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Chemokines and angiogenesis in rheumatoid arthritis

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1. ABSTRACT

In rheumatoid arthritis, chemokines mediate the migration of inflammatory leukocytes into the synovium. Among the four known chemokine families, CXC, CC chemokines and fractalkine seem to be of outstanding importance in this process. Angiogenesis, the formation of new vessels, is also important during the perpetuation of inflammation underlying rheumatoid arthritis. In this review, authors discuss the role of the most important chemokines and chemokine repetors in arthritis-associated neovascularization. The process and regulation of angiogenesis are described in this context as well. Apart from discussing the pathogenic role of chemokines and chemokine receptors in arthritic vessel formation, authors also review the important relevance of chemokines and angiogenesis for therapeutic intervention.

2. INTRODUCTION

Rheumatoid arthritis (RA) is associated with increased synovial vascularity. The large number of blood vessels observed in the RA synovium are derived from endothelial progenitor cells or pre-existing vessels. These two processes are termed vasculogenesis and angiogenesis, respectively (1-10). In RA, leukocytes extravasate through the vascular endothelium and form inflammatory infiltrates within the synovium. The transendothelial migration of leukocytes involve numerous inflammatory chemokines (5,12-15). Some of these chemokines are also involved in synovial neovascularization (5,6,15). On the other hand, some chemokines suppress angiogenesis and thus synovial inflammation (5,11,14). Accelerated angiogenesis may result in an expanded endothelial surface, which may promote more intense inflammatory cell ingress into the synovium (13,16).

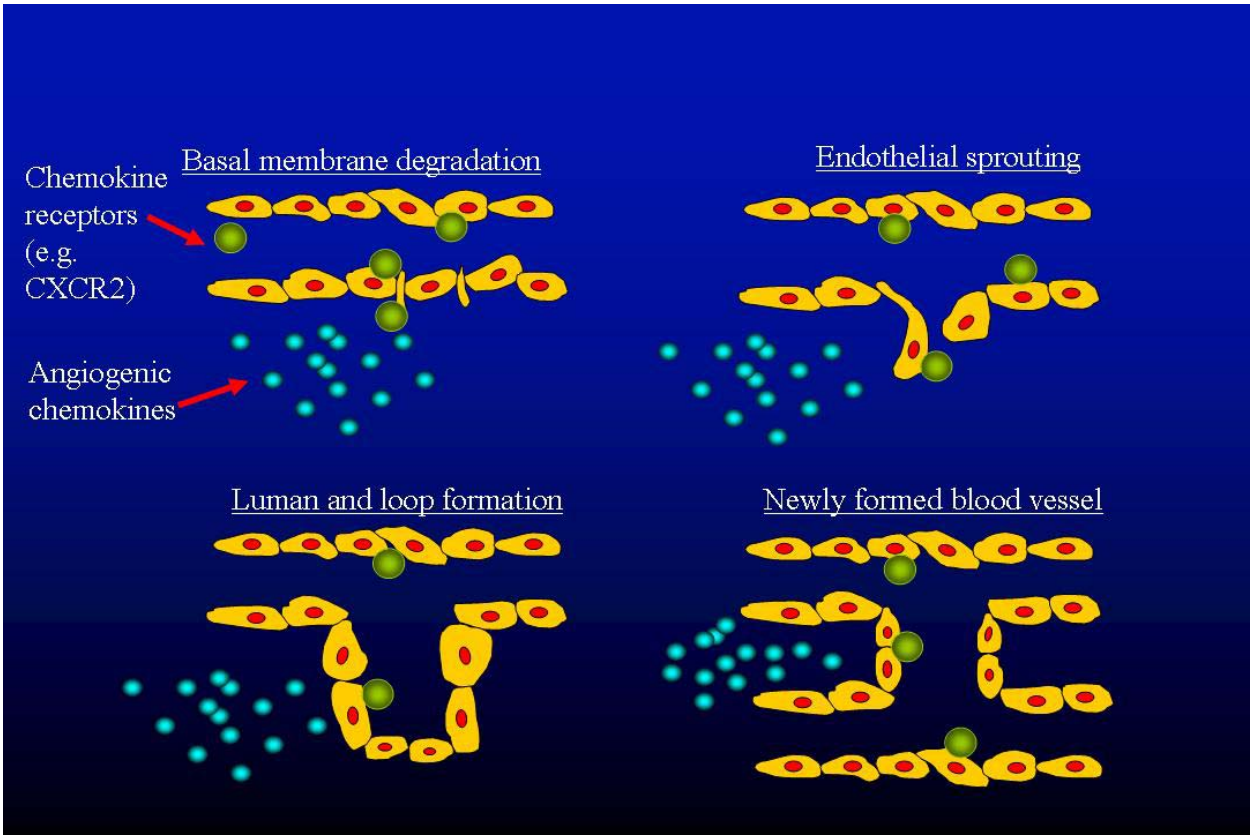

Figure 1. The role of chemokines and endothelial cell-bound chemokines receptors in angiogenesis.

