Angiogenesis and chemokines in rheumatoid arthritis and other systemic inflammatory rheumatic diseases

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Abstract

Angiogenesis, the formation of new vessels, is important in the pathogenesis of rheumatoid arthritis (RA) and other inflammatory diseases. Chemotactic cytokines termed chemokines mediate the ingress of leukocytes, including neutrophils and monocytes into the inflamed synovium. In this review, authors discuss the role of the most important angiogenic factors and angiogenesis inhibitors, as well as relevant chemokines and chemokine receptors involved in chronic inflammatory rheumatic diseases. RA was chosen as a prototype to discuss these issues, as the majority of studies on the role of angiogenesis and chemokines in inflammatory diseases were carried out in arthritis. However, other systemic inflammatory (autoimmune) diseases including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome (SS), mixed connective tissue disease (MCTD), polymyositis/dermatomyositis (PM/DM) and systemic vasculitis are also discussed in this context. As a number of chemokines may also play a role in neovascularization, this issue is also described here. Apart from discussing the pathogenic role of angiogenesis and chemokines, authors also review the regulation of angiogenesis and chemokine production by other inflammatory mediators, as well as the important relevance of neovascularization and chemokines for antirheumatic intervention.

Keywords: angiogenesis • chemokine • chemokine receptor • rheumatoid arthritis • systemic lupus erythematosus • systemic sclerosis • mixed connective tissue disease • Sjögren's syndrome • polymyositis • dermatomyositis • vasculitis

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Angiogenesis in rheumatoid arthritis

Angiogenesis, the formation of new blood vessels, is a crucial process in a number of physiological processes, such as reproduction, development and tissue repair, as well as in disease states including, among others, rheumatoid arthritis (RA) and other inflammatory diseases. The angiogenic process, 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 are extensively discussed in a number of reviews [1-9]. In contrast, less information is available on the role of neovascularization in other systemic inflammatory (autoimmune) conditions, such as systemic sclerosis (scleroderma, SSc), systemic lupus erythematosus (SLE), polymyositis/ dermatomyositis (PM/DM), Sjögren's syndrome (SS), mixed connective tissue disease (MCTD) or systemic vasculitides [10-18]. Therefore, the most important angiogenic mediators and inhibitors, and their role in neovascularization will be discussed in context with RA. Scattered publications are available regarding the other diseases listed above.

Angiogenesis is a well-programmed cascade of events, which contains a number of distinct steps. Angiogenic factors activate endothelial cells, which, in turn, produce proteolytic enzymes including matrix metalloproteinases and plasminogen activators. This results in the degradation of the basement membrane and the perivascular extracellular matrix. Endothelial cells proliferate and migrate into the perivascular area and thus "primary sprouts" are formed. The lumenation of sprouts leads to the formation of "capillary loops" followed by synthesis of new basement membrane and finally, capillary formation. Endothelial cells are released from the primary sprouts and loops, in order to form secondary and further generations of sprouts and loops. A number of inflammatory mediators, as angiogenic factors, promote this process [reviewed in 5, 7].

In RA, leukocytes emigrate into the synovium through the vascular endothelium. The RA synovium is rich in newly formed vessels. Increased angiogenesis found in RA further perpetuates the extravasation of leukocytes and thus synovitis, which leads to the progression of RA. Therefore, RA is considered an important candidate

for "angiogenic diseases" [4-7]. The angiogenic process and the outcome of such "angiogenic diseases" are dependent on the balance or imbalance between angiogenic mediators and inhibitors (Table 1). In RA, there is an excess of many angiogenic factors over angiogenesis inhibitors. In order to reset this balance, one needs to suppress neovascularization by blocking the action of angiogenic mediators, or administer angiostatic compounds. These strategies may be useful in controlling the progression of RA and thus may have therapeutic benefit for patients [reviewed in 4-9].

A number of *in vitro* and *in vivo* models are available to study angiogenesis. *In vitro* systems include endothelial cultures grown on extracellular matrix, such as the laminin-containing Matrigel, tissue culture systems or endothelial chemotaxis assays [4-8, 19-22]. *In vivo* neovascularization has been investigated using the rat, murine, rabbit, or guinea pig corneal micropocket, the chick embryo chorioallantoic membrane, the hamster cheek pouch, the mesenteric, the implanted matrix assays, sponge models, as well as other systems [4-8]. These models are suitable to test soluble or cell-bound mediators for their capacity to induce or suppress angiogenesis. This may be important to investigate the role of angiogenesis in the pathogenesis of certain diseases but also to design strategies for anti-angiogenesis therapies.

Angiogenic mediators involved in the progression of RA include a wide variety of growth factors, cytokines, chemokines, cell adhesion molecules, extracellular matrix components, proteolytic enzymes and several other factors (Table 1). Most of these mediators are released by endothelial cells and macrophages; cells present in high quantities in the RA synovium [reviewed in 2-9].

Among *growth factors*, basic (bFGF) and acidic fibroblast growth factors (aFGF), vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF)/scatter factor are bound to heparin or heparan sulfate in the interstitial matrix. During the process of angiogenesis, these mediators are released from the matrix by endothelial-derived heparanase and plasmin [4-8, 23]. Recent studies revealed, that VEGF, at least in part, stimulated angiogenesis via cyclooxygenase-2 (COX-2) induction [24]. A novel function of VEGF in angiogenesis has been described recently in one

Table 1. Some angiogenic mediators and inhibitors in rheumatoid synovitis.

