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Targeting Angiogenesis in Rheumatoid Arthritis

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Abstract

Angiogenesis, the development of new capillaries, is a crucial process in health and disease. The perpetuation of neovascularization in rheumatoid arthritis is highly involved in leukocyte extravasation into the synovium and pannus formation. Numerous soluble and cell surface-bound angiogenic mediators, including growth factors, cytokines, proteases, matrix macromolecules, cell adhesion receptors, chemokines and chemokine receptors, have been implicated in the process of neovascularization. Endogenous angiostatic factors, primarily angiostatin, endostatin, IL-4, IL-13, some angiostatic chemokines may be used to downregulate neovascularization. In addition, angiogenesis might be targeted by several specific approaches against VEGF, angiopoietin, $\alpha_v\beta_3$ integrin or by exogenously administered compounds including DMARDs, anti-TNF agents, fumagillin analogues or thalidomide. Potentially all anti-angiogenic could be tried in order to control synovitis.

Keywords

Angiogenesis; rheumatoid arthritis; targeting; angiogenic mediators; angiostasis

INTRODUCTION

Angiogenesis, the formation of new capillaries from pre-existing vessels, is involved in organ development, tissue repair, as well as in pathological states including inflammation and malignancies. Wound healing, inflammation and tumor progression are all associated with accelerated neovascularization [1–7]. Rheumatoid arthritis (RA) may be considered as an “angiogenic” disease, as the perpetuation of neovascularization is associated with synovitis and pannus formation [1–8]. There is also evidence that the blockade of neovascularization may lead to the suppression of synovial inflammation and proliferation [1–5,9]. In this review, we will summarize the most relevant angiogenic mediators and inhibitors in brief (Table 1). Then we will focus on current and future anti-angiogenic strategies developed to control RA-associated vessel formation (Table 2).

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ANGIOGENIC MEDIATORS AND INHIBITORS IN RA

Imbalance in the Regulation of Neovascularization in RA

In RA, inflammatory cells emigrate into the synovium through the vascular endothelium. The RA synovium is rich in newly formed blood vessels [1–5]. Mediators that induce and/or sustain angiogenesis include growth factors, some proinflammatory cytokines and chemokines, extracellular matrix components, cell adhesion molecules, proteolytic enzymes, hypoxia and numerous other factors. Angiostatic agents, such as anti-inflammatory cytokines, some chemokines and other factors, are also released in the RA synovium in order to control neovascularization and thus inflammation [1–5] (Table 1). However, there is an overproduction of angiogenic mediators and a lack of some inhibitors in RA leading to an imbalance and to excessive capillary formation in the synovium [1–5]. Most angiogenic and angiostatic agents discussed below have been detected in the RA synovium [1,2,4,6,7] (Table 1).

Angiogenic Factors

Among growth factors, some are bound to heparin and are released by proteases during angiogenesis. Vascular endothelial growth factor (VEGF) is a crucial regulator of angiogenesis in RA. VEGF is essential for early vascular morphogenesis, endothelial cell proliferation and migration [6]. The synovial release of VEGF is stimulated by hypoxia, as well as pro-inflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1) and transforming growth factor- β (TGF- β) [1,3,6]. VEGF is abundantly produced in the RA synovium [10]. Other angiogenic mediators, such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), hypoxia-inducible factor 1 α (HIF-1 α), nitric oxide (NO) or prostaglandins, may act indirectly by stimulating VEGF production [1,6,11].

Hypoxia enhances neovascularization both directly, and indirectly, *via* the HIF-VEGF pathway [2,4,12]. Hypoxia is a major trigger of synovial neovascularization. Hypoxia stimulates the formation and stabilization of the heterodimer HIF-1 α /HIF-1 β . The formation of this heterodimer then leads to increased VEGF production [7,13]. There is an interaction between hypoxia, HIFs, VEGF and the angiopoietin-1 (Ang1)-Tie2 system, which is involved in the stabilization of newly formed vessels [6,14]. Ang1 and Ang2 are vascular growth factors that regulate endothelial cell function upon stimulation by other growth factors, primarily VEGF. Both Ang1 and Ang2 interact with Tie2, an endothelial tyrosine kinase receptor [6,15]. The interaction of Ang1 and Tie2 results in vessel stabilization [16], while Ang2-Tie2 antagonizes Ang1 and thus stimulates vascular invasion and inhibits vessel maturation [4,6,14]. There is abundant expression of Ang1, Ang2 and Tie2 in the RA synovium [6,17,18]. Interactions between VEGF, angiopoietins and TNF- α may transduce signals resulting in endothelial plasticity and survival. Survivin, an inhibitor of apoptosis, is also involved in endothelial cell survival and VEGF-mediated angiogenesis [6,19]. Survivin, as well as VEGF, the Tie proteins and Ang1, have been detected in the RA joint [6,10,17,18]. In conclusion, vessels undergoing angiogenesis exhibit in a plasticity state, stay responsive to VEGF and thus remodeling and sprouting [6].

