Angiogenesis in rheumatoid arthritis

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Abstract

Angiogenesis is the formation of new capillaries from pre-existing vessels. A number of soluble and cell-bound factors may stimulate neovascularization. The perpetuation of angiogenesis involving numerous soluble and cell surface-bound mediators has been associated with rheumatoid arthritis (RA). These angiogenic mediators, among others, include growth factors, primarily vascular endothelial growth factor (VEGF) and hypoxia-inducible factors (HIFs), as well as pro-inflammatory cytokines, various chemokines, matrix components, cell adhesion molecules, proteases and others. Among the several potential angiogenesis inhibitors, targeting of VEGF, HIF-1, angiogenic chemokines, tumor necrosis factor-α and the αVβ3 integrin may attenuate the action of angiogenic mediators and thus synovial angiogenesis. In addition, some naturally produced or synthetic compounds including angiostatin, endostatin, paclitaxel, fumagillin analogues, 2-methoxyestradiol and thalidomide may be included in the management of RA.

Keywords

angiogenesis; rheumatoid arthritis; vascular endothelial growth factor; angiostasis therapy

Introduction

Increased angiogenesis has been associated with various inflammatory disease states including rheumatoid arthritis (RA), as well as malignancies and ocular angiogenic diseases [1-10]. Angiogenesis is new capillary outgrowth from existing vessels that is a well-orchestrated sequence of events. Angiogenic mediators released by or expressed on various types of cells within the synovium activate endothelial cells (ECs). ECs produce proteolytic enzymes that degrade the underlying endothelial basement membrane, as well as the synovial extracellular matrix. ECs then proliferate and emigrate into the interstitial tissue and form primary and then further generation capillary sprouts. After lumen is formed within the sprout resulting in capillary loops, ECs synthesize new basement membrane and

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thus new capillaries are generated [1,2,5,7,11]. Some mediators also produced during the inflammatory process, as well as externally administered organic or synthetic compounds may disrupt neovascularization. These agents may be used to suppress angiogenesis in inflammatory and malignant diseases [6,12].

Here we review the most important mechanisms, mediators and inhibitors underlying inflammatory angiogenesis. When describing the basic mechanisms, we concurrently present therapeutic options aiming at the suppression of angiogenesis by inhibiting the action of angiogenic mediators or by the administration of angiostatic agents. Some of these treatment modalities have already been administered to patients with arthritis, as well as cancer, or at least to arthritic animals, while others may be potentially used in the future.

Basic mechanisms

In inflammatory arthritis, leukocytes migrate from the bloodstream through the vessel wall into the synovium. Leukocyte transendothelial migration involves a number of cell adhesion molecules, such as integrins, selectins and their respective ligands [1,3,13]. The perpetuation of angiogenesis associated with inflammatory states may lead to increased number of blood vessels, as well as that of total endothelial surface. Mechanistically, this process may result in enhanced leukocyte ingress into the synovium [13,14]. Some inflammatory mediators including pro-inflammatory cytokines and chemokines may promote both EC adhesion receptor expression and angiogenesis. Furthermore, as discussed later, some adhesion molecules themselves induce neovascularization. Thus, there is a collaboration between various soluble and cell surface-bound mediators during the angiogenic process [1,3,4,8,13,14] (Figure 1).

Angiogenic mediators and possibilities of therapeutic inhibition

As mentioned here, both soluble and cell-bound mediators including numerous growth factors, proinflammatory cytokines and chemokines, components of the synovial matrix, matrix-degrading proteases, cellular adhesion molecules and others [1-3,5,8]. Most of these mediators are released by macrophages and vascular EC into the RA synovium [1-3,5,8,14] (Table I).