1. Growth factors	BFGF, aFGF VEGF HGF PDGF, PD-ECGF EGF IGF-1 TGF- β *	TGF- β *
2. Cytokines	TNF- α IL-1* IL-6* IL-13 IL-15 IL-18	IL-1* IL-4 IL-6* IFN- α , - β
3. Chemokines	IL-8 ENA-78 Gro α CTAP-III MCP-1 Fractalkine SDF-1	PF4 IP-10 MIG
4. Matrix molecules	Type I collagen Fibronectin, laminin Heparin, heparan sulphate	RGD sequence Thrombospondin
5. Proteolytic enzymes/inhibitors	Matrix metalloproteinases Plasminogen activators	Metalloproteinase inhibitors Plasminogen activator inhibitors
6. Adhesion molecules	β 1, β 3 integrins Soluble E-selectin Soluble VCAM-1 Endoglin CD31 (PECAM-1) Lewis-Y/H MUC18	RGD sequence
7. Others	Angiogenin PAF Substance P Prolactin Prostaglandin E2	Some antirheumatic drugs Some antibiotics SPARC Angiostatin Endostatin

study. VEGF upregulated decay accelerating factor (DAF) expression on endothelial cells. It was suggested that VEGF, via the induction of DAF, protects endothelial cells against complement-mediated injury during angiogenesis [25]. Other investigators characterized a subpopulation of circulating human CD34⁺ cells expressing the VEGF-2 receptor. These cells seem to be functional endothelial precursors playing a role in angiogenesis [26]. Other growth factors that mediate neovascularization, such as platelet-derived (PDGF), platelet-derived endothelial cell (PD-ECGF), epidermal (EGF), insulin-like (IGF-I) and transforming growth factor (TGF)- β , do not bind to heparin. However, these growth factors may also promote capillary formation [4-7, 27, 28].

Among pro-inflammatory *cytokines*, which also play a role in RA, tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-8, IL-13, IL-15, and possibly IL-6 are involved in angiogenesis [4-9, 29]. The role of C-X-C chemokines containing the ELR motif in angiogenesis will be discussed later.

In addition to growth factors, cytokines and chemokines, *extracellular matrix components* including type I collagen, fibronectin, heparin, laminin, tenascin; *proteolytic enzymes*, such as matrix metalloproteinases (MMP) and plasminogen activators; as well as *some cellular adhesion molecules* including soluble E-selectin and soluble vascular cell adhesion molecule-1 (VCAM-1), some endothelial β 1, β 3 and β 5 integrins, platelet-endothelial cell adhesion molecule (PECAM; CD31) and endoglin (CD105) have been implicated in angiogenesis. These molecules play an important role in cell adhesion and migration underlying synovial inflammation [reviewed in 5, 2, 4, 6, 8, 9]. We have recently described that glycoconjugates may also serve as angiogenic mediators. In our hands, Lewis-y/H, which is structurally related to the E-selectin ligand sialyl-Lewis-x, promoted neovascularization using both *in vitro* and *in vivo* models. This glycoconjugate was detected in the RA synovium [30]. MUC18 (CD146) is a marker for melanoma metastatic potential. This is a molecule with adhesive properties. Levels of MUC18 in RA synovial fluids were correlated with synovial angiogenesis [31]. The role of most MMPs has been widely studied in RA. A novel family of metalloproteinases termed ADAMTS proteinases includes aggrecanase-1 and -2. These aggrecanases

are expressed in the RA synovium, mostly at sites of neovascularization [32].

The role of the cyclooxygenase/prostaglandin system in angiogenesis has been described. Prostaglandin E2 was found to be angiogenic [5, 8]. In addition, the role of COX-2 in VEGF-dependent neovascularization has recently been discussed [24, 33].

Other angiogenic molecules, also produced by synovial cells, including angiogenin, platelet-activating factor (PAF), substance P have been suggested to play a role in RA-associated angiogenesis [reviewed in 4-9]. Recently, prolactin and prolactin-like polypeptides were detected in RA synovial tissues. Prolactin was found to play an important role in T cell activation, cell communication and synovial angiogenesis [34].

Recent studies revealed that preferential endothelial precursor cells may exist within the population of blood stem cells. These reports suggest, that a distinct subpopulation of CD34⁺ cells carrying VEGF receptors may, under circumstances, develop into endothelial cells [26]. These cells may be important in the induction and perpetuation of angiogenesis and they may also be used for the induction of neovascularization in future therapeutic trials carried out in patients with certain vascular disorders.

Angiogenesis inhibitors in RA include a few cytokines and growth factors, some of which may also stimulate neovascularization under different circumstances, such as TGF- β , IL-1 α , IL-1 β , IL-4, IL-6, IL-12, interferon- α (IFN- α) and IFN- γ , leukemia inhibitory factor (LIF) as well as ELR- C-X-C chemokines [reviewed in 4-9, 35] (Table 1). The role of angiostatic chemokines will be discussed later.

In addition, a number of antirheumatic drugs currently used in the treatment of RA, such as corticosteroids, as well as most disease-modifying antirheumatic drugs (DMARD) including chloroquin, sulfasalazine, cyclosporin, gold salts and methotrexate inhibit angiogenesis. Protease inhibitors including tissue inhibitors of metalloproteinases (TIMP) and plasminogen activator inhibitors (PAI); thrombospondin-1; derivatives of antibiotics including fumagillin and minocyclin; some cartilage-derived inhibitors, tumor-derived angiostatic agents including angiostatin and endostatin; cytoskeleton-

disassembling agents including taxol; Secreted Protein Acidic and Rich in Cysteine (SPARC)/osteonectin; as well as several other compounds block neovascularization [reviewed in 4-9, 35] (Table 1). Low endostatin levels were detected in RA peripheral blood and synovial fluid samples [36]. According to recent reports, thalidomide, a TNF- α antagonist compound, which has currently been reintroduced into immunosuppressive therapy, inhibits neovascularization [37, 38]. Many of these factors influence the progression of RA and thus, they may be useful for the management of this disease.

The angiogenic process and the outcome of angiogenesis, and thus the extent of leukocyte ingress into the synovium, depends on the imbalance between angiogenic and angiostatic mediators mostly produced by synovial macrophages, endothelial cells and fibroblasts [reviewed in 4-9] (Table 1). Several intermolecular interactions and feedback loops exist in the RA synovial tissue, as well as in other inflamed tissues, which regulate capillary formation. Some of these key mechanisms will be discussed later.

