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The Pathogenic Role of Angiogenesis in Rheumatoid Arthritis

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Abstract

Angiogenesis is the formation of new capillaries from pre-existing vasculature, which plays a critical role in the pathogenesis of several inflammatory autoimmune diseases such as rheumatoid arthritis (RA), spondyloarthropathies, psoriasis, systemic lupus erythematosus, systemic sclerosis and atherosclerosis. In RA, excessive migration of circulating leukocytes into the inflamed joint necessitates formation of new blood vessels to provide nutrients and oxygen to the hypertrophic joint. The dominance of the pro-angiogenic factors over the endogenous angiostatic mediators triggers angiogenesis. In this review article, we highlight the underlying mechanisms by which cells present in the RA synovial tissue are modulated to secrete pro-angiogenic factors. We focus on the significance of pro-angiogenic factors such as growth factors, hypoxia inducible factors, cytokines, chemokines, matrix metalloproteinase and adhesion molecules on RA pathogenesis. As pro-angiogenic factors are primarily produced from RA synovial tissue macrophages and fibroblasts, we emphasize the key role of RA synovial tissue lining layer in maintaining synovitis through neovascularization. Lastly, we summarize the specific approaches utilized to target angiogenesis. We conclude that the formation of new blood vessels plays an indispensable role in RA progression. However since the function of several pro-angiogenic mediators is cross regulated, discovering novel approaches to target multiple cascades or selecting an upstream cascade that impairs the activity of a number of pro-angiogenic factors may provide a promising strategy for RA therapy.

Keywords

RA; angiogenesis; growth factors; cytokines; chemokines; matrix metalloproteinase and adhesion molecules

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INTRODUCTION

Formation of new capillaries from the pre-existing vessels is defined as angiogenesis [1-4]. Rheumatoid arthritis (RA) is a chronic systemic disorder in which angiogenesis can foster the infiltration of inflammatory cells into the joints leading to synovial hyperplasia and progressive bone destruction [1,5,6,4]. Angiogenesis is involved in several physiological events including embryonic organ development, reproduction, tissue repair and wound healing. However, uncontrolled neovascularization can contribute to angiogenic disorders including RA, psoriasis, atherosclerosis and tumor formation [5,7-12]. Angiogenesis involves several steps and each step is modulated by specific factors. The process starts with growth factors such as VEGF and FGF binding to their cognate receptors on endothelial cells and activation of these cells to produce proteolytic enzymes. Subsequently, the basement membrane is degraded by matrix metalloproteinases (MMP)s which results in migration and further endothelial proliferation to vascular tubules that are in part developed by adhesion molecules such as integrins. Lastly, blood vessels are stabilized by pro-angiogenic factors such as Ang1, followed by incorporation of pericytes into the newly formed basement membrane to facilitate the blood flow process [5,13,9,3,14] (Fig. 1).

In RA, the excessive pro-angiogenic factors counteract the angiogenic inhibitors to support the elevated transendothelial leukocyte infiltration that fosters synovial inflammation as well as the bone and cartilage destruction. Conversely, inhibition of joint neovascularization can alleviate synovitis and pannus formation [15,14,16].

Previous studies document that synovial macrophages and fibroblasts exert a predominant role in RA angiogenesis. Consistent with this notion, the number of synovial tissue macrophages is the most reliable marker for assessing disease severity and response to therapy as the number of myeloid cells correlates with RA synovial inflammation, joint pain and bone destruction [17-20]. The cell-to-cell contact between RA fibroblasts and macrophages in the lining layer amplifies the inflammatory signaling cascades since the mere contact of these cells provokes IL-6 and IL-8 production [21]. In this review, we categorize pro-angiogenic factors based on their mechanism of function and cell origination. Since the vast majority of these angiogenic factors are secreted from RA synovial tissue macrophages and fibroblasts, we have therefore highlighted the importance of these cell types in RA angiogenesis. In addition, we discuss factors that are highly pathogenic due to their multifunctional effect on leukocyte migration and neovascularization. Finally, we conclude that the anti-angiogenic agents may offer a promising therapy for RA and different types of cancer.

