease-modifying antirheumatic drugs, RA: rheumatoid arthritis

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