The hypoxia-vascular endothelial growth factor (VEGF)-angiopoietin-Tie2 system

VEGF may be of outstanding importance in angiogenesis associated with both malignancies and inflammation. As a consequence, VEGF inhibitors have been introduced to arthritis, as well as cancer clinical trials [1,10,15-18]. Pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) stimulate synovial fibroblasts and other cells to release VEGF [1,2,14-17]. As described later, numerous other mediators including IL-6, IL-17, IL-18, nitric oxide (NO), hepatocyte growth factor (HGF), macrophage migration inhibitory factor (MIF), endothelin-1 (ET-1) and prostaglandins act indirectly on angiogenesis by promoting VEGF production [1,3,17,19-23]. VEGF induces EC proliferation and migration in in vitro culture systems and it also stimulates capillary formation in in vivo models of angiogenesis [15,17]. VEGF-induced angiogenesis also involve cyclooxygenase-2 (COX-2) induction [1,16,18].

VEGF targeting is in the focus of cancer and inflammation research [9,10,16]. One can inhibit VEGF-mediated neovascularization by using monoclonal antibodies to VEGF or VEGF receptors (VEGFR), soluble VEGFR constructs, small molecule VEGF and VEGFR inhibitors or inhibitors of VEGF and VEGFR signaling [6,12,16,17,24-28]. Some of these compounds have been first administered to cancer patients, primarily in colorectal, lung, renal and liver malignancies [6,9,12,16,17]. VEGF or VEGFR inhibition has been introduced to the treatment of neovascular eye diseases [10] and recently also to arthritis.
Bevacizumab, a human monoclonal antibody to VEGF has been approved for the treatment of various types of cancer, as well as angiogenic oculur diseases [6,10,16]. Anti-VEGFR antibodies are also under development [28]. The VEGF-Trap construct is a composite decoy receptor based on the fusion of VEGFR1 and VEGFR2 with IgG1-Fc (24).

Several small molecule VEGFR tyrosine kinase inhibitors including vatalanib, sunitinib malate, sorafenib, vandetanib (ZD6474), cediranib (AZD2171), axatinib (AG013736), KRN-951 and CEP-7055 have been developed [6,16,17]. In cancer studies, these orally administered compounds exerted favorable safety profiles [6,16,17]. Semaphorin-3A and soluble Fas ligand (sFasL, CD178) are functional inhibitors of the 165 amino-acid form of VEGF (VEGF165) [27,29]. Both agents suppressed EC survival and angiogenesis [27,29] (Table II).

Regarding experience in arthritis, a soluble VEGFR1 chimeric protein dose-dependently inhibited synovial EC proliferation [25]. An anti-VEGFR1 antibody suppressed arthritis including clinical scores, leukocyte infiltration and the number of CD31+ ECs in murine CIA [28]. Among VEGFR protein kinase inhibitors mentioned above, vatalanib also inhibited knee arthritis in rabbits [6,26]. sFasL suppressed VEGF165 production by RA synovial fibroblasts [27].

Hypoxia has been detected in the arthritic joint [19,30]. Intraarticular hypoxia induces branching of capillaries at least in part by the stimulation of hypoxia-inducible factor (HIF-1 and HIF-2) production. In response, HIFs induce the release of VEGF [30,31]. Hypoxia may also act via HIF-independent regulatory pathways. For example, after an ischemic insult peroxisome-proliferator-activated receptor-γ (PPARγ) and PPARγ coactivator 1α (PGC-1α) induce VEGF production and the reconstitution of capillaries [32]. The PPARγ ligands rosiglitazone and pioglitazone inhibit VEGF-induced angiogenesis [33]. Furthermore, pioglitazone also improved joint and skin symptoms in psoriatic arthritis [34]. Apart from PPARγ, endothelial PPARβ/δ has also been implicated in EC proliferation and angiogenesis [35].

Hypoxia-HIF-mediated neovascularization may also be targeted. For example, YC-1, a superoxide-sensitive stimulator of soluble guanylyl cyclase, also inhibits HIF-1. This compound has been developed for the treatment of hypertension and thrombosis but may potentially be used to suppress inflammatory angiogenesis [6,36]. There have been attempts to target HIF-1 signaling in inflammatory bowel disease [37] (Table II).