Pro-angiogenic factors released from RA synovial tissue myeloid cells and fibroblasts

RA Macrophages—Tissue-resident macrophages are long-living phagocytic cells that persist in many tissues and are characterized by high surface expression of CD64, MerTK, and CD14. Tissue-resident macrophages originate primarily from embryonic progenitors and to less extent from circulating monocyte intermediates, additionally many of them are capable of self-renewal [22-25]. In contrast, other tissues have mobile, short-living populations of mononuclear phagocytes that patrol different tissues and are previously classified as monocyte derived macrophages. These cells are characterized by the high

surface expression of Ly6C, CCR2, CD11b, and low/absence of tissue-resident macrophages markers CD64, MerTK, and CD14 [25-27,24,28,29]. The recruited population of monocyte derived macrophages significantly increase during inflammatory conditions such as RA.

Circulating monocytes infiltrate from blood into the inflamed RA joint where they differentiate into macrophages. Macrophages are classified into two groups namely M1 and M2 macrophages. M1 macrophages are the classically activated cells that produce pro-inflammatory cytokines mediating resistance to pathogens and tissue destruction, whereas M2 macrophages are the alternatively activated cells that produce anti-inflammatory cytokines which promote tissue repair [30,31]. M1 macrophages express cell surface markers such as CCR7, CD215, CD80 and CD86 and secrete TNF, IL-6 and IL-1β CCL2, IL-8, IL-12 and IL-23 upon activation with interferon (IFN)γ, lipopolysaccharides (LPS) or granulocyte macrophage colony stimulating factor (GM-CSF) [32-34]. However M2 macrophages are distinguished by CD206, CD209 and Dectin1 surface markers and are capable of producing TGF-β and IL-10 upon IL-4, IL-13, glucocorticoid, IL-10 and macrophage colony stimulating factor (M-CSF) stimulation [32].

RA synovial tissue fibroblasts—RA synovial tissue fibroblasts reside in the most superficial part of the lining layer where they are in direct contact with macrophages [35,36]. RA synovial tissue fibroblasts that become exposed to TLR endogenous ligands and pro-inflammatory cytokines produced from their neighboring macrophages, transform into “tumor like” cells [37]. During active disease, these transformed RA synovial tissue fibroblasts are triggered by inflammatory mediators or hypoxia to produce pro-angiogenic growth factors, cytokines, chemokines, MMPs and adhesion molecules [38,39,35,36] (Fig. 1). As discussed below a tightly regulated network of pro-angiogenic factors come together to pathologically alter the endothelial cell function and foster joint angiogenesis in order to exacerbate RA severity.

Growth Factors

VEGF and HIF connection—TNF, IL-1, IL-6 and IL-18 secreted from TLR driven M1 macrophages combined with the local hypoxic conditions activate RA macrophages and synovial tissue fibroblasts to secrete growth factors such as vascular endothelial growth factor (VEGF) and/or basic fibroblast growth factor (bFGF) [40-43,34,44] (Fig. 2). VEGF and bFGF are the key regulators of angiogenesis since they are associated with proliferation, migration and vascular tube formation as well as the prevention of endothelial cell apoptosis [44]. Hypoxia, induced by the metabolic demand of the increasing number of leukocytes recruited into the RA joint, leads to the accumulation of hypoxia inducible factor-1α (HIF-1α) in the cytoplasm which translocates to the nucleus where it associates with HIF-β and other co-activators and finally induces the expression and secretion of VEGF by macrophages and RA synovial tissue fibroblasts (Fig. 2) [34,44]. Interestingly, during hypoxia, angiogenesis can be triggered by the positive feedback regulation detected between HIF-1α and VEGF pathways [45].