Angiogenesis research has important practical clinical - prognostic and therapeutic - relevance. Regarding its diagnostic, prognostic value, the number of synovial blood vessels in biopsy specimens may reflect the progression of the disease, similarly to the correlation between angiogenesis and the metastatic potential of tumors [reviewed in 4-9]. We and others have demonstrated increased vascularity in arthritic compared to normal synovial tissues [39, 40]. The elevated concentration of the angiogenic soluble E-selectin in the synovial fluid of RA patients may also be a useful marker of increased endothelial activation and neovascularization [41, 42]. The therapeutic relevance of angiogenesis will be discussed later in this review.

Angiogenesis in systemic autoimmune diseases

There is relatively little information available on the role of angiogenesis in other systemic inflammatory diseases. In SLE, thalidomide, a potent angiogenesis inhibitor with other anti-

inflammatory effects had some effect on clinical and laboratory markers of disease activity [10].

There are controversial results on neovascularization in SSc. We reported that monocytes isolated from SSc patients show impaired angiogenic activity upon LPS stimulation [14]. In addition, increased concentrations of the angiostatic endostatin was detected in the sera of SSc patients [12]. These studies suggest that decreased angiogenesis may be responsible for aberrant vascular proliferation and ischemic manifestations seen in SSc. On the other hand, SSc skin biopsy explants stimulated neovascularization in the chick embryo chorioallantoic membrane assay [13]. There is a possibility, that SSc is associated with altered systemic angiogenesis, but the local up-regulation of neovascularization and production of angiogenic mediators may be involved in the local wound healing process. Anyway, relaxin, a potent stimulator of angiogenesis, is in clinical trials in SSc [11].

We have not found any data in the literature in angiogenesis in MCTD, PM/DM or SS. Regarding systemic vasculitis, most data on angiogenesis concern Kawasaki disease. In this type of vasculitis, increased production of VEGF and TGF- β was found. There was a correlation between plasma levels of VEGF and TGF- β in acute vasculitis [16]. In a murine model of Kawasaki disease, AGM-1470, a potent angiogenesis inhibitor, suppressed coronary vasculitis [15]. Increased serum levels of TGF- β 1 were found in three types of ANCA-associated vasculitis namely Wegener's granulomatosis, Churg-Strauss syndrome and microscopic polyangiitis. TGF- β 1 levels were correlated with disease activity in Wegener's granulomatosis. In addition, TGF- β 1 was found to be a potent translocation factor for the ANCA autoantigen proteinase 3 in neutrophils [17]. Finally, haptoglobin has recently been identified as an angiogenic factor, which is involved in vasculitis-associated neovascularization [18].

Chemokines, chemokine receptors and their role in rheumatoid arthritis

Chemotactic cytokines termed chemokines are involved in leukocyte chemotaxis and migration

through the endothelial barrier into the inflamed synovium, which is an important process in the pathogenesis of RA [reviewed in 43-45]. Chemokines have been classified into four distinct supergene families, such as C-X-C, C-C, C and C-X3-C chemokines, based on the location of conserved cysteine residues [reviewed in 43, 46-49]. Members of these chemokine families bind to their receptors designated as CXCR, CCR, CR and CX3CR chemokine receptors, respectively [reviewed in 9, 43, 50]. Recently, a new classification system has been introduced where chemokines are considered as chemokine ligands and each chemokine has been assigned a designation of CXCL (CXCL1 to CXCL15), CCL (CCL1 to CCL27), XCL and CX3CL1 [50] (Table 2).

Recent reviews discuss the role of chemokines, mostly members of the C-X-C and C-C families, in RA [reviewed in 9, 43, 44] (Tables 2 and 3). It has been shown by us and other investigators that among *C-X-C chemokines*, interleukin-8 (IL-8;

CXCL8), epithelial-neutrophil activating protein-78 (ENA-78; CXCL5), growth-related gene product α (gro α ; CXCL1), and connective tissue activating protein-III (CTAP-III; CXCL6) play a role in the pathogenesis of RA synovitis [reviewed in 43, 44, 51]. These chemokines mediate the chemotaxis of neutrophils [9, 43, 44, 51]. In addition, these chemokines promote angiogenesis [9, 52, 53] (Table 2). It has been shown, that IL-8, ENA-78, gro α and CTAP-III contain the ELR (glutamyl-leucyl-arginyl) amino acid sequence, which motif is responsible for their angiogenic activity [52-54]. In contrast to these “pro-inflammatory C-X-C chemokines”, other C-X-C chemokines, such as platelet factor-4 (PF4; CXCL4), monokine induced by interferon- γ (MIG; CXCL9), interferon- γ -inducible protein (IP-10; CXCL10) and stromal-derived factor-1 (SDF-1; CXCL12) may rather exert anti-inflammatory action [reviewed in 9, 43, 49, 50] (Table 1). These latter C-X-C chemokines lack the ELR motif and

Table 2 Some chemokines with importance in inflammatory rheumatic diseases.

C-X-C chemokines

Interleukin-8 (IL-8, CXCL8)
 Epithelial-neutrophil activating protein-78 (ENA-78, CXCL5)
 Growth-related gene product α (gro α , CXCL1)
 Connective tissue activating protein-III (CTAP-III, CXCL6)
 Interferon- γ -inducible protein (IP-10, CXCL10)
 Platelet factor 4 (PF4, CXCL4)
 Monokine induced by IFN- γ (MIG, CXCL9)
 Stromal cell-derived factor (SDF-1, CXCL12)
 B cell-attracting chemokine (BCA-1, CXCL13)

C-C chemokines

Monocyte chemoattractant protein-1 (MCP-1, CCL2)
 Macrophage inflammatory protein-1 α (MIP-1 α , CCL3)
 Macrophage inflammatory protein-3 α (MIP-3 α , CCL20)
 Regulated upon activation normally T cell expressed and secreted (RANTES, CCL5)

C chemokines

Lymphotactin (XCL1)

C-X3-C chemokines

Fractalkine (CX3CL1)

Table 3 Some relevant chemokine receptors with ligands involved in arthritis. See Table 2 and text for abbreviations.