The angiopoietin-1 (Ang1)/Tie-2 complex interacts with VEGF during the stabilization of newly formed blood vessels [38,39]. In contrast, Ang2, an antagonist of Ang1, inhibits vessel maturation [17,38]. Survivin, an apoptosis inhibitor, is also involved in VEGF-induced angiogenesis [40]. VEGF, hypoxia, HIF-1, HIF-2, Ang1, Tie2 and survivin have been all detected within the RA synovium [3,5,30,31,39,41]. This system may also be targeted. A soluble Tie2 receptor transcript delivered via an adenoviral vector to mice attenuated the incidence and severity of collagen-induced arthritis (CIA) [42].

Other growth factors

Some growth factors including basic (bFGF), acidic fibroblast growth factors (aFGF) and HGF are bound to heparin and heparin sulfate within the synovial interstitial matrix. During inflammatory neovascularization, these growth factors are released by matrix-degrading heparanase and plasmin [1-3,5]. Other, non-heparin-bound angiogenic growth factors include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor-I (IGF-1), keratinocyte growth factor (KGF) and transforming growth factor-β (TGF-β) [1-3]. Recently, placenta growth factor (PIGF) has been implicated in arthritis-
associated inflammation and angiogenesis. PIGF, as well as VEGF, binds to the flt-1 receptor. There is abundant expression of PIGF in the synovial tissue of mice with CIA [43].

Imatinib mesylate is a specific inhibitor of PDGF receptor activation. This compound inhibits the excessive growth of RA synovial fibroblasts and thus pannus formation [44]. Imatinib mesylate both preventively and therapeutically inhibited the development of arthritis in the murine CIA model [45]. The PPARγ agonists rosiglitazone and pioglitazone suppressed bFGF-mediated neovascularization [33]. An anti-flt-1 hexapeptide, GNQWFI abrogated PIGF-induced angiogenesis, cytokine production and the development of CIA in mice [43] (Table II).

**Angiogenic chemokines and chemokine receptors**

Chemokines and chemokine receptors have also been implicated in synovial inflammation, as well as angiogenesis [3,5,8,46]. Chemokines have been classified into CXC, CC, CX3C and C families based on the location of cystein (C) residues [8,46]. The angiogenic nature of most CXC chemokines has been associated with the glutamyl-leucyl-arginyl (ELR) amino acid motif within their structure [46]. These chemokines include IL-8/CXCL8, epithelial neutrophil activating protein-78 (ENA-78)/CXCL5, growth-related oncogene α (groα)/CXCL1 and connective tissue activating protein-III (CTAP-III)/CXCL6 [8]. Stromal cell-derived factor-1 (SDF-1)/CXCL12, a key regulator of lymphoid neogenesis and vasculogenesis within the RA synovium, does not contain the ELR sequence, however, yet this chemokine promotes synovial angiogenesis [47,48]. Hypoxia stimulates RA synovial fibroblasts to produce SDF-1/CXCL12 [47,48]. SDF-1/CXCL12 expression in tumors may have prognostic value [49]. Among CC chemokines, MCP-1/CCL2 is involved in angiogenesis as this chemokine supports the angiogenic effects of growth factors [8,50,51]. Fractalkine/CX3CL1 also promotes synovial neovascularization [52]. These chemokines are also involved in leukocyte recruitment into the inflamed synovium [8,46,47,50,52].

Regarding chemokine receptors, CXCR2 is the most important receptor for ELR+ CXC chemokines on ECs [1,8]. CXCR4, the receptor for SDF-1/CXCL12 and CCR2, the receptor for MCP-1/CCL2 are also involved in chemokine-dependent angiogenesis [8,47,53].

