

## Review

**Vascular involvement in rheumatic diseases:  
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*Arthritis Research & Therapy* 2008, **10**:224 (doi:10.1186/ar2515)**Abstract**

The vasculature plays a crucial role in inflammation, angiogenesis, and atherosclerosis associated with the pathogenesis of inflammatory rheumatic diseases, hence the term 'vascular rheumatology'. The endothelium lining the blood vessels becomes activated during the inflammatory process, resulting in the production of several mediators, the expression of endothelial adhesion molecules, and increased vascular permeability (leakage). All of this enables the extravasation of inflammatory cells into the interstitial matrix. The endothelial adhesion and transendothelial migration of leukocytes is a well-regulated sequence of events that involves many adhesion molecules and chemokines. Primarily selectins, integrins, and members of the immunoglobulin family of adhesion receptors are involved in leukocyte 'tethering', 'rolling', activation, and transmigration. There is a perpetuation of angiogenesis, the formation of new capillaries from pre-existing vessels, as well as that of vasculogenesis, the generation of new blood vessels in arthritis and connective tissue diseases. Several soluble and cell-bound angiogenic mediators produced mainly by monocytes/macrophages and endothelial cells stimulate neovascularization. On the other hand, endogenous angiogenesis inhibitors and exogenously administered angiostatic compounds may downregulate the process of capillary formation. Rheumatoid arthritis as well as systemic lupus erythematosus, scleroderma, the antiphospholipid syndrome, and systemic vasculitides have been associated with accelerated atherosclerosis and high cardiovascular risk leading to increased mortality. Apart from traditional risk factors such as smoking, obesity, hypertension, dyslipidemia, and diabetes, inflammatory risk factors, including C-reactive protein, homocysteine,

folate deficiency, lipoprotein (a), anti-phospholipid antibodies, antibodies to oxidized low-density lipoprotein, and heat shock proteins, are all involved in atherosclerosis underlying inflammatory rheumatic diseases. Targeting of adhesion molecules, chemokines, and angiogenesis by administering nonspecific immunosuppressive drugs as well as monoclonal antibodies or small molecular compounds inhibiting the action of a single mediator may control inflammation and prevent tissue destruction. Vasoprotective agents may help to prevent premature atherosclerosis and cardiovascular disease.

**Introduction**

Vessels and the vascular endothelium are involved in the pathogenesis of inflammatory rheumatic diseases. Rheumatoid arthritis (RA) serves as a prototype of these diseases as it is the most common type of arthritis and a great body of data is available regarding leukocyte recruitment into the synovium, angiogenesis, and accelerated atherosclerosis. The term 'vascular rheumatology' has been accepted by many investigators and includes both microvascular and macrovascular involvement in rheumatic diseases. Apart from RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), the antiphospholipid syndrome (APS), and systemic vasculitides have been associated with vascular inflammation, altered angiogenesis, and increased cardiovascular morbidity and mortality. In this review, we will discuss the most relevant

β2GPI = β2 glycoprotein I; AECA = anti-endothelial cell antibody; Ang = angiopoietin; anti-CCP = anti-cyclic citrullinated peptide; anti-oxLDL = anti-oxidized low-density lipoprotein; APA = antiphospholipid antibody; APS = antiphospholipid syndrome; C = cysteine; CAM = endothelial adhesion molecule; cclMT = common carotid intima-media thickness; CRP = C-reactive protein; CTAP-III = connective tissue-activating peptide-III; CVD = cardiovascular disease; DMARD = disease-modifying antirheumatic drug; EC = endothelial cell; ECM = extracellular matrix; EGF = epidermal growth factor; ELR = glutamic acid-leucine-arginine; ENA-78 = epithelial neutrophil-activating protein-78; EPC = endothelial progenitor cell; FGF = fibroblast growth factor; FMD = flow-mediated vasodilation; groα = growth-regulated oncogene-α; HEV = high endothelial venule; HIF = hypoxia-inducible factor; ICAM = intercellular adhesion molecule; IFN = interferon; IL = interleukin; IP-10 = interferon-γ-inducible 10-kDa protein; JAM = junctional adhesion molecule; LDL = low-density lipoprotein; LFA = lymphocyte function-associated antigen; MCP-1 = monocyte chemoattractant protein-1; Mig = monokine induced by interferon-γ; MIP-1α = macrophage inflammatory protein-1-α; MMP = matrix metalloproteinase; MTX = methotrexate; oxLDL = oxidized low-density lipoprotein; PAPS = primary antiphospholipid syndrome; PECAM-1 = platelet-endothelial cell adhesion molecule-1; PF4 = platelet factor-4; RA = rheumatoid arthritis; SDF-1 = stromal cell-derived factor-1; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; TGF-β = transforming growth factor-β; TNF = tumor necrosis factor; VCAM = vascular cell adhesion molecule; VEGF = vascular endothelial growth factor.

information on arthritis-related vascular inflammation, including the role of endothelial cells (ECs), endothelial adhesion molecules (CAMs) and chemokines, as well as the involvement of neovascularization and some aspects of accelerated atherosclerosis in rheumatic diseases. We will discuss RA in more detail, and other connective tissue diseases described above will also be mentioned. Finally, some aspects of vascular targeting in rheumatology will also be briefly summarized.