In addition to the role of chemokines in angiogenesis, this issue may have important relevance for antirheumatic therapy. For example, small molecular chemokine or chemokine receptor inhibitors or anti-chemokine biologics that also suppress neovascularization may be used in the therapy of arthritis (1,5,6,11,14).

3. ANGIOGENESIS IN RHEUMATOID ARTHRITIS

Although the role of chemokines and chemokine receptors in synovial neovascularization will be discussed in more detail, we will first briefly describe angiogenesis in RA. RA is considered an "angiogenic" disease state as there is a perpetuation of neovascularization in the synovium associated with synovial inflammation (1-5). The angiogenic process itself, its mediators and inhibitors, cellular and molecular interactions underlying neovascularization, as well as the role of angiogenesis and the possibilities of angiostatic targeting in RA have been extensively discussed in a number of recent reviews (1-6). In RA, the synovial tissue is rich in newly formed vessels. The high turnover of capillary formation leading to increased vascular endothelial surface may enable the extravasation of inflammatory leukocytes into the synovium and thus the progression of RA (1-5) (Figure 1).

Angiogenic mediators also involved in the pathogenesis of RA include numerous growth factors, cytokines, chemokines, extracellular matrix macromolecules, cell adhesion receptors, proteolytic enzymes and other factors. Most of these mediators are released by endothelial cells and macrophages; cells also present in high quantities in the RA synovium (1,2,12). Angiogenesis inhibitors in RA include cytokines, chemokines, a number of antirheumatic drugs, protease inhibitors, antibiotics and other compounds (1-7). Many of these factors may influence the progression of RA and thus, they may be useful for the management of this disease.

The outcome of neovascularization, and thus the extent of leukocytic invasion through the newly formed vessels into the synovium, greatly depends on the imbalance between angiogenic and angiostatic mediators. Several interactive and feedback mechanisms exist in the RA synovial tissue, which up- or down-regulate the angiogenic process (1-7,11,14).

4. CHEMOKINES AND CHEMOKINE RECEPTORS IN SYNOVIAL ANGIOGENESIS

4.1. Chemokines and chemokine receptors in rheumatoid arthritis

Among CXC chemokines, interleukin-8 (IL-8)/CXCL8, epithelial-neutrophil activating protein-78 (ENA-78)/CXCL5, growth-related gene product α (groα)/CXCL1, connective tissue activating protein III (CTAP-III)/CXCL7, granulocyte chemotactic protein 2 (GCP-2)/CXCL6, interferon-γ-inducible protein 10 (IP-10)/CXCL10, monokine induced by interferon-γ

Table 1. Chemokine receptor-ligand pairs involved in RA-associated angiogenesis

Chemokine receptor	Chemokine ligand
CXC chemokine receptors	
CXCR1	IL-8/CXCL8
CXCR2	IL-8/CXCL8, ENA-78/CXCL5, Groα/CXCL1, CTAP-III/CXCL7
CXCR3	IP-10/CXCL10[1], PF4/CXCL4[1], Mig/CXCL9[1]
CXCR4	SDF-1/CXCL12
CXCR7	SDF-1/CXCL12
C-C chemokine receptors	
CCR1	MPIF-1/CCL23
CCR2	MCP-1/CCL2
CCR7	SLC/CCL21[1]
C-X3-C chemokine receptors	
CX3CR1	Fractalkine/CX_3CL1
Other	
DARC	Duffy antigen, some CC and CXC chemokines

[1]Angiostatic chemokines. See text for abbreviations.

(Mig)/CXCL9, platelet factor 4 (PF4)/CXCL4, stromal cell-derived factor-1 (SDF-1)/CXCL12, B cell activating chemokine 1 (BCA-1)/CXCL13 and CXCL16 have been implicated in the pathogenesis of RA. Although some of these chemokines also exert homeostatic properties, these mediators may all be considered "inflammatory" (5,12,14,17,18). As discussed later, a number of CXC chemokines have been implicated in RA-associated angiogenesis (5,6,11) (Table 1) (Figure 1).