Chemokine and chemokine receptor targeting may suppress synovitis, as well as synovial angiogenesis. For example, CXCR2 blockade resulted in the attenuation of tumor-induced angiogenesis [8,54]. Mig/CXCL9 gene therapy in addition to cytotoxic agents exerted strong angiostatic and tumor-suppressive effects in cancer trials [55]. Bicyclam (AMD3100), a highly selective antagonist of SDF-1/CXCL4, inhibits EC proliferation and migration [56] (Table II).

**Extracellular matrix constituents, cell adhesion molecules and proteases**

The ingress of inflammatory leukocytes into the synovium, as well as synovial angiogenesis involves basal membrane and interstitial matrix macromolecules, cellular adhesion receptors, as well as matrix-degrading proteases [11,57]. Among extracellular matrix components including matrix molecules within the EC basement membrane, such as type I collagen, laminin, fibronectin, vitronectin, tenascin and various proteoglycans have been implicated in EC migration during angiogenesis [1,2,11,57]. Some studies suggest that partial loss of basement membrane constituents results in the widening and enlargement of vessels that enables the process of new capillary formation [11].

Among adhesion receptors, most β₁ and β₃ integrins, E-selectin, the L-selectin ligand CD34, selectin-related glycoconjugates including Lewis²/H and MUC18, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-2 (ICAM-2), platelet-EC adhesion
molecule-1 (PECAM-1), endoglin and junctional cell adhesion molecules A (JAM-A) and C (JAM-C) are expressed on the endothelial surface and promote angiogenesis [1-3,13,58-64]. The αVβ3 integrin seems to be of significant importance. This adhesion receptor is involved in osteoclast activation leading to the development of erosions, as well as synovial angiogenesis in RA [13,58,61]. The αV subunit of this integrin is encoded by the ITGAV gene. A significant genetic association has been found between the ITGAV rs3738919-C allele and RA in the European Caucasian population [65]. Focal adhesion kinases (FAK) are involved in αVβ3 integrin signaling. FAKs have been detected in the RA synovium suggesting their role in synovial inflammation and angiogenesis [66]. Mast cells are also involved in integrin-dependent angiogenesis and joint destruction as mast cell silencing with salbutamol or cromolyn prevented αVβ3 integrin activation and angiogenesis in mice [67].

Adhesion receptor blockade may effectively suppress synovial angiogenesis, as well as leukocyte migration in RA. For example, Vitaxin, a humanized antibody to the αVβ3 integrin inhibited synovial neovascularization in animal models of arthritis [6,13,58], yet, very little efficacy was observed in a phase II human RA trial [6]. Statins, currently used for the treatment of dyslipidemia, also modify endothelial function and adhesion receptor expression [68] (Table II).

Angiogenic proteases include matrix metalloproteinases (MMPs) and plasminogen activators [5,8]. Numerous protease inhibitors including tissue inhibitors of metalloproteinases (TIMPs) and plasminogen activator inhibitors (PAIs) that antagonize the effects of proteases have been tried in angiogenesis models [5,6,69].

**Pro-inflammatory and angiogenic cytokines**

Pro-inflammatory cytokines may exert direct angiogenic activity or may act indirectly via VEGF-dependent pathways. TNF-α, IL-1, IL-6, IL-15, IL-17, IL-18, oncostatin M, MIF, granulocyte (G-CSF) and granulocyte-macrophage colony-stimulating factors (GM-CSF) have been implicated in synovial inflammation and angiogenesis [1-3,70-76]. TNF-α itself promotes neovascularization [74] and it may also regulate capillary formation via the Ang1-Tie2-VEGF network [75]. IL-6 may also act via the induction of VEGF production [76]. IL-17 synergizes with TNF-α in stimulating VEGF, EGF, HGF and KGF production by synovial fibroblasts [1,70]. IL-17 also acts through CXCR2-dependent pathways [77]. IL-18 induces the synthesis of VEGF, as well as the SDF-1/CXCL12 and MCP-1/CCL2 angiogenic chemokines by synovial fibroblasts [20]. Oncostatin M induces ICAM-1 expression on RA synovial ECs and fibroblasts and it also stimulates EC migration and capillary formation [78]. MIF is primarily produced by synovial macrophages and is involved in macrophage-derived synovial angiogenesis [14,21,79,80]. MIF acts via the induction of VEGF and IL-8/CXCL8 release by RA synovial fibroblasts [21].