## Endothelial biology and leukocyte trafficking through the vessel wall

### Vascular permeability and vascular damage underlying inflammation

In arthritis, leukocyte ingress into the synovium occurs by leukocyte adhesion to ECs and then by transendothelial migration [1-8]. The chemotaxis of these leukocytes is regulated mainly by various chemokines [1,8,9-14]. Several CAMs have been implicated in leukocyte-EC interactions [1-4,7,8]. ECs play an active role in inflammation. Synovitis is associated with vasodilation and increased endothelial permeability (leakage) and vascular injury followed by endothelial regeneration [4-6]. ECs secrete several vasodilatory mediators, including nitric oxide, prostacyclin (PGI<sub>2</sub>), platelet-activating factor, histamine, and others [4-6]. Increased vascular permeability associated with EC retraction and contraction may be a physiological process, while in inflammation, pro-inflammatory mediators trigger vascular damage [4-6]. Increased vascular permeability is induced primarily by vasoactive agents such as histamine, serotonin, bradykinin, and others [4-6,15]. Vascular injury is caused primarily by activated neutrophils, inflammatory mediators released by these cells, including reactive oxygen intermediates and matrix metalloproteinases (MMPs). Anti-EC antibodies (AECAs), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), or interferon- $\gamma$  (IFN- $\gamma$ ) stimulates EC injury [4-6,15]. The abundant production of AECAs, markers of vascular damage, has been reported in RA, SLE, systemic vasculitis, and other rheumatic diseases [15] (Table 1). Injury is followed by endothelial regeneration, which may be associated with angiogenesis or may occur without the formation of new blood vessels [5,6,16].

### Intercellular adhesion molecules in arthritis

The cascade of leukocyte transendothelial migration begins with the adhesion of leukocytes, including neutrophils, lymphocytes, and monocytes, to postcapillary venules. Leukocyte recruitment occurs through the wall of these venules. In some RA patients, specialized ECs resembling high endothelial venules (HEVs) are found in the synovium. These HEVs are surrounded by lymphoid aggregates composed of T cells [1,2,8]. Inflammatory leukocyte recruitment into inflamed tissue is very similar to the 'homing' associated with physiological immune surveillance [1-3]. Leukocyte adhesion to ECs or to extracellular matrix (ECM) constituents is mediated by endothelial CAMs and their counter-receptors on infiltrating white blood cells. Primarily

**Table 1**

### Some important inflammatory mediators released by vascular endothelial cells

Cytokines	Interleukin-1 Interleukin-6
Chemokines	Interleukin-8/CXCL8 Monocyte chemoattractant protein-1/CCL2 Growth-regulated oncogene- $\alpha$ /CXCL1
Growth factors	Endothelial cell-derived growth factor Transforming growth factor- $\beta$
Colony-stimulating factors	Granulocyte colony-stimulating factor Granulocyte-macrophage colony-stimulating factor
Others	Platelet-activating factor Nitric oxide Prostacyclin (PGI <sub>2</sub> )

selectins, integrins, and some members of the immunoglobulin superfamily of adhesion molecules (CAMs) have been implicated in leukocyte extravasation, but some other CAMs may also play a role in this process [2,3,7]. These CAMs are summarized in Table 2. During leukocyte transendothelial migration, selectins mediate the initial 'tethering' and 'rolling' of leukocytes whereas integrins and other CAMs are involved in firm adhesion and migration of leukocytes [1,3,8]. All selectins, most integrins, and members of the immunoglobulin superfamily are abundantly expressed in arthritic synovial tissues [2,3]. Other CAMs involved in leukocyte-EC adhesion underlying inflammation include intracellular adhesion molecule-3 (ICAM-3), the lymphocyte function-associated antigen-3 (LFA-3)-CD2 counter-receptors, various alternative forms of CD44, vascular adhesion proteins (VAP-1 and VAP-2), endoglin (CD105), E-cadherin, N-cadherin, cadherin-11, platelet-endothelial cell adhesion molecule-1 (PECAM-1) (CD31), junctional adhesion molecules (JAMs), CD99, and others [1-3,7]. All of these CAMs have been detected in arthritic synovial tissues [1-3].

### Chemokines and chemokine receptors in synovial inflammation

Chemokines are small proteins exerting chemotactic activity toward leukocytes [9-12,14,17,18]. Chemokines have been classified into supergene families according to the location of cysteine (C) in their molecular structure. These families are designated as CXC, CC, C, and CX<sub>3</sub>C chemokines; the particular chemokine ligand members are CXCL, CCL, CL, and CX<sub>3</sub>CL, and the four chemokine receptor groups are CXCR, CCR, CR, and CX<sub>3</sub>CR, respectively [9,10,12]. To date, more than 50 chemokines and 19 chemokine receptors have been identified [9,10,12] (Table 3). Most CXC chemokines chemoattract neutrophils, but platelet factor-4 (PF4)/CXCL4 and IFN- $\gamma$ -inducible 10-kDa protein (IP-10)/CXCL10 recruit lymphocytes and monocytes [9]. Among CXC chemokines, IL-8/CXCL8, epithelial neutrophil-activating

**Table 2**

**Relevant members of the selectin, integrin, and immunoglobulin adhesion molecule superfamilies**

Adhesion receptors	Ligands
Selectins	
L-selectin (CD62L, LAM-1)	Sialylated carbohydrates, GlyCAM-1
E-selectin (CD62E, ELAM-1)	Sialyl-Lewis-X
P-selectin (CD62P, PADGEM)	Sialyl-Lewis-X, other carbohydrates
Integrins	
$\beta_1$ integrins	Laminin, collagen, fibronectin
$\alpha_4\beta_1$ integrins	Fibronectin, VCAM-1
$\beta_2$ integrins	ICAM-1, ICAM-2, ICAM-3, JAM-A
$\beta_3$ integrins	Vitronectin, von Willebrand factor, other matrix molecules
Immunoglobulin superfamily	
ICAM-1, ICAM-3	$\alpha_L\beta_2$ (LFA-1), $\alpha_M\beta_2$ (Mac-1, CR3)
VCAM-1	$\alpha_4\beta_1$ , $\alpha_4\beta_7$
CD2	LFA-3
PECAM-1 (CD31)	PECAM-1, $\alpha_V\beta_3$ integrin