Other growth factors implicated in neovascularization include basic and acidic fibroblast growth factors (bFGF and aFGF), HGF, platelet-derived growth factor (PDGF), EGF, insulin-like growth factor-I (IGF-I), HIF-1 α , HIF-2 α and TGF- β [1,2,4,5].

TNF- α , IL-1, IL-6, IL-15, IL-18 and possibly IL-17 are also involved in angiogenesis [1,2,4,20–24]. These proinflammatory cytokines have all been implicated in the pathogenesis of RA. TNF- α may also regulate angiogenesis *via* the Ang1-Tie2 system [25]. Other angiogenic cytokines include granulocyte and granulocyte-macrophage colony-stimulating factors (G-CSF and GM-CSF), oncostatin M and macrophage migration

inhibitory factor (MIF) [1,4,26–28]. MIF induces the production of the angiogenic VEGF and IL-8/CXCL8 by RA synovial fibroblasts [29,30].

CXC chemokines containing the ELR (glutamyl-leucyl-arginyl) amino acid motif in general stimulate angiogenesis. These mediators include IL-8/CXCL8, epithelial neutrophil activating protein-78 (ENA-78)/CXCL5, growth-related oncogene α (gro α)/CXCL1 and connective tissue activating protein-III (CTAP-III)/CXCL6 [2,31]. On the contrary, as we will describe later, CXC chemokines that lack the ELR sequence suppress neovascularization [2,31]. As one exception to this rule, stromal cell-derived factor-1 (SDF-1)/CXCL12 lacks ELR, but despite this is angiogenic [2,32]. Among CC and CX₃C chemokines, monocyte chemoattractant protein-1 (MCP-1)/CCL2 and fractalkine/CX₃CL1 are angiogenic [2,4,33,34]. CXCR2 is the most important chemokine receptor on endothelial cells for angiogenic CXC chemokines [1,2,4]. CXCR4, the receptor for SDF-1/CXCL12, has also been implicated in synovial neovascularization [35].

Extracellular matrix components, such as type I collagen, fibronectin, laminin, vitronectin, tenascin and proteoglycans, as well as cell adhesion molecules including (β_1 and β_3 integrins, E-selectin, selectin-related glycoconjugates including Lewis^x/H and melanoma cell adhesion molecule (MUC18), vascular cell adhesion molecule-1 (VCAM-1), platelet-endothelial cell adhesion molecule-1 (PECAM-1) and endoglin are involved in endothelial cell adhesion and migration during neovascularization [1,4,36]. Among adhesion molecules, the $\alpha_v\beta_3$ integrin is of outstanding importance. This integrin exerts abundant expression in the RA synovium, and it mediates angiogenesis and osteoclast-mediated bone resorption [37]. Some proteolytic enzymes, such as matrix metalloproteinases and plasminogen activators are involved in matrix degradation and thus they also promote angiogenesis [1,4,5,30,38].

Other angiogenic factors not classified above include prostaglandin E₂, angiogenin, angiotropin, pleiotrophin, platelet-activating factor (PAF), histamine, substance P, erythropoietin, adenosine, prolactin, thrombin and others [1,4,5].