Anti-cytokine therapy influences several inflammatory mechanisms including angiogenesis in arthritis. For example, TNF-α blockade by infliximab administered in combination with methotrexate reduced VEGF expression and vascularity within the RA synovium [6,81]. Anti-TNF therapy reduced synovial Ang1-Tie2 and survivin but upregulated Ang2 expression [6,75]. Suppression of circulating IL-6 levels by various DMARDs has been associated with decreased EC activation in RA [82]. The anti-IL-6 receptor antibody tocilizumab, which has recently been approved for the treatment of RA, decreased serum levels of VEGF [76] (Table II).

**Other angiogenic mediators**

Other mediators not mentioned above include ET-1, serum amyloid A (SAA), members of the COX-2-prostaglandin E2 network, angiogenin, angiotropin, pleiotrophin, platelet-
activating factor (PAF), substance P, erythropoietin, adenosine, histamine, prolactin and thrombin [1-3,5,7,83-86]. For example, ET-1 stimulates VEGF production, EC proliferation and angiogenesis [83,84]. ET-1 is abundantly produced in RA and scleroderma [83,84]. SAA is an important acute-phase reactant also implicated in arthritis. SAA acts via the formyl peptide receptor-like 1 (FPRL1). Interaction of SAA with FPRL1 stimulates EC proliferation, migration and neovascularization, as well as synovitis [85,86].

ET-1 antagonists currently used in the treatment of primary and scleroderma-associated pulmonary hypertension may also exert anti-angiogenic effects [83] (Table II).

**Angiogenesis inhibitors and their use in arthritis therapy**

There is a great number of naturally produced or synthetic angiostatic molecules. Most angiostatic molecules block the action of angiogenic mediators, such as VEGF, HIFs or the αVβ3 integrin, and thus they indirectly suppress neovascularization [5,6,12,17]. Some of these compounds have already been tried to target tumor- or inflammation-associated neovascularization [1,5,6,12] (Tables I and II).

Angiostatic cytokines include interferon-α (IFN-α), IFN-γ, IL-4, IL-12 and leukemia inhibitory factor (LIF). These cytokines inhibit the release of VEGF and other angiogenic mediators [5,6,12,70,87]. For example, IL-4 blocks VEGF release by RA synovial fibroblasts [87]. IL-4 and IL-13 gene transfer inhibited synovial inflammation and angiogenesis in rats [88,89] (Table II).

Angiostatic CXC chemokines that lack the ELR motif include platelet factor-4 (PF4)/CXCL4, monokine induced by interferon-γ (MIG)/CXCL9 and interferon-γ-inducible protein 10 (IP-10)/CXCL10 [2,8,90,91]. These chemokines may regulate VEGF-dependent angiogenesis. For example, VEGF stimulates the release of IP-10/CXCL10 and, in turn, IP-10/CXCL10 suppresses VEGF-induced angiogenesis [16,90]. Secondary lymphoid tissue chemokine (SLC)/CCL21 is an angiostatic CC chemokine that inhibits tumor progression [92]. CXCR3 that binds most ELR−CXC chemokines is possibly the most important chemokine receptor that confers angiostasis [8]. Angiostatic chemokines may also be used in cancer or arthritis therapy. For example, PF4/CXCL4 has been tried in rodent models of arthritis [8,91] (Table II).

Among currently used antirheumatic drugs, rofecoxib, dexamethasone, chloroquine, sulfasalazine, methotrexate, azathioprine, cyclophosphamide, leflunomide, thalidomide, minocycline and some anti-TNF agents, apart from several other anti-inflammatory effects, also inhibit EC migration and synovial angiogenesis [1,2,12,93]. Results are rather conflicting regarding methotrexate. This DMARD inhibited tumor angiogenesis but exerted no such effects in psoriatic arthritis [12] (Table II).