Chemokine receptor	Ligand with importance in arthritis
<i>C-X-C chemokine receptors</i>	
CXCR1	IL-8
CXCR2	IL-8, ENA-78, gro α
CXCR3	IP-10, MÍG
CXCR4	SDF-1
CXCR5	BCA-1
DARC (Duffy antigen receptor for chemokines)	IL-8, ENA-78, gro α
<i>C-C chemokine receptors</i>	
CCR1	MIP-1 α , RANTES
CCR2	MCP-1
CCR3	RANTES
CCR4	
CCR5	MIP-1 α , MIP-1 β , RANTES
CCR6	MIP-3 α
CCR7	
CCR8	
CCR10	MCP-1, RANTES
<i>C-X3-C chemokine receptors</i>	
CX3CR1	Fractalkine

thus they inhibit neovascularization [52-54]. As an exception, the ELR-lacking SDF-1 is angiogenic [9, 54] (Table 3).

C-C chemokines chemoattract predominantly monocytes, although they may also chemoattract T and NK cells, basophils and eosinophils [43, 48]. C-C chemokines involved in the pathogenesis of RA include monocyte-chemoattractant protein-1 (MCP-1; CCL2), macrophage inflammatory protein-1 α (MIP-1 α ; CCL3), MIP-3 α (LARC; CCL20) and Regulated upon Activation Normally T-cell Expressed and Secreted (RANTES; CCL5)

[43, 49, 50, 55-58] (Table 2). Pro-inflammatory cytokines including TNF- α and IL-1 β stimulate the production of IL-8, ENA-78, gro α , MCP-1, MIP-1 α and RANTES [reviewed in 9, 43, 44].

Recently, C chemokines and C-X3-C chemokines have been described based on the unique position of cysteine residues [9, 43, 46]. The former family contains lymphotactin (XCL1), while the latter family includes fractalkine (CX3CL1) [9, 43, 50, 46, 59, 60]. Lymphotactin is involved in the migration of T cell subsets to inflammatory sites [60]. Fractalkine is expressed on

cytokine-activated endothelia, but not on peripheral blood leukocytes [46, 59].

Chemokine receptors exhibit a nonspecific affinity for their chemokine ligands (Table 3). The C-X3-C chemokine, fractalkine, has its own receptor, termed CX3CR1 [46, 59]. It has been suggested that chemokine receptors may play a differential role in various types of inflammation. For example, CCR3 is expressed by lymphocytes exhibiting the Th2, but not the Th1 phenotype. Accordingly, CCR3 is expressed in allergic lymphocytic infiltrates. In contrast, CCR5, present on most Th1, but not on Th2 type lymphocytes, has been detected in the RA synovium. CXCR3, expressed by both Th1 and Th2 type cells, was detected in both allergic and ST infiltrates [61]. Regarding angiogenesis, endothelial cells express receptors for angiogenic chemokines, most importantly CXCR2, which is important in chemokine-mediated neovascularization [9, 43, 49, 53, 62-64].

Regarding the production of specific C-X-C chemokines in RA, large amounts of bioactive IL-8 (CXCL8) were detected in the synovia and sera of RA patients [65-67]. In the RA synovium, interstitial macrophages, macrophage-derived synovial lining cells and endothelial cells express IL-8 [66, 68]. In a recent arthroscopic study, IL-8 protein and mRNA levels were increased in the involved joints compared to the uninvolved joints of RA patients [69]. IL-8 induced synovial inflammation after a single intraarticular injection of recombinant IL-8 administered into the rabbit knee joint. The histological picture resembled the human RA synovium [67]. IL-8 up-regulates leukocyte adhesion molecule expression in RA [70]. We have presented IL-8 as a mediator of angiogenesis [22, 68] (Table 4).

ENA-78 (CXCL5) is a potent chemotactic factor for neutrophils exerting angiogenic activity [49, 53, 68, 71] (Tables 2 and 4). Large amounts of ENA-78 were detected in RA synovia [57]. Synovial lining cells, interstitial macrophages, endothelial cells and fibroblasts produce ENA-78 [57]. We have studied the temporal expression of an ENA-78-like protein in the sera and joint homogenates of rats with adjuvant-induced arthritis (AIA). We found significant levels of this chemokine in the sera of arthritic rats. The levels of ENA-78-like protein in ankle joint homogenates were increased in arthritic rats later in the development of the disease [72].

Gro α (CXCL1), apart from its chemotactic effects on neutrophils, stimulates fibroblast growth and tissue fibrosis, as well as angiogenesis [49, 53] (Tables 2 and 4). Synovial neutrophils, mononuclear cells, isolated synovial fibroblasts and articular chondrocytes produce gro α [55, 73].

CTAP-III (CXCL6) is a human platelet α -granule derived growth factor [74]. CTAP-III is angiogenic and affects many aspects of connective tissue metabolism including the proliferation and proteoglycan production of synovial fibroblasts [52, 53, 74, 75] (Tables 2 and 4). RA sera and synovia contain high levels of CTAP-III [74, 75].

IP-10 (CXCL10), PF4 (CXCL4) and MIG (CXCL9), unlike other C-X-C chemokines described above, chemoattract monocytes and T cells rather than neutrophils and they exert mostly anti-inflammatory and anti-angiogenic effects [6, 49]. These chemokines lack the ELR domain in their structure and thus inhibit neovascularization [52, 53] (Tables 2 and 4). Very little IP-10 has been detected in the sera of RA patients [76]. On the other hand, significant amounts of IP-10 was found in RA synovial fluids and tissues [77]. MIG was also detected in RA synovia and in the lining layer of RA synovial tissues [77]. A PF4-derived peptide inhibited murine type II collagen-induced arthritis (CIA) [51].