Inhibitors of Angiogenesis

Among cytokines, interferon- α (IFN- α), IFN- γ , IL-4, IL-12, IL-13 and leukemia inhibitory factor (LIF) inhibit neovascularization by suppressing the production of numerous angiogenic mediators described above [1,3,39]. For example, IL-4 acts by inhibiting VEGF production by synovial fibroblasts [40]. Tissue inhibitors of metalloproteinases (TIMP) and plasminogen activator inhibitors (PAI) antagonize the effects of metalloproteinases and plasminogen activators, respectively [1,2,4,6,30,38]. Thrombospondin-1 and platelet factor 4 (PF4)/CXCL4 block growth factor binding to heparin [1,2,4,6]. Other chemokines lacking the ELR motif, such as monokine induced by interferon- γ (MIG)/CXCL9 and IFN- γ -inducible protein 10 (IP-10)/CXCL10 also inhibit angiogenesis [2,4,31].

Among antirheumatic drugs currently used in the treatment of RA, dexamethasone, gold salts, chloroquine, sulfasalazine, methotrexate, cyclosporine A, azathioprine, cyclophosphamide, leflunomide, thalidomide, minocycline and some anti-TNF agents may also inhibit neovascularization [1,2,4–6]. There are conflicting results regarding methotrexate, as in cancer studies it inhibited angiogenesis, while in psoriatic arthritis no such effect could be observed [6]. Some antibiotics and their derivatives suppress neovascularization *via* the inhibition of VEGF and other angiogenic mediators. Minocycline, fumagillin, deoxyspergualin and clarithromycin might also inhibit neovascularization [1,2,4].

Other angiostatic compounds include angiostatin (a fragment of plasminogen), endostatin (a fragment of collagen), paclitaxel, osteonectin, opioids, troponin I, and chondromodulin-1 [1–4].

Regulation of Synovial Angiogenesis Leading to Imbalance

Most angiogenic mediators described above, including growth factors, proinflammatory cytokines, chemokines and proteases are abundantly produced in the RA synovium [1,2,20,21,41]. In contrast, although numerous angiogenesis inhibitors are released in the inflamed synovium, there may be a relative deficiency of such factors in RA. For example, there is a low production of IFN- γ and PF4/CXCL4 in RA [2,20,41]. Furthermore, there are autocrine loops in the RA synovium leading to the perpetuation of angiogenesis associated with inflammation [1,2,4,5].

Endothelial progenitor cells (EPC) exist within the population of CD34⁺ blood stem cells. EPCs express VEGF receptors and they may develop into endothelial cells [42]. In RA, there is an $\alpha_4\beta_1$ integrin/VCAM-1-mediated recruitment of EPCs from the blood into the synovium resulting in the depletion of these stem cells from the circulation [43–45]. Some studies suggest that the depiction of circulating EPC may be linked to increased cardiovascular morbidity in RA [44].

TARGETING OF ANGIOGENESIS IN RA

There are two major basic approaches for controlling angiogenesis in RA [1,3–6]. As discussed above, some angiogenesis inhibitors including cytokines, chemokines, protease inhibitors and others are naturally produced in the RA synovium, however, their amounts may not be enough to counterbalance enhanced neovascularization observed in arthritis. On the other hand, some externally administered compounds, such as corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) or antibiotic derivatives, might inhibit RA-associated neovascularization [1,3,4,6] (Table 2).

Regarding endogenous inhibitors (Table 2), both angiostatin and endostatin abrogated arthritis in various animal models [1–3,7,9,46]. Angiostatin gene transfer reduced synovial inflammation and hyperplasia in mice with collagen-induced arthritis (CIA) [7,46]. An inhibitor related to angiostatin, termed protease-activated kringle 1–5 (K1–5) suppressed murine CIA more potently than angiostatin itself [47]. Endostatin, a fragment of collagen, interferes with type 2 VEGF receptor signaling [6,9,48]. In animal models, endostatin improved arthritis, suppressed pannus formation and bone destruction [7,9]. Angiostatin and endostatin are currently being investigated in cancer clinical trials [4,6,49]. Thrombospondin 2 (TSP2) is a matrix component produced by RA synovial tissue macrophages and fibroblasts with angiostatic activity. TSP2 reduced synovial vascularization in the SCID mouse model of arthritis [50]. Most endogenous inhibitors act *via* $\alpha_v\beta_3$ integrin-dependent mechanisms [6,11]. In gene transfer studies, IL-4 and IL-13, two endogenously produced cytokines in RA, inhibited angiogenesis in rat adjuvant-induced arthritis [39,51]. The chemokine PF4/CXCL4, also produced in the RA synovium, has also been tested in rodent models of arthritis [2,4].