In experimental arthritis models, preventative treatment of anti-VEGF antibody delayed the collagen induced arthritis (CIA) onset, joint swelling and vascularization. In contrast, post

onset treatment with anti-VEGF antibodies did not affect severity or progression of the arthritis, suggesting that angiogenesis mediated by VEGF plays a crucial role in the early stage of arthritis development [46]. *In vitro* studies have shown that HIF-1α deletion impaired angiogenesis through a VEGF dependent mechanism. However, conditional knockout of HIF-1α in myeloid cells attenuated experimental arthritis in mice by decreasing myeloid cell homing and activation, independent of VEGF, suggesting that HIF-1α can modulate inflammation and arthritis, independent of its angiogenic effect [47].

Ang1, Ang2 and Tie2—We and others have shown that angiopoietin (Ang)1 and its receptor tyrosine kinase receptor (Tie)2 are highly elevated in RA compared to normal synovial tissue lining, sublining macrophages and endothelial cells [48-50]. Previous studies have shown that Ang1 expression is differentially regulated in RA synovial tissue fibroblasts compared to endothelial cells, as TNF could strongly increase the concentration of Ang1 in RA fibroblasts while the levels of endothelial Ang1 was unaffected by the stimulation [50]. It was found that Ang1 acts at a later stage of angiogenesis compared to VEGF, in order to form and increase blood vessel stability [51]. Furthermore, the endogenous antagonist to the Tie2, Ang2 can destabilize VEGF mediated angiogenesis [52] suggesting that there is a crosstalk between Ang and VEGF cascades. The depletion of Tie2, by adenoviral expression of a soluble Tie2 receptor, ameliorated CIA joint vascularization, swelling and bone destruction indicating that inhibition of neovascularization can prevent ankle edema and osteoclastic bone erosion [53].

Other growth factors—IL-17 and TNF synergize in producing growth factors such as keratinocyte growth factor (KGF), hepatocyte growth factor (HGF) and heparin-binding endothelial growth factor (HB-EGF) from RA synovial tissue fibroblasts [54]. Two of the other growth factors expressed in RA joints are platelet-derived growth factor (PDGF) and transforming growth factor (TGF)β that can together with TNF increase the hypertrophic architecture of the RA synovial tissue lining layer. These growth factors elevate the RA synovial fibroblast expression of matrix metalloproteinase-3 (MMP3), Cadherin-11, and PI3Kδ, demonstrating that multiple factors contribute to the synovial tissue lining hyperplasia in RA [55]. Potent pro-angiogenic factors such as PDGF and VEGF promote angiogenesis through activation of receptor tyrosine kinases (RTKs) [44,55]. Imatinib mesylate (Imatinib, an inhibitor for tyrosine kinases such as PDGFR) was primarily developed to treat chronic myelogenous leukemia (CML) and other cancers [56]. Additionally, Imatinib was capable of attenuating the clinical and histological signs of collagen antibody induced arthritis (CAIA) as well as reducing the joint VEGF levels [56], suggesting that ligation of PDGF to PDGFR plays an essential role both in early and late stages of RA.

Pro-inflammatory Cytokines

Pro-inflammatory cytokines produced from M1 macrophages include TNF, IL-1, IL-6, IL-8, IL-18 and macrophage migration inhibitory factor (MIF) play a central role in RA angiogenesis both through their direct effect on endothelial cells as well as their indirect effect on different cell types in RA synovium to produce pro-angiogenic factors (Fig. 2).