Thalidomide is a potent TNF-α antagonist and an angiogenesis inhibitor [6,94]. The net effect of thalidomide on synovial angiogenesis is not fully clear as in one rodent study it suppressed, while in another report it did not influence VEGF production [6,95]. Yet, thalidomide suppressed both synovitis and angiogenesis in vivo [6,95] suggesting that its angiostatic effects may be, in part, independent of VEGF. CC1069, a thalidomide analogue, is an even more potent angiogenesis inhibitor than thalidomide itself [6,96]. Regarding human thalidomide trials, it showed little efficacy in RA and moderate clinical response was observed in systemic lupus erythematosus (SLE) [6] (Tables I and II).

Thrombospondin-1 (TSP1) and TSP2 that are angiostatic extracellular matrix components naturally produced within the RA synovium [6,97,98]. A TSP1 peptide suppressed synovial inflammation and angiogenesis in a rat arthritis model [97]. TSP2 inhibited synovial
neovascularization in the severe combined immunodeficiency (SCID) mouse model of arthritis [98] (Tables I and II).

Antibiotic derivatives including minocyclin, fumagillin analogues, deoxyspergualin and clarithromycin also inhibit the release of VEGF and other angiogenic mediators and thus neovascularization [6,12,99-101]. Fumagillin is a naturally occurring product of Aspergillus fumigatus. Its synthetic derivatives, TNP-470 and PPI-2458 inhibit VEGF, as well as methionine aminopeptidase-2, an enzyme involved in angiogenesis [6,99]. In a study of 60 early RA patients, minocycline was clinically more effective than hydroxychloroquine [102]. Minocycline treatment was associated with clinically significant improvement in RA, yet, its effects are rather moderate in comparison to other currently used DMARDs (103). In a 6-month study on 81 early RA patients, clarithromycin was more effective than placebo [104]. In rodent models, deoxyspergualin, as well as the fumagillin analogs TNP-470 and PPI-2458 suppressed the development of arthritis [100,101,105,106] (Table II).

Angiostatin, a fragment of plasminogen, endostatin, a fragment of type XIII collagen and their derivatives block αVβ3 integrin-dependent angiogenesis [6,12,107-109]. Endostatin also interferes with VEGFR 2 signaling [6,109] and induces apoptosis of synovial fibroblasts [110]. Some of these agents, particularly angiostatin and endostatin, gave promising results in cancer therapy trials, as well as pre-clinical arthritis studies [1,6,12,107,108]. For example, angiostatin gene transfer attenuated murine CIA [6,108]. Endostatin both prophylactically and therapeutically suppressed arthritis scores, pannus formation and the development of joint erosions in rodent arthritis models [6,107,109,111,112]. The angiostatin-like protease-activated kringle 1-5 (K1-5) may be a more potent angiogenesis inhibitor than angiostatin itself [113]. Serum levels and synovial tissue expression of kallistatin was increased in RA [114]. Intraarticular injection of kallistatin attenuated rat arthritis using gene therapy [114]. Type IV collagen derivatives including arrestin, canstatin and tumstatin also inhibit neovascularization [115]. Regarding human studies, both angiostatin and endostatin have been introduced to clinical trials in cancer [6,12] (Tables I and II).

2-Methoxyestradiol (2-ME) is a natural metabolite of estrogen with low affinity for estrogen receptors. 2-ME inhibits angiogenesis by disrupting microtubules and by suppressing HIF-1α activity [116]. In recent preclinical studies, 2-ME suppressed arthritis in the rat CIA model [117]. On the other hand, 2-ME suppressed arthritis, but synovial vascularity in another study [118] suggesting that 2-ME may also have angiogenesis-independent effects on synovial inflammation.