TNP-470 and PPI2458 are two angiostatic analogues of fumagillin, a naturally occurring product of *Aspergillus fumigatus*. These compounds inhibit methionine aminopeptidase-2, an enzyme crucial for endothelial cell migration and angiogenesis [52]. Both agents decrease serum levels of VEGF and inhibit angiogenesis in animal models [1,3,7]. TNP470 prevented arthritis before disease onset and also successfully improved the disease [7,53]. Combination of this agent with either cyclosporine A or paclitaxel further improved efficacy [7]. In various animal models of arthritis, PPI2458 also effectively improved arthritis and prevented

the development of erosions [54]. 2-methoxyestradiol is a natural metabolite of estrogen. It blocks angiogenesis by disrupting microtubules and by suppressing HIF-1 α activity [55].

As far as externally administered angiogenesis inhibitors are concerned (Table 2), several antirheumatic drugs including classical DMARDs and biologics, inhibit neovascularization [2,4,6]. In RA, infliximab treatment in combination with methotrexate resulted in decreased serum VEGF levels and synovial VEGF expression, as well as synovial vascularity [4,6,56]. Anti-TNF therapy in patients with psoriatic arthritis reduced Ang1-Tie2 expression, stimulated Ang2 expression [6,25], and also downregulated survivin expression [6]. Thalidomide, already used in the therapy of multiple myeloma, is a potent TNF- α antagonist and angiogenesis inhibitor [7,57]. The effects of thalidomide on neovascularization is not fully clear, as in one rodent study it suppressed VEGF secretion [58], while in rat CIA this compound did not influence VEGF and TNF- α production [59]. Nevertheless, thalidomide suppressed capillary tube formation and synovitis in animal models of arthritis [7,58]. CC1069, a thalidomide analogue, even more potently inhibited rat adjuvant-induced arthritis [7]. Thalidomide has been tried in numerous RA studies but it demonstrated only limited efficacy [7].

There have been several attempts to target VEGF by using synthetic VEGF and VEGF receptor inhibitors, anti-VEGF antibodies, as well as inhibitors of VEGF and VEGF receptor signaling [1,3,4,60]. Small molecule VEGF receptor tyrosine kinase inhibitors under development in cancer include vatalanib, sunitinib malate, sorafenib, vandetanib and AG013736 [7,60]. In general, these small molecules are administered orally and exert favorable safety profiles. Among these molecules, vatalanib inhibited knee swelling in rabbit arthritis [7,61]. The VEGF-Trap construct is a composite decoy receptor based on VEGFR1 and VEGFR2 fused to IgG1-Fc [62]. Bevacizumab, a human monoclonal antibody to VEGF has been approved for the treatment of colon cancer [7]. However, to date neither bevacizumab, nor VEGF-Trap has been studied in arthritis. Semaphorin-3A blocks the function of the 165 amino-acid form of VEGF (VEGF165). It also suppressed endothelial cell survival and neovascularization [49].

As far as the hypoxia-HIF-VEGF system is concerned, YC-1, a superoxide-sensitive stimulator of soluble guanylyl cyclase originally developed for the management of hypertension and thrombosis, also inhibits HIF-1 [63]. This agent has not yet been tried in arthritis, but it may have the potential to suppress hypoxia- and HIF-1-mediated angiogenesis in the RA joint [7]. Microtubule destabilizers, such as 2-methoxyestradiol mentioned above, as well as paclitaxel, a drug already used in human cancer, both also down-regulate HIF-1 α expression and activity [7]. In a phase I study, paclitaxel was found to be effective and safe in RA patients [7].

Regarding the Ang-Tie system described above, a soluble Tie2 receptor transcript was delivered *via* an adenoviral vector to mice with CIA. Inhibition of Tie2 resulted in attenuated onset, incidence and severity of arthritis [64].

Among other external blockade strategies, inhibition of CXCR2 suppressed tumor-induced angiogenesis [65]. Combination of Mig/CXCL9 chemokine gene therapy with cytotoxic compounds improved the therapeutic efficacy of the latter drug in cancer [66].