ELAM-1, endothelial-leukocyte adhesion molecule-1; GlyCAM-1, glycosylation-dependent cell adhesion molecule-1; ICAM, intracellular adhesion molecule; JAM-A, junctional adhesion molecule-A; LAM-1, leukocyte adhesion molecule-1; LFA, lymphocyte function-associated antigen; Mac-1, macrophage integrin; PADGEM, platelet activation-dependent granule-external membrane protein; PECAM-1, platelet-endothelial cell adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

protein-78 (ENA-78)/CXCL5, growth-regulated oncogene-alpha (gro $\alpha$ )/CXCL1, connective tissue-activating peptide-III (CTAP-III)/CXCL7, granulocyte chemotactic protein-2/CXCL6, IP-10/CXCL10, PF4/CXCL4, monokine induced by IFN- $\gamma$  (Mig)/CXCL9, stromal cell-derived factor-1 (SDF-1)/CXCL12, B cell-activating chemokine-1/CXCL13, and CXCL16 have been implicated in the pathogenesis of synovial inflammation [14,17,18]. CC chemokines stimulate monocyte chemotaxis and some of them also chemoattract lymphocytes [10]. Monocyte chemoattractant protein-1 (MCP-1)/CCL2, macrophage inflammatory protein-1-alpha (MIP-1 $\alpha$ )/CCL3, MIP-3 $\alpha$ /CCL20, RANTES (Regulated upon Activation, Normal T-cell Expressed and Secreted)/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 synovitis [14,17,18]. The C chemokine family contains two members: lymphotactin/XCL1 and single C motif-1-beta (SCM-1 $\beta$ )/XCL2 [12]. Lymphotactin/XCL1 has been detected on synovial T cells in RA [14,18]. The CX<sub>3</sub>C chemokine subfamily contains fractalkine/CX<sub>3</sub>CL1 [12,19]. This chemokine chemoattracts mononuclear cells and also serves as a CAM [17,19]. Fractalkine/CX<sub>3</sub>CL1 has also been detected in RA synovial tissues [19]. Fractalkine/CX<sub>3</sub>CL1 has also been implicated in the development of accelerated atherosclerosis [18], a topic discussed later. Chemokines bind to their seven-transmembrane domain receptors expressed on the target

cells [12,18]. Some of these receptors have numerous chemokine ligands whereas others are specific receptors for single ligands [14]. Chemokine receptors have also been associated with various histological subtypes of inflammation. For example, whereas CXCR3 and CCR5 may be involved primarily in Th1 type diseases (such as RA), CCR3, CCR4, and CCR8 may play a role in leukocyte migration underlying Th2 type inflammation (such as asthma) [11]. Most CXC and CC chemokine receptors mentioned above as well as XCR1 and CX<sub>3</sub>CR1 are expressed in the arthritic synovium [14,17,18].

**The process of leukocyte recruitment into inflamed tissues**

Leukocyte adhesion to ECs occurs following a cascade of events. White blood cells in the bloodstream weakly adhere to the endothelium lining the inner vessel wall (tethering) followed by rolling of leukocytes on the endothelial layer. Tethering and rolling are mediated primarily by selectins and their ligands. These events are followed by leukocyte activation, which is dependent upon interactions between chemokine receptors expressed on leukocytes and proteoglycans on ECs. Activation-dependent firm adhesion occurs next, involving  $\alpha_4\beta_1$  integrin/VCAM-1 (vascular cell adhesion molecule-1),  $\beta_2$  integrin/ICAM-1, and JAM/integrin interactions. This is associated with the secretion of chemokines. These chemokines may also upregulate integrin expression on the adhering cells via PI3K (phosphatidylinositol 3-kinase)-

**Table 3****Chemokine receptors with ligands relevant for arthritis and angiogenesis**

Chemokine receptor	Chemokine ligand
CXC chemokine receptors	
CXCR1	IL-8/CXCL8
CXCR2	IL-8/CXCL8, ENA-78/CXCL5, gro $\alpha$ /CXCL1, CTAP-III/CXCL7
CXCR3	IP-10/CXCL10, PF4/CXCL4, Mig/CXCL9, ITAC/CXCL11
CXCR4	SDF-1/CXCL12
C-C chemokine receptors	
CCR1	MIP-1 $\alpha$ /CCL3, RANTES/CCL5, MCP-3/CCL7, MPIF-1/CCL23
CCR2	MCP-1/CCL2, MCP-3/CCL7
CCR6	MIP-3 $\alpha$ /CCL20
CCR7	MIP-3 $\beta$ /CCL19, SLC/CCL21
C chemokine receptors	
XCR1	Lymphotactin/XCL1
C-X3-C chemokine receptors	
CX <sub>3</sub> CR1	Fractalkine/CX <sub>3</sub> CL1

CTAP-III, connective tissue-activating peptide-III; ENA-78, epithelial neutrophil-activating protein-78; gro $\alpha$ , growth-regulated oncogene-alpha; IL-8, interleukin-8; IP-10, interferon-gamma-inducible 10-kDa protein; ITAC, interferon-inducible T-cell alpha chemoattractant; MCP, monocyte chemoattractant protein; Mig, monokine induced by interferon-gamma; MIP, macrophage inflammatory protein; MPIF-1, myeloid progenitor inhibitory factor-1; PF4, platelet factor-4; RANTES, Regulated upon Activation, Normal T-cell Expressed and Secreted; SDF-1, stromal cell-derived factor-1; SLC, secondary lymphoid tissue chemokine.

mediated pathways. Leukocyte diapedesis through the endothelial layer involving integrins occurs when chemokines bind to endothelial heparan sulphate. Chemokines preferentially chemoattract EC-adherent leukocytes. These processes lead to the transmigration of leukocytes into the inflamed tissue [1,8].