Paclitaxel (taxol) is a microtubule disrupting agent that diminishes HIF-1α expression and activity and thus indirectly inhibits angiogenesis [6,116]. This anti-cancer agent has been found effective and safe in a phase I RA clinical trial [6]. Further compounds not discussed here include osteonectin, opioids, troponin I, and chondromodulin-1 [6,12,17].

**Regulation of synovial angiogenesis**

*Macrophages* and mediators produced by these cells definitely play a central role in the regulation of synovial angiogenesis [14]. Synovial macrophages express CXCRII and CXCR4, chemokine receptors implicated in CXC chemokine-mediated neovascularization [5,8,14]. In addition, macrophages also release important soluble angiogenic mediators, such as IL-8/CXCL8, ENA-78/CXCL5, groa/CXCL1, CTAP-III/CXCL7, MCP-1/CCL2, TNF-α, IL-15, IL-18, VEGF, bFGF, aFGF, HGF, PDGF and MMPs [2,5,8,14,53]. On the other hand, macrophages are also involved in angiostasis, as they produce IP-10/CXCL10, MIG/CXCL9, IFN-γ and TIMPs [8,14].
Several regulatory interactions and loops exist in sites of angiogenesis and inflammation. Regarding specific antagonistic pairs, there is an abundance of ELR$^+$ over ELR$^-$ CXC chemokines, MMPs over TIMPs, pro-inflammatory, angiogenic over anti-inflammatory, angiostatic cytokines [2,5,6]. Also, different angiogenic mediators may have additive effects. For example, TNF-$\alpha$ stimulates the production of various angiogenic chemokines, growth factors, other cytokines or adhesion receptors [2,5,6,13]. Furthermore, as described here, numerous angiogenic mediators indirectly promote, while various angiostatic agents inhibit VEGF-dependent neovascularization [1,5,16]. Apart from natural regulatory networks described here, the administration of compounds with angiostatic activity may also interfere with neovascularization [6,12].

Conclusions

In this review, we discussed the putative role of angiogenesis in RA. Synovial angiogenesis may increase the total vascular endothelial surface and thus may enhance the ingress of leukocytes into the synovial tissue. Several soluble and cell surface-bound mediators of angiogenesis including VEGF and other growth factors, cytokines, chemokines, extracellular matrix constituents, cell adhesion molecules, proteases and others have been described in relation to synovitis.

When describing the action of the most relevant angiogenic mediators we also presented therapeutic strategies that may suppress the production of these mediators and thus attenuate synovial angiogenesis, as well as inflammation. On the other hand, some endogenous angiogenesis inhibitors are naturally produced to counterbalance excessive neovascularization associated with RA. Yet, the amount and activity of these endogenous agents are insufficient to control inflammatory angiogenesis in arthritis. Inhibitors of VEGF and VEGFR, angiogenic chemokines and chemokine receptors, integrins, currently used DMARDs and biologics, thalidomide, taxol, 2-ME, fumagillin analogues, angiostatin and endostatin may be included in future anti-angiogenic, as well as anti-inflammatory treatment.

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Figure 1.
Soluble and cell surface-bound angiogenesis mediators and inhibitors in synovial neovascularization.
Table I

Relevant mediators and inhibitors of angiogenesis in RA.\(^a\)