Vitaxin, a humanized antibody to the angiogenic $\alpha_v\beta_3$ integrin, inhibited synovial angiogenesis in animal models of arthritis [1,4,7]. However, in a phase II human RA trial it showed poor clinical benefit and thus the study was interrupted [7]. Numerous metalloproteinase inhibitors have been tested in animal angiogenesis models [38]. Soluble Fas ligand (CD178), which is a member of the TNF- α superfamily, inhibited VEGF165 production by RA synovial fibroblasts, as well as neovascularization [67]. Pioglitazone, a

novel PPAR γ agonist developed for the treatment of diabetes, is anti-angiogenic. It showed some efficacy in controlling psoriatic arthritis in 10 patients [6,68].

In general, most naturally produced and externally administered angiogenesis inhibitors may have therapeutic relevance for RA-associated angiogenesis. Most inhibitors act through the modification of VEGF- and $\alpha_v\beta_3$ -mediated pathways. Many of these compounds are already in pre-clinical or clinical trials. It is most likely, that multipotent rather than specific immunotherapy may be useful for the therapy of RA. Using an anti-inflammatory and/or anti-angiogenic agent against one specific target may have limited and transitional efficacy, as inflammatory and angiogenic pathways are abundant. In contrast, classical DMARDs or anti-TNF- α agents have several modes of action including the suppression of inflammatory mediator production and neovascularization [2,5].

CONCLUSION

The perpetuation of angiogenesis involving numerous soluble and cell surface-bound mediators has been associated with RA. There are numerous potential endogenous or exogenously administered compounds that inhibit neovascularization. Theoretically all these agents may be used to control synovial inflammation. Currently, classical DMARDs, TNF blockers and thalidomide have been tried in humans. Among the several potential angiogenesis inhibitors, targeting of VEGF, HIF-1, angiopoietin and the $\alpha_v\beta_3$ integrin, as well as some endogenous or synthetic compounds including angiostatin, endostatin, paclitaxel and fumagillin analogues seem to be of outstanding interest.

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Table 1

Some Important Mediators and Inhibitors of Angiogenesis in Rheumatoid Arthritis*

Class	Mediators	Inhibitors
Growth Factors	VEGF, HGF, EGF, HIF-1, PDGF, aFGF, bFGF, IGF-I, TGF- β	-
Pro-inflammatory cytokines	TNF- α , IL-1, IL-6, IL-15, IL-17, IL-18, G-CSF, GM-CSF, oncostatin M, MIF	Interferons, IL-4, IL-12, IL-13, LIF
Chemokines	ELR ⁺ CXC chemokines, SDF-1/CXCL12, MCP-1/CCL2, fractalkine/CXC3CL1	ELR CXC chemokines
Extracellular Matrix Components	Collagen, laminin, fibronectin, vitronectin tenascin	Thrombospondin 1, thrombospondin 2
Cell Adhesion Molecules	$\alpha_v\beta_3$ integrin, E-selectin, VCAM-1, endoglin, MUC18, Lewis ^x /H, PECAM-1	-
Proteases	MMPs, plasminogen activators	TIMPs, PAIs
Environmental Factors	Hypoxia	
Vessel Stabilizers Apoptosis Inhibitors	Ang1-Tie2, survivin	
Others	Prostaglandin E2, angiogenin, angiotropin, PAF, prolactin, substance P, etc.	DMARDs, antibiotics, angiostatin, endostatin, paclitaxel, troponin, osteonectin, chondromodulin, etc.

* See text for abbreviations.

Table 2**Anti-Angiogenic Targets***

Endogenous Inhibitors	<ul style="list-style-type: none"> • angiostatin and related agents • endostatin • thrombospondin 2 • IL-4, IL-13 • PF4/CXCL4 • fumagillin • 2-methoxyestradiol
Exogenous Inhibitors	<ul style="list-style-type: none"> • classical DMARDs • anti-TNF agents • thalidomide • VEGF inhibitors • HIF inhibitors • Ang1/Tie2 inhibitors • $\alpha_v\beta_3$ integrin inhibitors • microtubule destabilizers (e.g. paclitaxel) • others (soluble FasL, PPARγ agonists)

* See text for abbreviations.