#### Targeting of cell adhesion, chemokines, and leukocyte recruitment

Inhibition of cell adhesion, chemokines, and migration using specific antibodies or purified ligands has provided an important perspective on the molecular pathogenesis of RA. In addition, some of these strategies may be included in the future therapy of arthritis [20]. Regarding anti-CAM trials, an anti-human ICAM-1 antibody (enlimomab) was tried in refractory RA with little success [2,20]. Other antiadhesion strategies have been introduced into the treatment of other inflammatory diseases. For example, efalizumab (anti-LFA-1) and alefacept (LFA-3-Ig fusion protein) have been tried in psoriasis, natalizumab (anti- $\alpha_4$  integrin) in multiple sclerosis and Crohn disease, and an anti- $\alpha_4\beta_7$  integrin monoclonal antibody in ulcerative colitis [2,3,20]. These and other anti-CAM strategies may be tried in arthritis as well [2,3,20]. Chemokines and chemokine receptors can be targeted in a number of ways. Disease-modifying antirheumatic drugs (DMARDs) and anti-TNF biologics, currently used in the treatment of RA, may indirectly influence chemokine produc-

tion [18]. Antibodies to IL-8/CXCL8, ENA-78/CXCL5, CXCL16, MIP-1 $\alpha$ /CCL3, MCP-1/CCL2, and fractalkine/CX<sub>3</sub>CL1 have been used to control arthritis in various rodent models [18-20]. Several oral chemokine receptor antagonists, including CXCR2, CXCR4, CCR1, CCR2, and CCR5 inhibitors, have been tried in human RA as well as in animal models of arthritis [18,20-22].

#### Angiogenesis and vasculogenesis in rheumatic diseases

##### The processes of angiogenesis and vasculogenesis

Angiogenesis is the formation of new capillaries from pre-existing vessels, whereas vasculogenesis involves circulating endothelial progenitor cells (EPCs) [14,16,23-27]. Angiogenesis involves cell surface-bound and soluble angiogenic mediators, which activate vascular ECs (Table 4). In response, ECs release MMPs, which digest the underlying basal membrane and the ECM enabling the emigration of ECs. Single ECs will then gather to form capillary sprouts. Lumen formation within the sprouts leads to capillary loops. Finally, the synthesis of new basement membrane leads to the formation of new capillaries [23]. Regarding vasculogenesis, a subpopulation of circulating CD34<sup>+</sup> cells expressing the vascular endothelial growth factor-2 (VEGF-2) receptor has been identified and characterized as functional EPCs. Decreased numbers of EPCs as well as impaired vasculogenesis have been associated with arthritis [27,28].



The major chemoattractant that drives EPCs is the SDF-1/CXCL12 chemokine and its receptor, CXCR4 [29]. In arthritis, proinflammatory cytokines stimulate the production of SDF-1/CXCL12 and thus tissue vasculogenesis by recruiting CXCR4<sup>+</sup> EPCs [14,17,29].

### Angiogenic mediators and inhibitors in rheumatoid arthritis

The hypoxia-VEGF-angiopoietin pathway is an essential angiogenic network in synovitis [16,23-25,30]. VEGF, a growth factor that binds to heparin in the synovial ECM, plays a central role in the regulation of neovascularization [23,30]. There is hypoxia present within the joint cavity, and hypoxia as well as TNF- $\alpha$  and IL-1 stimulate VEGF release [16]. Hypoxia acts through the hypoxia-inducible factor heterodimer, HIF-1 $\alpha$ /HIF-1 $\beta$  [16]. Several other angiogenic mediators also act indirectly via VEGF [23]. Angiopoietin-1 (Ang1) and Ang2 regulate EC functions upon stimulation by VEGF. Both Ang1 and Ang2 interact with the Tie2 endothelial tyrosine kinase receptor [16,24]. Ang1-Tie2 interactions result in vessel stabilization. On the other hand, Ang2, an antagonist of Ang1, inhibits vessel maturation [24]. Another important player in this network is survivin, an apoptosis inhibitor, which is also involved in VEGF-induced angiogenesis and EC survival [16]. VEGF, HIF-1, Ang1, Tie2, and survivin are all expressed in the arthritic synovium [16,25]. Growth factors other than VEGF but implicated in angiogenesis include fibroblast (FGF-1 and FGF-2), hepatocyte, platelet-derived, epidermal (EGF), insulin-like, and transforming (TGF- $\beta$ ) growth factors [16,24,25]. Among chemokines described above, CXC chemokines that contain the ELR (glutamic acid-leucine-arginine) amino acid motif promote angiogenesis [13]. ELR<sup>+</sup> CXC chemokines that stimulate angiogenesis and also synovial inflammation include IL-8/CXCL8, ENA-78/CXCL5, gro $\alpha$ /CXCL1, and CTAP-III/CXCL7. SDF-1/CXCL12 is a unique CXC chemokine as it exerts mainly a homeostatic function, yet it has been implicated in inflammation such as in RA [13,14,17,29]. Moreover, this chemokine lacks the ELR motif but is still angiogenic [14,29]. The crucial role of SDF-1/CXCL12 in vasculogenesis is discussed above [29]. In contrast to angiogenic CXC chemokines, the ELR<sup>-</sup> PF4/CXCL4, IP-10/CXCL10, and Mig/CXCL9 suppress neovascularization [13,14,17]. Regarding CC chemokines, MCP-1/CCL2 promotes neovascularization induced by growth factors [14,17]. The sole CX<sub>3</sub>C chemokine, fractalkine/CX<sub>3</sub>CL1, also promotes synovial angiogenesis [14,17,19]. Regarding chemokine receptors, CXCR2, which binds most ELR<sup>+</sup> CXC chemokines described above, is a crucial chemokine receptor in angiogenesis [13,14,17]. CXCR4 has been implicated in SDF-1/CXCL12-induced neovascularization in arthritis [14,17,29]. In contrast, CXCR3, a receptor for the angiostatic IP-10/CXCL10 and Mig/CXCL9, may be involved in chemokine-mediated angiostasis [14,17]. Numerous proinflammatory cytokines, such as TNF- $\alpha$ , IL-1, IL-6, IL-15, IL-17, IL-18, granulocyte and granulocyte-macrophage colony-stimulating factors, oncostatin M, and macrophage