<table>
<thead>
<tr>
<th>Mediators</th>
<th>Inhibitors</th>
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<tbody>
<tr>
<td>Growth factors</td>
<td>–</td>
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<tr>
<td>Cytokines</td>
<td>IFN-(\alpha), IFN-(\gamma), IL-4, IL-12, LIF</td>
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<tr>
<td>Chemokines/receptors</td>
<td>PF4/CXCL4, MIG/CXCL9, IP-10/CXCL10, SLC/CCL21, CXCR3</td>
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<tr>
<td>Matrix molecules</td>
<td>Thrombospondin-1, -2</td>
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<tr>
<td>Cell adhesion molecules</td>
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<tr>
<td>Proteolytic enzymes</td>
<td>TIMPs, PAIs</td>
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<tr>
<td>Antirheumatic drugs</td>
<td>Dexamethasone, rofecoxib, classical DMARDs, thalidomide, minocycline, anti-TNF biologics</td>
</tr>
<tr>
<td>Antibiotic derivatives</td>
<td>Minocycline, fumagillin analogs, deoxyspergualin, clarithromycin</td>
</tr>
<tr>
<td>Environmental factors</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Others</td>
<td>Angiopoietin 2, angiotatin, endostatin, kallistatin, type IV collagen derivatives, paclitaxel, 2-methoxyestradiol, osteonectin, opioids, troponin I, chondromodulin</td>
</tr>
</tbody>
</table>

\(^a\)See text for abbreviations.
Table II

Angiogenesis targeting strategies in animal models of arthritis and human RA.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Compound</th>
<th>Animal (A)/Human (H) study\textsuperscript{b}</th>
<th>Reference(s)</th>
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<td><strong>Endogenous inhibitors</strong></td>
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<tr>
<td>Angiostatin</td>
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</tr>
<tr>
<td>Endostatin</td>
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<td>[6,107,109,111,112]</td>
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<tr>
<td>Protease-activated kringles 1-5 (K1-5) (angiostatin analogue)</td>
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<td>[113]</td>
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<td>Kallistatin</td>
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<td>[114]</td>
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<td>Thrombospondin-1-derived peptide</td>
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<td><strong>Exogenous inhibitors</strong></td>
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<td>Anti-VEGFR1 antibody</td>
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<td>Vatalanib (VEGF-R tyrosine kinase inhibitor)</td>
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<td>Anti-flt-1 hexapeptide (PIGF and VEGF antagonist)</td>
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<tr>
<td>Bicyclam (AMD3100)</td>
<td>H (culture)</td>
<td>[56]</td>
</tr>
<tr>
<td>Soluble Tie2 vector</td>
<td>A</td>
<td>[42]</td>
</tr>
<tr>
<td>Vitaxin (anti-(\alpha)(\beta) integrin)</td>
<td>A, H (RA)</td>
<td>[6,13,58]</td>
</tr>
<tr>
<td>Traditional DMARDs (methotrexate, sulfasalazine, etc.)</td>
<td>H (RA)</td>
<td>[1,2,12]</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>H (culture)</td>
<td>[93]</td>
</tr>
<tr>
<td>Infliximab</td>
<td>H (RA)</td>
<td>[6,75,81]</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>H (RA)</td>
<td>[76]</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>A, H (RA)</td>
<td>[6,95]</td>
</tr>
<tr>
<td>CC1069 (thalidomide analogue)</td>
<td>A</td>
<td>[96]</td>
</tr>
<tr>
<td>TNP-470 (fumagillin analogue)</td>
<td>A</td>
<td>[6,99]</td>
</tr>
<tr>
<td>PPI2458 (fumagillin analogue)</td>
<td>A</td>
<td>[99,101,106]</td>
</tr>
<tr>
<td>Statins</td>
<td>H (culture)</td>
<td>[68]</td>
</tr>
<tr>
<td>ET-1 antagonists</td>
<td>H</td>
<td>[83]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>H</td>
<td>[6,116]</td>
</tr>
<tr>
<td>Minocycline</td>
<td>H (RA)</td>
<td>[102,103]</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>H (RA)</td>
<td>[104]</td>
</tr>
<tr>
<td>Deoxyxyspergualin</td>
<td>H (RA)</td>
<td>[105]</td>
</tr>
<tr>
<td>PPAR(\gamma) agonists (pioglitazone, rosiglitazone)</td>
<td>H (arthritis)</td>
<td>[33,34]</td>
</tr>
</tbody>
</table>

\textsuperscript{a}See text for abbreviations

\textsuperscript{b}Human studies include both in vitro studies with isolated cell cultures, as well as in vivo RA studies.