SDF-1 (CXCL12) specifically binds to CXCR4 (fusin) (Tables 2 and 4). SDF-1 is expressed by synovial endothelial cells and is involved in synovial T cell adhesion [78]. SDF-1 has been implicated in CD4⁺ T cell recruitment into the RA synovium [79]. SDF-1 may be a unique chemokine as it lacks the ELR motif, but, in contrast to IP-10, PF4 and MIG, promotes angiogenesis [54, 80] (Tables 2 and 4).

Among C-C chemokines, MCP-1 (CCL2) is chemotactic for monocytes, T cells, NK cells and basophils [48]. MCP-1 induces capillary formation both *in vitro* and *in vivo* [63]. High levels of MCP-1 were detected in the sera and synovial fluids of RA patients [56, 81]. The main function of MCP-1 in the joint may be the recruitment of macrophages, as injection of MCP-1 into rabbit joints resulted in marked macrophage infiltration of the synovium [81].

MIP-1 α (CCL3) is chemotactic for monocytes, T, B and NK cells, basophils and eosinophils [43, 48]. Large amounts of MIP-1 α were found in RA synovial fluid samples [82]. Synovial mononuclear

Table 4 Effects of chemokines in inflammatory rheumatic conditions.

Chemokine	Proinflammatory	Angiogenesis
<i>C-X-C chemokines</i>		
IL-8	+	+
ENA-78	+	+
gro α	+	+
CTAP-III	+	+
IP-10	-	-
PF4	-	-
MIG	-	-
SDF-1	+/-	+
<i>C-C chemokines</i>		
MCP-1	+	+
MIP-1 α	+	ND
MIP-3 α	+	ND
RANTES	+	ND

ND Abbreviations +: stimulation; -: inhibition; ND: not determined. See text for additional abbreviations

cells and fibroblasts abundantly produce MIP-1 α [55, 82].

MIP-3 α (CCL20) is a recently identified C-C chemokine with chemotactic activity towards memory T cells, naive B cells, monocytes and immature dendritic cells. This chemokine binds to its specific receptor CCR6 [83, 84] (Tables 2 and 3). MIP-3 α was detected in RA synovial fluids and tissues. Synovial lining cells and infiltrating mononuclear cells expressed this chemokine [83, 84].

RANTES (CCL5) is a chemotactic factor for monocytes, memory T lymphocytes, NK cells, eosinophils and basophils [48, 84]. RA synovial fibroblasts produce RANTES mRNA upon stimulation with TNF- α or IL-1 [55, 58]. RANTES was detected in RA synovial tissue lining layer and sites of lymphocytic infiltration [86].

There is relatively little information available on the role of the C chemokine lymphotactin (XCL) in

arthritis. In one *in vitro* study using a transwell system, lymphotactin stimulated the transmigration of the CD45RO+/CD45RB- T cell subset. This subpopulation of T lymphocytes preferentially accumulates *in vivo* within the affected joint of RA patients [60].

Fractalkine (CX3CL1), the only known CX3C chemokine, is chemotactic for monocytes and lymphocytes and also serves as a cellular adhesion molecule [46, 59]. High levels of fractalkine were found in RA sera and synovial fluids. RA synovial tissue macrophages, fibroblasts, endothelial and dendritic cells expressed fractalkine [59, 87].

Among C-X-C chemokine receptors, CXCR3, and among C-C chemokine receptors, CCR5 show strong expression on RA synovial T cells [61]. Others found high expression of CCR5 and CXCR3 on synovial fluid T cells in juvenile RA associated with a high IFN- γ /IL-4 ratio, suggesting a preferential Th1 over Th2 phenotype of these T

cells [88]. Among chemokines listed in Table 2, the main ligand for CXCR3 is IP-10, while the main ligands for CCR5 are MIP-1 α and RANTES (Table 3). Apart from CCR5 and CXCR3, other chemokine receptors may also be involved in RA. For example, CCR6, a receptor for MIP-3 α , was detected on infiltrating leukocytes in the RA synovium [83]. CXCR4, the only receptor for SDF-1, may play a role in the SDF-1-derived retention of T cells within the RA synovial tissue [78, 79]. We have compared chemokine receptor expression on peripheral blood, synovial fluid and synovial tissue monocytes/macrophages in RA. In our hands, RA blood monocytes expressed CCR1, CCR2, CCR3, CCR4 and CCR5. Synovial fluid cells expressed CCR3 and CCR5, but very little CCR1, CCR2, and CCR4. In RA synovial tissues, CCR1, CCR2 and CCR5-immunoreactivity was detected in areas of CD68+ macrophages. We suggested that while some chemokine receptors may play a role in monocyte recruitment from the circulation, others may be involved in monocyte retention in the joint [89].

Chemokines and their receptors in systemic inflammatory diseases

The production of various chemokines and chemokine receptors has been investigated in *SLE*. IP-10 is a potent chemoattractant for Th1 cells. As both Th1 cells and IFN- α are involved in the development of SLE, serum IP-10 levels were measured in this disease. Serum IP-10 levels were elevated in SLE and correlated with disease activity. IP-10 concentrations correlated positively with anti-DNA autoantibody levels and negatively with serum complement concentrations [90]. Regarding C-C chemokines, serum MCP-1, RANTES, but not MIP-1 α levels were also increased in SLE patients compared to healthy controls [91]. Serum MCP-1 concentrations increased with the progression of SLE disease activity [91]. In a cDNA array assay, the expression pattern of 375 genes potentially relevant for SLE were analyzed using peripheral blood mononuclear cells from SLE patients and normal controls. Among other genes, IL-8 gene exhibited more than 2.5-fold difference in expression level in SLE compared to control subjects [92]. Regarding

chemokine receptors, CCR4 seems to be an important receptor in the pathogenesis of SLE. CCR4 is selectively expressed on Th2 type T cells. Higher expression of CCR4 was found on peripheral blood CD4⁺ T cells from active SLE patients in comparison to cells from inactive SLE patients or healthy controls. In addition, CCR4 expression correlated with SLE disease activity index (SLEDAI) scores [93]. In another study, most T cells infiltrating the renal tissue taken from lupus nephritis patients expressed CCR4 but not CCR5 [94].