migration inhibitory factor, also induce synovial angiogenesis [16,31]. In contrast, other cytokines, such as IFN- $\alpha$ , IFN- $\gamma$ , IL-4, IL-12, IL-13, and leukemia inhibitory factor, suppress the production of angiogenic mediators and thus inhibit neovascularization [16,31,32]. ECM components, matrix-degrading proteases, and cellular adhesion molecules described above may be involved in EC emigration, sprouting, and thus angiogenesis. Among ECM components, various types of collagen, fibronectin, laminin, vitronectin, tenascin, and proteoglycans promote neovascularization [16]. Proteolytic enzymes, such as MMPs and plasminogen activators, play a role in matrix degradation underlying synovial angiogenesis [16,25]. On the other hand, tissue inhibitors of metalloproteinases and plasminogen activator inhibitors antagonize the angiogenic effects of proteases described above [16,32]. Among CAMs,  $\beta_1$  and  $\beta_3$  integrins, E-selectin, glycoconjugates (including Lewis<sup>x</sup>/H), melanoma cell adhesion molecule (MUC18), VCAM-1, PECAM-1, and endoglin have been implicated in neovascularization [2,16,25,33,34]. The  $\alpha_v\beta_3$  integrin is of outstanding importance as this CAM mediates both synovial angiogenesis and osteoclast-mediated bone resorption and the development of erosions in RA [34]. Other important angiogenic factors not mentioned above include endothelin-1, angiogenin, angiotropin, and many others [16,25] (Table 4). Angiostatic mediators and compounds also include angiostatin (a fragment of plasminogen), endostatin (a fragment of type XIII collagen), thrombospondin-1, 2-methoxyestradiol, paclitaxel, osteonectin, chondromodulin-1, and others [16,30,32,35] (Table 4). These molecules suppress the action of angiogenic mediators, such as VEGF, HIFs, or the  $\alpha_v\beta_3$  integrin [16,30,32,35].

### Angiogenesis in other types of arthritis and connective tissue diseases

Differential vascular morphology may exist in the synovia of RA versus psoriatic arthritis (PsA) patients [16,25]. Furthermore, VEGF production may be associated with increased disease activity and accelerated angiogenesis in PsA and ankylosing spondylitis [16]. In SLE, angiogenic EGF, FGF, and IL-18 as well as angiostatic endostatin have been detected in the sera of patients. Serum VEGF levels were correlated with the SLAM (systemic lupus activity measure) activity score [16,25]. Angiogenesis in SSc is somewhat controversial. On one hand, there is significant loss of vessels in scleroderma despite severe tissue hypoxia associated with increased concentrations of the angiostatic endostatin [16,28]. On the other hand, SSc skin biopsy explants stimulated neovascularization and there is increased production of VEGF in the sera and skin of scleroderma patients [16,28]. Thus, hypoxia may induce angiogenesis in SSc but this is transient and the newly formed vessels are rather unstable in this disease [28]. Furthermore, sustained production of VEGF results in the formation of giant capillaries seen using capillaroscopy in SSc [16,28]. Similarly to SSc, in inflammatory myopathies, expression of hypoxia-associated increased HIF-1,  $\alpha_v\beta_3$  integrin, and VEGF receptor in muscle biopsies

Table 4

**Some angiogenic and angiostatic factors in arthritis**

	Mediators	Inhibitors
Chemokines	IL-8/CXCL8, ENA-78/CXCL5, gro $\alpha$ /CXCL1, CTAP-III/CXCL7, SDF-1/CXCL12, MCP-1/CCL2, SLC/CCL21, MPIF/CCL23, fractalkine/CX <sub>3</sub> CL1	PF4/CXCL4, IP-10/CXCL10, Mig/CXCL9, SLC/CCL21
Matrix molecules	Type I collagen, fibronectin, laminin, heparin, heparan sulphate	Thrombospondin, RGD sequence
Cell adhesion molecules	$\beta_1$ and $\beta_3$ integrins, E-selectin, P-selectin, CD34, VCAM-1, endoglin, PECAM-1, vascular endothelial-cadherin, Lewis <sup>x</sup> /H, MUC18	RGD sequence (integrin ligand)
Growth factors	VEGF, bFGF, aFGF, PDGF, EGF, IGF-I, HIF-1, TGF- $\beta^a$	TGF- $\beta^a$
Cytokines	TNF- $\alpha$ , IL-6 <sup>a</sup> , IL-15, IL-18	IL-4, IL-6 <sup>a</sup> , IFN- $\alpha$ , IFN- $\gamma$
Proteases	MMPs, plasminogen activators	TIMPs, plasminogen activator inhibitors
Others	Angiogenin, substance P, prolactin	DMARDs, infliximab, etanercept, angiostatin, endostatin