TNF—Levels of TNF and its receptor, sTNFRII, are markedly elevated prior to RA onset [57], and TNF directly affects endothelial migration and proliferation as well as the formation of new blood vessels [58]. Moreover, angiogenesis can be indirectly promoted by TNF through its synergic effect with IL-1β and IL-17 in producing VEGF from RA synovial tissue fibroblasts [54]. Previous studies document that in RA patients who respond to TNF blockers, serum VEGF levels are markedly reduced by treatment, indicating that TNF may play a role in VEGF mediated neovascularization [59]. TNF is also involved in regulation of Ang1/Tie2 network [60]. As such, anti-TNF therapy has shown to reduce RA joint vascularization by suppressing the expression levels of Ang1/Tie2 and survivin through Ang2 stimulation [60]. TNF together with IL-1, IL-6 and IL-23 promote TH-17 cell differentiation [61] and IL-17 has been shown to be important for RA angiogenesis [62,63]. Consistently, RA patients who responded to anti-TNF therapy, had reduction in the number of circulating TH-17 cells as well as lower serum concentrations of IL-17, IL-6, IL-21 and IL-23 [64]. In contrast, TNF non-responders had a markedly elevated number of circulating TH-17 cells and serum IL-17 levels suggesting that TNF is important for TH-17 cells differentiation in RA [64]. Others have shown that TNF can impact RA angiogenesis by modulating endothelial cell secretion of pro-angiogenic adhesion molecules (E-selectin, ICAM1 and VCAM1) and chemokines (CXCL1, CXCL5, CXCL8, CCL2 and CCL5) [65,63].

IL-1β—In contrast to TNF, IL-1β has no direct effect on RA angiogenesis. However, IL-1β can induce expression of Ang1, Tie2 and VEGF from RA synovial tissue fibroblasts [66] in addition to its synergistic effect with IL-17 on the production of VEGF from RA fibroblasts [54]. IL-1β can also upregulate RA fibroblast expression of CCL21 which can bind to its corresponding receptor, CCR7 on endothelial cells and facilitate cell migration, capillary tube formation and *in vivo* blood vessel formation [67]. Furthermore, endothelial CXCR6 is elevated by IL-1β and ligation of CXCR6 to CXCL16 fosters RA angiogenesis [68]. These finding suggest that IL-1β can indirectly contribute to angiogenesis by enhancing the expression levels of growth factors, chemokines or chemokine receptors from the cells present in the RA synovium. Studies have shown that IL-1β driven arthritis was in part due to IL-17 function; since the spontaneous development of arthritis detected in IL-1R antagonist knockout mice was impaired in IL-17 deficient mice [69]. This may also indicate that IL-1β mediated RA angiogenesis can in part be due to IL-17 produced from TH-17 cells.

IL-6—IL-6 is mainly secreted from pro-inflammatory M1 macrophages and RA synovial tissue fibroblasts [70,71] and the cell-to-cell contact of myeloid cells with RA fibroblasts facilitates this process [72]. TNF and IL-1 can synergize with IL-6 in stimulating VEGF production from RA fibroblasts [73]. As such, serum VEGF levels are elevated in RA patients and anti-IL-6R antibody therapy can normalize the VEGF concentration in the sera [73]. Furthermore, treatment of RA synovial tissue fibroblasts with anti-IL-6R antibody impairs the synergistic effect of IL-6, IL-1β, and TNF on VEGF production, while the blockade of IL-1β or TNF has no effect on this function [73].

In RA fibroblasts and endothelial cells co-culture system, IL-6 was capable of inducing VEGF and Ang2 protein levels [74]. In endothelial cells, IL-6 potentiates TNF mediated angiogenesis through induction of NF-κB and IL-8 [75]**.** Furthermore, the pro-angiogenic chemokine, CCL28 and its corresponding receptor CCR10, are modulated by IL-6 in RA macrophages [76]. Together with IL-1β, IL-6 plays an indispensable role for TH-17 cell differentiation, which is important in RA angiogenesis [62,63]. The use of Tocilizumab (TCZ), an anti-IL-6 antibody, both as monotherapy and in combination with Methotrexate or other disease modifying anti-rheumatic drugs (DMARDs), can effectively reduce joint inflammation and radiological disease progression [77], suggesting that IL-6 contributes to angiogenesis and RA pathogenesis.