Regarding *SSc*, isolated *SSc* dermal fibroblasts showed abundant expression of MCP-1 mRNA. Increased production of MCP-1 by these fibroblasts resulted in higher chemotactic activity for monocytes in a transmigration assay. In addition, MCP-1 protein was detected in fibroblasts, keratinocytes and infiltrating leukocytes in the *SSc* skin [95]. In another study, MCP-1 induced α 1(I) collagen mRNA expression in dermal fibroblasts suggesting the role of MCP-1 in dermal fibrosis [96]. Finally, significantly higher frequency of two single-nucleotide polymorphisms in the IL-8-receptor CXCR2 gene was found in *SSc* patients compared to healthy controls [97].

In *SS*, chemokine expression in minor salivary gland biopsies was investigated. Ductal epithelial cells showed abundant expression of IL-8, MIP-1 α , MIP-1 β and RANTES. These results suggest that ductal epithelial cells may chemoattract inflammatory leukocytes by producing chemokines [98]. In another study, chemokine mRNA expression in *SS* salivary glands was investigated using RT-PCR and in situ hybridization. Monocyte-derived chemokine/STCP-1 and TARC mRNA were expressed in the majority of *SS* salivary glands. The main cellular sources of chemokine mRNA were ductal epithelial cells and infiltrating mononuclear cells [99]. *SS* is associated with the formation of germinal center-like structures containing large number of B cells. The expression of B cell-attracting chemokine 1 (BCA-1, CXCL13) and SDF-1 (CXCL12) was investigated in salivary gland biopsies. BCA-1 was expressed within lymphoid aggregates resembling germinal centers, but was totally absent from non-*SS* salivary glands. In addition, BCA-1 showed ectopic expression on salivary gland endothelial cells. SDF-1 was expressed on epithelial cells, while

CXCR4, the receptor for SDF-1 was detected on periductal T cells. Thus, ductal epithelial SDF-1 and ectopic, endothelial BCA.1 expression may create a local environment supportive of local B cell aggregation and differentiation [100-102]. In the autoimmune sialoadenitis model of SS raised in MRL/lpr mice, a number of C-C chemokines including MCP-1, MIP-1 α , MIP-1 β and RANTES showed abundant expression in the salivary gland tissue [103].

C-C chemokines seem to play an important role in the pathogenesis of inflammatory myopathies including PM/DM. MCP-1 protein and mRNA expression was abundant in perivascular mononuclear cells in frozen muscular tissues [104]. Significant expression of MCP-1, MIP-1 α and RANTES proteins and mRNA were detected in most muscle biopsy samples taken from PM/DM patients [105, 106].

Regarding *systemic vasculitides*, a Th2 dominance associated with high expression of CCR3 by infiltrating cells was found in nasal mucosa biopsy samples taken from Wegener's granulomatosis patients [107]. In addition, CCR3 and its ligand, eotaxin showed abundant expression in unstable atherosclerotic lesions showing high degree of inflammation [108]. ANCA autoantibodies may also play a role in chemokine production, as the incubation of human peripheral blood mononuclear cells with cANCA IgG or pANCA IgG resulted in a release of MCP-1 into the conditioned medium [109]. Thus, chemokines and their receptors are involved in the inflammatory processes underlying several systemic autoimmune diseases.

Chemokines and chemokine receptors in angiogenesis

Angiogenic chemokines facilitate inflammatory cell recruitment into the synovium not only by stimulating leukocyte chemotaxis, but also by increasing the number of newly formed vessels. A number of C-X-C chemokines have been implicated in neovascularization underlying RA [reviewed in 5, 9, 42, 43, 49] (Tables 1 and 4). As discussed above, the ELR motif found in a number of C-X-C chemokines is responsible for the angiogenic

activity of these chemotactic cytokines [reviewed in 4, 5, 9, 49, 52-54, 110]. It has been shown, that C-X-C chemokines bind to endothelial cells via specific endothelial chemokine receptors, such as CXCR2 [54, 64, 110]. C-X-C chemokines lacking the ELR motif, such as PF4, IP-10 and MIG are potent angiostatic factors [4, 5, 9, 49, 52-54, 110].

In a recent study, we examined the role of IL-8 and ENA-78 in RA-associated angiogenesis. In the RA synovium, chemokine-expressing cells were localized in the proximity of factor VIII-related antigen expressing endothelial cells. RA synovial tissue homogenates produced significantly more ENA-78 and IL-8, exhibited increased chemotactic activity towards endothelial cells and were more angiogenic in the rat cornea assay than homogenates prepared from normal synovial tissues [68].

SDF-1 differs from other C-X-C chemokines, as it lacks the ELR amino acid sequence but still promotes angiogenesis [54, 80]. SDF-1 induced endothelial chemotaxis *in vitro* and dermal angiogenesis in mice *in vivo* [80]. Thus, SDF-1 may be the first angiogenic C-X-C chemokine that lacks the ELR motif.

There is relatively little information available on the possible role of C-C chemokines in RA-associated angiogenesis. MCP-1 induced endothelial chemotaxis *in vitro*, as well as angiogenesis in the chick chorioallantoic membrane assay *in vivo*. MCP-1-induced neovascularization was associated with abundant endothelial expression of CCR2 [63].

Fractalkine is the only characterized C-X₃-C chemokine. This chemokine is expressed on cytokine-activated endothelia [46, 59, 87]. In our hands, fractalkine enhanced neovascularization both *in vitro* and *in vivo* [59, 87].