Regarding CC chemokines, monocyte chemoattractant protein-1 (MCP-1)/CCL2, macrophage inflammatory protein 1α (MIP-1α)/CCL3, MIP-3α/CCL20, Regulated upon Activation, Normal T-cell Expressed and Secreted (RANTES)/CCL5, Epstein-Barr virus-induced gene 1 ligand chemokine (ELC)/CCL19, secondary lymphoid tissue chemokine (SLC)/CCL21 and, chemokine-like factor 1 (CKLF1) have been implicated in inflammatory mechanisms underlying RA (5,11,14,19,20). Yet, only very few CC chemokines are involved in synovial angiogenesis (5,21,22).

The only member of the CX_3C chemokine family, fractalkine/CX_3CL1, has been associated with inflammatory synovitis and angiogenesis (5,23-25).

Chemokines described above bind to their 7-transmembrane domain receptors expressed on the target cells (26). Some of these receptors, such as CXCR2, CCR1 or CCR3 have numerous chemokine ligands, while others, such as CXCR6, CCR8, CCR9 or CX_3CR are specific receptors for one single ligand (5,26).

4.2. Chemokines in angiogenesis

Regarding the possible angiogenic or angiostatic action of CXC chemokines, those containing the ELR amino acid motif, such as IL-8/CXCL8, ENA-78/CXCL5, groα/CXCL1, and CTAP-III/CXCL7, promote vessel formation (Figure 1). In contrast, ELR^- CXC chemokines including PF4/CXCL4, IP-10/CXCL10 and Mig/CXCL9 inhibit angiogenesis (5,27,28). SDF-1/CXCL12 lacks the ELR sequence, nevertheless it stimulates neovascularization (5,28) (Table 1).

IL-8/CXCL8 is chemotactic and mitogenic for vascular endothelial cells (5,14,27,28). This chemokine binds to one of its receptors, CXCR2, on endothelial cells (5,14,21). ENA-78/CXCL5, CTAP-III/CXCL7 and groα/CXCL1 have also been implicated in angiogenesis (1,5,27,29,30). Prostaglandin E_2 is also angiogenic and it acts in part by inducing groα/CXCL1 expression (31). All these cytokines are abundantly produced in the RA synovium (1,5,11,14).

IP-10/CXCL10 exerts proinflammatory action in RA, however, this chemokine inhibits neovascularization (5,14,27,28,32). This ELR-lacking chemokine has been shown to suppress neovascularization (27,28). IP-10/CXCL10 inhibits VEGF-induced endothelial migration (33). On the other hand, VEGF induces endothelial expression of IP-10/CXCL10 (33). Thus, IP-10/CXCL10 may be an autocrine inhibitory regulator of VEGF-mediated angiogenesis: VEGF induces IP-10/CXCL10 production, and the chemokine, in turn, suppresses VEGF-induced capillary formation (32,33).

Other ELR^- chemokines, such as Mig/CXCL9 and PF4/CXCL4 are also angiostatic (5,28,34). All ELR^- angiostatic chemokines have been detected in RA synovial tissues (5,11,14). Recently, a nonallelic variant of PF4/CXCL4 termed PF4var/CXCL4L1 has been described. This variant is also a potent inhibitor of angiogenesis and it inhibits melanoma and lung carcinoma proliferation (35,36). PF4var/CXCL4L1 expression in sarcoma cells could be induced by IL-1 or IL-17 (35). The role of this chemokine variant in RA needs to be elucidated.

SDF-1/CXCL12, the specific ligand for CXCR4, may be a key regulator of angiogenesis and vasculogenesis, despite lacking the ELR sequence (37-39). SDF-1/CXCL12 induced endothelial cell chemotaxis, as well as dermal angiogenesis (38). Hypoxia induces the release of this chemokine by RA synovial fibroblasts (37). Furthermore, the SDF-1/CXCL12-CXCR4 interaction induces Akt phosphorylation resulting in the stimulation of VEGF release via the phosphatidyl inositol 3 kinase (PI3K)/Akt pathway (40). Thus, SDF-1/CXCL12 may induce angiogenesis indirectly via VEGF (40). SDF-1/CXCL12-mediated angiogenesis also involves the activation of heme oxygenase 1 (41). This chemokine also synergizes with granulocyte colony-stimulating factor during vessel formation (42). During angiogenesis, SDF-1/CXCL12 becomes immobilized on heparan sulfate produced by endothelial cells (37). SDF-1/CXCL12 expression has also been associated with the growth of gliomas, thus, it may serve as an indicator of tumor neovascularization and as a prognostic marker (43).