<sup>a</sup>Mediators with both proangiogenic and antiangiogenic effects. aFGF, acidic fibroblast growth factor; bFGF, basic fibroblast growth factor; CTAP-III, connective tissue-activating peptide-III; DMARD, disease-modifying antirheumatic drug; EGF, epidermal growth factor; ENA-78, epithelial neutrophil-activating protein-78; gro $\alpha$ , growth-regulated oncogene- $\alpha$ ; HIF-1, hypoxia-inducible factor-1; IFN, interferon; IGF-I, insulin-like growth factor-I; IL, interleukin; IP-10, interferon- $\gamma$ -inducible 10-kDa protein; MCP-1, monocyte chemoattractant protein-1; Mig, monokine induced by interferon- $\gamma$ ; MMP, matrix metalloproteinase; MPIF, myeloid progenitor inhibitory factor; MUC18, melanoma cell adhesion molecule; PDGF, platelet-derived growth factor; PECAM-1, platelet-endothelial cell adhesion molecule-1; PF4, platelet factor-4; RGD, arginine-glycine-aspartic acid; SDF-1, stromal cell-derived factor-1; SLC, secondary lymphoid tissue chemokine; TGF- $\beta$ , transforming growth factor-beta; TIMP, tissue inhibitors of metalloproteinase; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

was not sufficient to compensate the loss of blood vessels [16,25]. Regarding systemic vasculitides, abundant production of angiogenic VEGF and TGF- $\beta$  has been associated with Kawasaki syndrome [16]. Increased serum levels of TGF- $\beta$  were found in ANCA (antineutrophil cytoplasmic antibody)-associated vasculitides, including Wegener granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis [16,25].

### Targeting of angiogenesis in inflammatory rheumatic diseases

There may be two major strategies to control angiogenesis in arthritis as well as in malignancies [16,32,35]. Endogenous inhibitors of neovascularization described above, including cytokines, chemokines, protease inhibitors, and others, are naturally produced in the arthritic synovium. However, angiogenic mediators are abundant within the inflamed tissue; therefore, these endogenous angiostatic molecules need to be administered in excess in order to attenuate neovascularization. In addition, numerous synthetic compounds currently used to control inflammation and to treat arthritis may, among other effects, inhibit capillary formation as well. These exogenous angiostatic compounds include corticosteroids, traditional disease-modifying agents (DMARDs) and biologics, antibiotic derivatives, thalidomide, and others [16,32,35] (Table 5). Among endogenous angiogenesis inhibitors, angiostatin and endostatin block  $\alpha_v\beta_3$  integrin-dependent angiogenesis and both molecules inhibited the development of arthritis in various animal models [16,35]. Thrombospondin-1 and -2 are angiostatic ECM components

produced by RA synovial macrophages and fibroblasts [16,32]. IL-4 and IL-13 gene transfer attenuated synovial inflammation and angiogenesis in rats [16]. The PF4/CXCL4 chemokine has also been tried in rodent models [16]. Fumagillin analogs, such as TNP-470 and PPI2458, also exert angiostatic and antiarthritic properties [16,32,35]. Traditional DMARDs and biologics exert various anti-inflammatory effects. In addition, these compounds may inhibit synovial vessel formation by nonspecifically blocking the action of angiogenic mediators [16,17]. Thalidomide, recently introduced into the treatment of RA and lupus, is a potent TNF- $\alpha$  antagonist and angiogenesis inhibitor [16,35]. CC1069, a thalidomide analog, even more potently inhibited arthritis in rats [35]. The hypoxia-HIF pathway may also be targeted using nonspecific inhibitor compounds, including YC-1 [16,35]. 2-Methoxyestradiol, mentioned above, and paclitaxel (taxol), a drug already used in human cancer, destabilize the intracellular cytoskeleton and also block HIF-1 $\alpha$  [35]. Soluble Fas ligand (CD178) inhibited synovial VEGF production and angiogenesis [16]. Pioglitazone, an anti-diabetic PPAR- $\gamma$  (peroxisome proliferator-activated receptor- $\gamma$ ) agonist, is also angiostatic. Pioglitazone effectively controlled psoriatic arthritis in 10 patients [16,35]. Regarding specific exogenous strategies, VEGF is the key target [30,35]. Numerous synthetic VEGF and VEGF receptor inhibitors (including vatalanib, sunitinib, sorafenib, and vandetanib), anti-VEGF antibodies (including bevacizumab), and inhibitors of VEGF and VEGF receptor signaling inhibit neovascularization and are under development for cancer therapy [30,35]. To date, vatalanib has been tried and