Regarding the possible role of chemokine receptors in angiogenesis, a number of these receptors may be detected on endothelial cells, thus playing a role in chemokine-derived angiogenesis. There is a growing body of evidence that CXCR2 may be the most important endothelial receptor for angiogenic C-X-C chemokines containing the ELR amino acid sequence including IL-8, ENA-78 and gro α [49, 53, 54, 62, 110, 111] (Tables 3 and 4). IL-8- and MCP-1-induced neovascularization was associated with abundant endothelial expression of CCR2 [62, 63]. On the other hand, as angiostatic

chemokines, such as IP-10, MIG and the recently described SLC all bind to the CXCR3 chemokine receptor, this receptor may play a role in chemokine-mediated angiogenesis inhibition [43, 44, 112].

Cytokine-chemokine interactions in the regulation of chemokine production and angiogenesis

A regulatory network of pro-inflammatory cytokines, such as TNF- α and IL-1, chemokines and other angiogenic factors, such as matrix components, adhesion molecules, proteolytic enzymes and others exists in the inflamed synovium [reviewed in 4, 5, 9, 43]. Monocyte/macrophages in RA constitutively express most chemokines, including IL-8, ENA-78, gro α , MCP-1 and MIP-1 α [56, 57, 66, 73, 82], resting synovial fibroblasts and articular chondrocytes produce only small amounts of chemokines. However, TNF- α and IL-1 further stimulate chemokine production by fibroblast-derived synoviocytes [9, 43, 55].

In the synovium, regulatory cytokines may variably influence the production of chemokines, as well as the pro- versus anti-inflammatory chemokine balance. For example, IL-8 secretion by RA synovial fibroblasts is upregulated by IL-4, a Th2 cytokine, but inhibited by IFN- γ , a Th1 cytokine. In contrast, cytokine-dependent RANTES production by the same cells is decreased by IL-4 but stimulated by IFN- γ [58]. Thus, the type of cellular infiltrate, namely the dominance of Th1 or Th2 type lymphocytes, as well as their characteristic cytokine production, may result in a differential local chemokine pattern.

There are two-way interactions between chemokines and cytokines in the inflamed synovium. As discussed above, pro-inflammatory cytokines may stimulate chemokine production [9, 43]. On the other hand, for example, MIP-1 α stimulates the synthesis of IL-1, TNF- α or IL-6 by murine macrophages [9, 43]. In our hands, treatment of rat AIA with a polyclonal antibody to an ENA-78-like protein resulted in a downregulation of synovial IL-1 expression suggesting the role of ENA-78 in the production of pro-inflammatory cytokines [72].

These cytokine-chemokine interactions may be important in the onset and perpetuation of inflammatory synovitis. Such interactions, as well as the involvement of other soluble and cell surface-bound factors in this network, may also be involved in the regulation of angiogenesis as well. As several angiogenic mediators are present in the inflamed synovium, and RA is a representative "angiogenic disease", the complexity of interactions between endothelium and soluble mediators during angiogenesis can be demonstrated. As described above, a number of cytokines, chemokines and growth factors have been associated with angiogenesis. The proliferating synovium is rich in extracellular matrix components. These macromolecules and adhesion molecules regulated by cytokines and chemokines play an important role in the adhesive interactions of endothelial cells during emigration. A number of endothelial adhesion molecules show up-regulated expression in the RA synovial tissue. Pro-inflammatory, also angiogenic cytokines may also induce the expression of some adhesion molecules. The interactions between cytokines, chemokines and adhesion molecules may have additive stimulatory effects on neovascularization. There is evidence for direct interactions between several other angiogenic mediators, which could further perpetuate angiogenesis [reviewed in 5, 7, 35].

Possibly the most important mechanisms in the regulation of angiogenesis are as follows:

- 1) balance between antagonistic angiogenic and angiostatic couples;
- 2) concentration-dependent regulation of neovascularization by bifunctional mediators;
- 3) direct or indirect interactions between soluble and cell-bound angiogenic factors;
- 4) stimulation of angiostatic factor production by angiogenic mediators;
- 5) downregulation of the production of angiogenic mediators by angiostatic agents;
- 6) angiogenesis stimulation or inhibition by administered drugs or other compounds [reviewed in 2-9, 35].

In conclusion, a regulatory network of monocyte/macrophages and endothelial cells, as well as soluble angiogenic and angiostatic factors, extracellular matrix components and adhesion molecules exists in RA, and likely in other

inflammatory “angiogenic diseases”. Angiogenesis inhibitors can interact with these mediators at any step of angiogenesis.

Possibilities of anti-angiogenesis and anti-chemokine targeting in antirheumatic therapy

Angiogenesis and chemokine research may have important clinical relevance in rheumatology. The most important *diagnostic and prognostic aspects* were discussed above. Briefly, the number of newly formed blood vessels in biopsy specimens may reflect the progression of the disease, similarly to the correlation between angiogenesis and the metastatic potential of tumors [reviewed in 2-9]. For example, significantly higher degree of vascularity exists in RA than in osteoarthritic or normal synovial tissues [5, 39].

Regarding applications for therapy, as elegantly summarized by Folkman, two central mechanisms may be targeted when developing antiangiogenic therapy. First, switch from the resting to the angiogenic endothelial phenotype could be inhibited by blocking the secretion, transport and extracellular matrix binding of angiogenic factors. Alternatively, vascular endothelial cell response to these mediators, including migration, proliferation, basement membrane production and degradation, and expression of endothelial adhesion molecules could be suppressed [19].

We have discussed above, that a number of antirheumatic drugs currently used in RA, including corticosteroids, non-steroidal antiinflammatory drugs or disease-modifying agents, inhibit angiogenesis or the production of macrophage-derived angiogenic mediators [5, 7, 9, 35]. In our recent study, sulfasalazine and sulfapyridine inhibited endothelial chemotaxis and tube formation on the laminin-containing matrix Matrigel [113].