Regarding vasculogenesis, a subpopulation of circulating $CD34^+$ cells expressing the VEGF-2 receptor have been identified. These cells are functional endothelial precursor cells (EPCs). The process of new vessel

formation from EPCs is termed vasculogenesis (8,9). Decreased number of EPCs, as well as impaired vasculogenesis have been associated with RA (10). Virtually all $CD34^+$/VEGF-2 $receptor^+$ EPCs also express CXCR4 and migrate in response to SDF-1/CXCL12 (9). The cytokine-mediated production of this chemokine induces tissue vascularization by recruiting $CXCR4^+$ EPCs (44). Thus, SDF-1/CXCL12 accelerates the revascularization of ischemic organs (39). Recently, an alternative receptor for SDF-1/CXCL12, as well as for IFN-inducible T cell α chemoattractant (I-TAC)/CXCL11, different from CXCR4, has been identified and implicated in chemokine-induced tumor angiogenesis (45). In conclusion, SDF-1/CXCL12 may serve as a "molecular hub" that modulates both angiogenesis and vasculogenesis (39).

Much less information is available on the possible angiogenic capacity of CC chemokines. MCP-1/CCL2 induced endothelial cell chemotaxis *in vitro* and angiogenesis *in vivo* (21,22). MCP-1/CCL2 stimulates vessel formation via its receptor, CCR2, which is expressed on the surface of endothelial cells (21). This chemokine exerts its angiogenic activity by the upregulation of the Ets-1 transcription factor. This process also involves integrins and ERK-1/2 activation (22). MCP-1/CCL2 is a mediator of TGF-β-induced angiogenesis. This chemokine stimulates the migration of vascular smooth muscle cells (46). Fibroblast growth factor 2 (FGF-2) enhances MCP-1/CCL2-driven vasculogenic signals (47). Thus, MCP-1/CCL2 may act in concert with other angiogenic mediators during angiogenesis and vasculogenesis (Table 1).

Among other CC chemokines, myeloid progenitor inhibitory factor 1 (MPIF-1)/CCL23 has been implicated in endothelial cell migration and metalloproteinase secretion (48). In contrast, secondary lymphoid tissue chemokine (SLC)/CCL21 exerts remarkable angiostatic effects and inhibits tumor progression (49). Yet, the role of CC chemokines in angiogenesis needs further investigation (Table 1).

Fractalkine/CX_3CL1 has been implicated in angiogenesis, as well as atherosclerosis (25,50,51). Fractalkine/CX_3CL1 stimulates neovascularization (24,25). Mice lacking the fractalkine receptor CX_3CR1 developed less pronounced atherosclerosis than wild type animals (50). In addition, an M280/I249 polymorphism in the CX_3CR1 gene has been associated with lower cardiovascular risk in humans (51). As fractalkine/CX_3CL1 is abundantly produced in RA (24,25) and increased cardiovascular risk is a leading mortality factor in RA, these observations may have important clinical relevance.

4.3. Chemokine receptors in neovascularization

CXCR2 recognizes the most important proinflammatory and pro-angiogenic, ELR^+ CXC chemokines (5,14) (Table 1; Figure 1). CXCR2 is expressed on RA macrophages, neutrophils, articular chondrocytes, as well as on endothelial cells during inflammation (5,14,21,52). As discussed above, CXCR4 has been implicated in SDF-1/CXCL12-induced synovial neovascularization (17,18). Hypoxia induces CXCR4 expression in glioblastoma via hypoxia-inducible factor 1 (HIF-1) and VEGF production (53). CXCR7 recognizing I-TAC/CXCR11 and SDF-1/CXCL12 may also be involved in angiogenesis (45) (Table 1).

CCR2 is a receptor for MCP-1/CCL2 and some other CC chemokines (5,14). As described above, MCP-1/CCL2 has been implicated in synovial angiogenesis (21). Among other CC chemokine receptors, CCR2 is also produced in the joint (52). In a recent study using a murine model of skeletal muscle injury, CCR2-deficient animals had delayed muscular angiogenesis and decreased VEGF production (54). Thus, CCR2 may be important in VEGF-mediated neovascularization.

DARC, originally described on red blood cells, binds the Duffy antigen, as well as some CXC and CC chemokines. RA synovial endothelium also expresses DARC (55). DARC has been implicated in breast cancer-associated neovascularization (56).

Chemokine receptors described above have been associated with angiogenesis. Conversely, CXCR3, which binds the angiostatic chemokines IP-10/CXCL10 and MIG/CXCL9, may be involved in chemokine-mediated angiogenesis inhibition (5).