**Table 5**

**Antiangiogenic targets**

Endogenous inhibitors	Angiostatin Endostatin Thrombospondin-2 Interleukin-4, interleukin-13 Platelet factor-4/CXCL4 chemokine
Exogenous inhibitors	Classical disease-modifying antirheumatic drugs Anti-tumor necrosis factor biologics Thalidomide Fumagillin analogs Vascular endothelial growth factor inhibitors Hypoxia-inducible factor heterodimer inhibitors Angiopoietin-1/Tie2 inhibitors $\alpha_v\beta_3$ integrin inhibitors Microtubule destabilizers (for example, paclitaxel) Others (for example, glitazones)

attenuated knee arthritis in rabbits [35]. The Ang-Tie system may also be targeted. A soluble Tie2 receptor transcript was delivered via an adenoviral vector to mice. The inhibition of Tie2 delayed the onset and attenuated the severity of arthritis [16,35]. Vitaxin, a humanized antibody to the  $\alpha_v\beta_3$  integrin, inhibited synovial angiogenesis [16,34] but, in a phase II human RA trial, showed only limited efficacy [35]. Numerous specific MMP inhibitors have been tried in angiogenesis models [16,35]. Endothelin-1 antagonists currently used in the therapy of primary and SSc-associated secondary pulmonary hypertension may also exert angiostatic effects [16,28].

**Accelerated atherosclerosis in rheumatic diseases**

**The basis of atherosclerosis and increased vascular risk**  
Accelerated atherosclerosis and increased cardiovascular morbidity and mortality have been associated with RA, SLE, APS, and SSc [36-41]. Cardiovascular disease (CVD) causes reduced life expectancy and became a major mortality factor in these diseases [36-41]. Atherosclerosis is also considered an inflammatory disease; thus, it may share common pathogenic mechanisms with rheumatic diseases [36,42,43] (Table 6). Numerous studies have demonstrated the role of traditional, Framingham, and inflammation-associated risk factors in atherosclerosis associated with arthritis [36-38,44]. Among traditional risk factors, cigarette smoking not only is a major risk factor for CVD but has recently been implicated in tissue citrullination, the production of anti-cyclic citrullinated peptide (anti-CCP) antibodies, and thus susceptibility to RA [36,38]. In addition to smoking, physical inactivity, obesity, hypertension, dyslipidemia, and diabetes mellitus may be implicated in accelerated atherosclerosis [36-38,44]. Yet excess CVD mortality occurs predominantly in RA patients with a higher degree of systemic inflammation [36]; therefore, accelerated atherosclerosis cannot be fully explained on the basis of traditional risk factors [42,43].

Indeed, several inflammatory and atherogenic mediators, including homocysteine, lipoprotein (a), C-reactive protein (CRP), hyperhomocysteinemia, and folate, and vitamin B<sub>12</sub> deficiency and decreased paraoxonase-1 activity are strongly associated with atherosclerosis and CVD [36,42,43]. Atherosclerotic plaques, similarly to the RA joint, are characterized by enhanced accumulation of inflammatory monocytes/macrophages and T cells. These inflammatory leukocytes abundantly produce proinflammatory cytokines, chemokines, and MMPs [42,43]. CD4<sup>+</sup> T cells, especially the CD4<sup>+</sup>/CD28<sup>-</sup> T-cell subset, have been associated with both arthritis and inflammation-related vascular damage [37,38,43]. Regarding proinflammatory cytokines, TNF- $\alpha$  and IL-6 play an important role in atherosclerosis as well as in RA [31,36,43]. Increased production of TNF- $\alpha$  and IL-6 has been associated with heart failure as well as with insulin resistance, dyslipidemia, and obesity [36,43]. In contrast, IL-4 and IL-10 may exert an anti-inflammatory role during the development of atherosclerosis by driving Th2 responses [31,43] (Table 6).

**Vascular involvement in various rheumatic diseases**

In RA, age, gender, ethnicity, traditional risk factors described above as well as (among RA-related risk factors) disease duration, activity, and severity, functional impairment, rheumatoid factor and anti-CCP status, CRP, radiographic indicators, presence of the shared epitope, and treatment modalities have been implicated in the development of accelerated atherosclerosis [36-38,44]. We have recently assessed common carotid intima-media thickness (ccIMT) indicating atherosclerosis and flow-mediated vasodilation (FMD), a marker of endothelial dysfunction in RA. Increased ccIMT and impaired FMD have been associated with age, disease duration, and anti-CCP, CRP, and IL-6 production [44]. In SLE, primary APS (PAPS) and secondary APS associated with SLE, traditional, and autoimmune-inflammatory factors are involved [40]. Among these factors, longer disease duration and cumulative corticosteroid dose seem to

Table 6

Common risk factors in the pathogenesis of atherosclerosis underlying rheumatic diseases

1. Traditional	Age Smoking Dyslipidemia Hypertension Diabetes mellitus Immobilization Sedentary lifestyle
2. Inflammatory	Acute-phase proteins (C-reactive protein, fibrinogen) Lipoprotein (a) Folate and vitamin B <sub>12</sub> deficiency Decreased paraoxonase activity CD4 <sup>+</sup> /CD28 <sup>-</sup> T cells Autoantibodies (anti-CCP, rheumatoid factor, anti-oxLDL, anti-phospholipid antibody, anti-hsp) Proatherogenic cytokines (tumor necrosis factor-alpha, interleukin-6) Chemokines Angiogenic growth factors Matrix-degrading metalloproteinases Increased cell adhesion molecule expression Hyperhomocysteinemia Defective apoptosis
3. Iatrogenic	Methotrexate - bimodal? Corticosteroids - bimodal?

anti-CCP, anti-cyclic citrullinated peptide; anti-oxLDL, anti-oxidized low-density lipoprotein.