The inhibition of several soluble cytokines, growth factors and chemokines can suppress the pathologic angiogenesis underlying RA. At this moment TNF- α seems to be a primary target for therapeutic trials, although IL-1, IL-6, IL-8 as well as other angiogenic mediators have recently been targeted in biological therapy trials [114]. For example, infliximab trials showed that blocking of

TNF- α reduced synovial VEGF expression [115]. A humanized anti-VEGF antibody has been introduced into preclinical studies, and this antibody successfully suppressed neovascularization [115].

Cellular adhesion molecules could also be targeted from that point of view. For example, fibronectin peptides containing the RGD sequence, which is recognized by several $\beta 1$ and $\beta 3$ integrins, suppress angiogenesis [116]. An $\alpha V\beta 3$ integrin antagonist inhibited rat arthritis and synovial angiogenesis [117].

Other angiostatic compounds could also be used to target neovascularization. CIA in rats was suppressed by a fumagillin-derivative antibiotic angiogenesis inhibitor, as well as by the microtubule stabilizer taxol. Cartilage-derived tissue inhibitors of angiogenesis may also be useful in the treatment of arthritis [reviewed in 5, 9, 35]. MMP inhibitors have been tried in several models of angiogenesis [118]. Theoretically, most angiogenesis inhibitors described above may undergo trials in arthritis models.

Chemokine and chemokine receptor targeting may also be feasible when designing new approaches to antirheumatic therapy. Chemokine production in the RA joint can be influenced in a number of ways. Non-specific strategies include the use of anti-inflammatory drugs, which, apart from many other mechanisms of action including angiogenesis inhibition, also affect chemokine production. For example, corticosteroids suppress the production of IL-8 and MCP-1 by synovial cells [119, 120]. In our hands sulfapyridine inhibited cytokine-stimulated endothelial cell expression of IL-8 and MCP-1 [113].

Alternatively, as pro-inflammatory cytokines, mainly TNF- α and IL-1, stimulate the production of most chemokines by RA synovial fibroblasts or macrophages, the use of cytokine antagonists, anti-cytokine antibodies or soluble cytokine receptors in biological therapy may indirectly downregulate chemokine synthesis. Most of these approaches have already been tried in RA. As an example, anti-TNF- α monoclonal antibody blockade using infliximab reduced synovial expression of IL-8 and MCP-1 in RA patients [121].

In addition to these indirect approaches, mostly animal studies using antibodies to chemokines and chemokine inhibitors suggest that specific chemo-

kine targeting may also be available in the near future. In our study, antibodies to IL-8, ENA-78 and gro α partially neutralized RA synovial fluid-derived chemotactic activity for neutrophils *in vitro* [73]. We have also used neutralizing anti-ENA-78 antibody to successfully prevent the evolution of adjuvant-induced arthritis in rats. Anti-ENA-78 administered intraperitoneally prior to the onset of arthritis attenuated the severity of the disease as determined by joint circumference measurements. In addition, anti-ENA-78 significantly reduced the number of IL-1 β immunoreactive cells in the synovial lining layer indicating the possible role of ENA-78 in the maintenance of cytokine production in the synovium. This antibody was unable to influence the disease course when injected during the development of arthritis [72]. Other anti-chemokine antibodies have also been tried in arthritis models. Passive immunization with anti-MIP-1 α delayed the onset and reduced the severity of murine CIA [43]. A neutralizing monoclonal antibody to MCP-1 reduced ankle swelling by 30% and significantly decreased the number of synovial macrophages in the rat CIA model [43]. Apart from antibodies, chemokine antagonists or angiostatic chemokines may also be used as antirheumatic agents. For example, a 67 amino acid sequence of MCP-1, which acts as an MCP-1 antagonist *in vitro*, abrogated arthritis in MRL-lpr autoimmune mice [122]. A bioactive synthetic peptide derived from PF4 suppressed type II collagen induced arthritis in mice [51]. These data suggest that angiostatic, as well as anti-chemokine strategies may be involved in biological therapy in the close future.

It is likely, that multipotent rather than specific immunotherapy may be useful for the therapy of RA and other systemic inflammatory rheumatic conditions. For example, anti-TNF- α targeting has several beneficial effects in RA, including cytokine, chemokine production and anti-angiogenesis [9, 4, 5, 9, 121]. Inhibition of ELR⁺ C-X-C chemokines or the administration of ELR⁻ chemokines also inhibits neovascularization [4, 5, 9, 43, 52]. We recently reported that antirheumatic drugs, such as sulfapyridine may inhibit endothelial chemokine production, as well as endothelial chemotaxis and tube formation [113]. Thus the role of chemokines and angiogenesis in RA is overlapping and may be useful for future targeting.

Conclusions

In this review we discussed the putative role of angiogenesis, chemokines and chemokine receptors in RA and other systemic inflammatory diseases including SLE, SSc, SS, PM/DM, MCTD and systemic vasculitides. RA and some other inflammatory rheumatic diseases discussed above are "angiogenic diseases". Increased neovascularization promotes the ingress of inflammatory cells into the synovium and thus perpetuates the progression of the disease. Scattered data support the role of angiogenesis in SLE, SSC and vasculitides. A number of C-X-C and C-C chemokines are involved in the inflammatory and angiogenic events underlying the pathogenesis of arthritis. Chemokines and their receptors may play a role in the pathogenesis of RA, SLE, SSc, SS, PM/DM and vasculitides. In addition, chemokine and angiogenesis research has important clinical implications. The assessment of synovial vascularization may have prognostic role for the progression of RA. Anti-chemokine and anti-angiogenesis targeting with currently used antirheumatic agents or specific inhibitors will lead to the development of specific immunomodulatory therapies that will prevent joint destruction and thus will benefit patients with inflammatory rheumatic conditions.

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