4.4. Regulation of chemokine-induced synovial angiogenesis

The outcome of synovial neovascularization depends on the imbalance between angiogenic mediators and angiogenesis inhibitors. There are several interactive mechanisms involving inflammatory mediators in the RA synovium (1,2,5,7). Some pro-inflammatory cytokines may directly stimulate angiogenesis or may act indirectly by enhancing the production of angiogenic chemokines. Indeed, TNF-α and IL-1 stimulate the release of chemokines by RA synovial fibroblasts (1-5). IL-18 exerts its proinflammatory and angiogenic effects at least in part by inducing the secretion of angiogenic SDF-1/CXCL12 and MCP-1/CCL2 by RA synovial tissue fibroblasts (57). Macrophage migration inhibitory factor (MIF) is a pro-inflammatoy and angiogenic cytokine in RA (58,59). MIF also stimulates the production of angiogenic chemokines, such as IL-8/CXCL8 (60,61). On the other hand, in a recent study, IL-13 gene transfer in rat adjuvant-induced arthritis resulted in the suppression of angiogenesis, which was associated with the downregulation of the angiogenic chemokines groα/CXCL1 and ENA-78/CXCL5 (62). Possible interactions between VEGF and HIFs or IP-10/CXCL10 are described above (5,33,34). Other regulatory mechanisms include the balance between specific antagonistic pairs, such as ELR^+ versus ELR^- chemokines (5,14,27,28). The effects of anti-chemokine therapy on angiogenesis will be discussed later.

5. PRACTICAL ISSUES WITH RESPECT TO CHEMOKINE-INDUCED ANGIOGENESIS IN RA

5.1. The possible prognostic value of chemokines and angiogenesis

The number of newly formed blood vessels in biopsy samples indicating the extent of neovascularization

may also reflect the progression of the disease, similarly to that, which has been observed in malignancies (1,2). For example, significantly higher number of synovial vessels have been detected histologically in RA in comparison to osteoarthritic or normal synovial tissues (5,63,64). The synovial expression of some angiogenic mediators including chemokines may also have some prognostic value. As described above, the expression of SDF-1/CXCL12 in gliomas correlated with tumor progression (43). Thus, the synovial expression of certain inflammatory and angiogenic chemokines may also be correlated with synovial inflammation.

5.2. Inhibition of angiogenic and use of angiostatic chemokines to control synovial neovascularization

As described above, numerous chemokines promote angiogenesis and these mediators may be targeted by small molecular inhibitors or specific antibodies. On the other hand, some ELR$^-$ chemokines suppress neovascularization (1-5,14).

Among anti-inflammatory and antirheumatic drugs currently used in the treatment of RA, corticosteroids, such as dexamethasone, effectively suppressed IL-8/CXCL8 and MCP-1/CCL2 production in RA (65,66). Non steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac and meloxicam attenuated IL-8/CXCL8 production in rat antigen-induced arthritis (67). Sulfapyridine, a constituent of sulfasalazine, inhibited the production of IL-8/CXCL8 by pro-inflammatory cytokine-stimulated endothelial cells (68). TNF-α blockade using infliximab reduced the serum levels and/or synovial expression of IL-8/CXCL8, MCP-1/CCL2, groα/CXCL1, as well as angiogenesis in RA patients (69,70). As discussed above, IL-13 gene transfer resulted in the suppression of angiogenesis and the production of angiogenic CXC chemokines (62).

Among angiostatic chemokines, PF4/CXCL4 has been tried in animal models of arthritis (2,7,34). Its variant, PF4var/CXCL4L1 inhibited tumor progression (36), and thus may also be used to control synovial angiogenesis. Mig/CXCL9 chemokine gene therapy improved the therapeutic efficacy of some cytotoxic agents in cancer (71). Blockade of CXCR2 also inhibited tumor-associated angiogenesis (72). In general, most angiostatic chemokines may have therapeutic relevance for RA-associated angiogenesis as well.

6. CONCLUSIONS

In this review, we have discussed the potential role of chemokines in arthritis-associated angiogenesis. A number of CXC chemokines, as well as some CC and CX_3C chemokines may be involved in the angiogenic, as well as inflammatory events underlying RA. In addition, chemokine-induced angiogenesis may have clinical relevance as well. The determination of synovial vascularity and the expression of angiogenic chemokines in the arthritic synovium may have some value for determining the progression of RA. Anti-angiogenesis targeting using chemokine or chemokine receptor inhibitors may control synovial inflammation.

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