be the major predictors of clinical atherosclerosis [37,38,40,41]. Additional inflammatory risk factors include CRP, fibrinogen, IL-6, costimulatory molecules (CD40/CD40L), CAMs, anti-phospholipid antibodies (APAs), including anti-cardiolipin and anti-β2 glycoprotein I (anti-β2GPI), anti-oxidized low-density lipoprotein (anti-oxLDL), anti-oxidized palmitoyl arachidonoyl phosphocholine (anti-oxPAPC), anti-HDL and anti-hsp antibodies, homocysteine, and lipoprotein (a) [37,40,41]. APAs are of importance in both SLE and APS. APAs may bind to neoepitopes of oxLDL as well as to oxLDL-β2GPI complexes, and both APA and anti-oxLDL antibodies have been implicated in the pathogenesis of atherosclerosis associated with SLE and APS [37,38,40,41]. Autoantibodies against oxLDL-β2GPI complexes have been detected in SLE and PAPS patients [40,41]. Both APA and anti-oxLDL may account for increased mortality in CVD [41]. The β2GPI phospholipid cofactor has been detected in the wall of large arteries in the vicinity of CD4<sup>+</sup> T-cell infiltrates. Macrophages and ECs bind to β2GPI during the atherosclerotic process [37,38,41]. Atherosclerosis is the most pronounced in lupus-associated secondary APS, in which traditional and nontraditional risk factors are multiplied and atherosclerosis occurs more prematurely [40,41]. SSc is associated with both macrovascular disease (including CVD, pulmonary hypertension, and peripheral arterial occlusion) and microvascular disease (including Raynaud phenomenon) [37-39, 45,46]. Pathogenic factors involved in SSc-associated vascular damage include increased LDL, homocysteine, and CRP production [37,39,46]. We recently described the association of 5,10-methylene-tetrahydrofolate reductase (MTHFR) C677T polymorphism with homocysteine, vitamin

B<sub>12</sub> production, and macrovascular abnormalities in SSc [46]. Increased arterial stiffness and cclMT as well as impaired FMD have been detected by us [39,45] and others [37] in scleroderma.

Therapeutic considerations

Anti-inflammatory treatment used in inflammatory rheumatic diseases may be either proatherogenic or antiatherogenic [37,47]. Corticosteroids are atherogenic by augmenting dyslipidemia, hypertension, and diabetes mellitus [36,47]. In autopsy studies, long exposure to corticosteroid therapy was associated with the development of atherosclerosis. However, other clinical studies could not confirm this association [36,47]. Glucocorticoids may exert a bimodal action as they are atherogenic but, on the other hand, also anti-inflammatory. There is evidence that the above-described inflammatory factors associated with more active disease may exert higher risk for atherosclerosis than anti-inflammatory treatment [37,47]. In contrast to corticosteroids, antimalarial drugs such as chloroquine and hydroxychloroquine may exert evident antiatherogenic properties. Antimalarials may reduce LDL cholesterol, very LDL cholesterol, and (in corticosteroid-treated patients) triglyceride production [36,37,47]. Methotrexate (MTX) exerts bipolar effects on atherosclerosis in RA: on one hand, MTX treatment increases plasma levels of homocysteine, but, on the other hand, MTX controls several other mediators of inflammation and thus may beneficially influence the net outcome of CVD in RA [36,47]. Concomitant folate supplementation prevented the increase of homocysteine production and reduced CVD mortality in MTX-treated patients [36]. Among biologic agents, TNF-α



blockers may have significant effects on the vasculature [48]. In RA, infliximab treatment reduced endothelial dysfunction and cclMT [48]. We recently proposed that rituximab may also exert favorable effects on FMD, cclMT, and dyslipidemia [49]. Atherosclerosis treatment strategies in rheumatic diseases should include an aggressive control of all traditional risk factors, including hyperlipidemia, hypertension, smoking, obesity, and diabetes mellitus. Both pharmacological treatment and changes in lifestyle should be introduced in these patients [47]. There is very little solid evidence from randomized controlled trials indicating the preventative action of any drugs in arthritis-associated CVD [47]. Drug therapy may include the use of antiplatelet agents, statins, folic acid, B vitamins, and (as described above) possibly antimalarials [36,47]. A recommendation from the European League Against Rheumatism for the prevention and management of CVD in arthritis is about to be published [50].

## Summary

In this review, we discussed the putative role of leukocyte-EC adhesion, chemokines, and angiogenesis in leukocyte recruitment underlying the pathogenesis of inflammatory synovitis. A number of CAMs are involved in this process. These CAMs interact with soluble inflammatory mediators such as cytokines and chemokines. The presence of various CAM pairs and the existence of distinct steps of rolling, activation, adhesion, and migration account for the diversity and specificity of leukocyte-EC interactions. Chemokines and their receptors drive inflammatory leukocytes into the synovium. A number of soluble and cell-bound factors may stimulate or inhibit angiogenesis. The outcome of inflammatory and other 'angiogenic diseases' such as various forms of arthritis depends on the imbalance between angiogenic and angiostatic mediators. There have been several attempts to therapeutically interfere with the cellular and molecular mechanisms described above. Specific targeting of leukocyte adhesion, CAMs, chemokines, chemokine receptors, and/or angiogenesis, primarily by using agents with multiple actions, may be useful for the future management of inflammatory rheumatic diseases.



## The Scientific Basis of Rheumatology: A Decade of Progress

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## Competing interests

The authors declare that they have no competing interests.

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