IL-8/CXCL8—IL-8 is predominantly secreted from RA macrophages and fibroblasts [78]. Macrophages produce IL-8 in response to CCL19 and CCL21 stimulation [67] and ligation of TLR2 and TLR4 [78], whereas, IL-17, IL-1β, and TNF induce the production of IL-8 from RA synovial tissue fibroblasts [79,80]. Results from earlier studies show that IL-8, like TNF, can directly trigger RA angiogenesis by binding to its corresponding receptors, CXCR1 and CXCR2 on endothelial cells and neutralization of IL-8 reduced the angiogenic activity of synovial tissue macrophage conditioned media [81].

IL-18—IL-18 is a member of IL-1 superfamily [82] that is produced from RA synovial lining macrophages and fibroblasts as well as from endothelial cells and synovial fluid neutrophils [83-85]. RA synovial tissue fibroblasts release biologically active IL-18 in response to TNF stimulation [86]. Interestingly, a number of factors are secreted from RA fibroblasts in response to IL-18 stimulation which consist of adhesion molecules (VCAM1, ICAM1), neutrophil chemoattractants (CXCL1, CXCL5, CXCL12), monocyte chemoattractants (CCL2, CXCL20) and proangiogenic factors (VEGF, IL-8), suggesting that IL-18 can contribute to RA pathogenesis through different mechanisms [87]. Early in disease, IL-18 promotes neutrophil migration [88] and during active disease, myeloid cells are recruited into the joints [89] and inflammation progresses by triggering angiogenesis [90,91]. In addition to IL-18 indirect effects on monocyte and endothelial cell migration [92-94], data obtained from our group of investigators, reveal that IL-18 present in RA synovial fluid can directly attract myeloid and endothelial cells into the inflamed joint [89,91].

Macrophage migration inhibitory factor (MIF)—MIF is highly expressed on RA synovial tissue macrophages, fibroblasts and endothelial cells in addition to RA sera and synovial fluid [95,96]. Human macrophages produce MIF following TLR4 ligation whereas in mouse macrophages, MIF is modulated by TNF stimulation [97]. Macrophages stimulated with MIF secrete M1 associated cytokines such as TNF, IL-1β, IL-8 and IL-6 [98,99]. RA synovial tissue fibroblasts activated with MIF produce IL-1β as well as MMP-3, 9, and 13 which play an important role in cartilage degradation [100,101]. MIF can directly promote *in vitro* endothelial cell migration and tube formation as well as developing blood vessel *in vivo,* in the matrigel plugs corneal bioassay, with an effect as potent as bFGF [102]. Consistent with this notion, immuno-neutralization of MIF abrogates tumor induced endothelial proliferation and tumor angiogenesis [103,104]. In preclinical arthritis models,

blockade of MIF function relieves arthritis and reduces joint recruitment of T and myeloid cells [105-107].

Chemokines

Chemokines are chemotactic cytokines that have been classified into the CXC, CC, C and CX3C families [108].

CXC Chemokines—The pro-angiogenic function of CXC chemokines involves three amino acid residues (Glu-Leu-Arg), the ELR amino acid motif, at the N terminus of the first cysteine residue of these chemokines [2]. The ELR-containing CXCL1, CXCL5, CXCL8 and CXCL16 are mainly produced by RA synovial tissue macrophages or fibroblasts in response to pro-inflammatory factors such as TNF, IL-1, IL-6 and IL-17 [109,41]. However, CXC chemokines that lack the ELR motif such as CXCL4, CXCL9, and CXCL10 inhibit RA neovascularization with the exception of CXCL12 which promotes angiogenesis in RA and cancer [110-115,2]. CXCR4, the CXCL12 receptor, is widely expressed on hemopoietic stem cells, monocytes and lymphocytes [115]. In RA synovial tissue, CXCR4 is highly expressed on synovial tissue lining and endothelial cells [116]. Although several CC and CXC chemokine receptors are expressed on endothelial cells, CXCR4 is the most abundant chemokine receptor on the endothelium and hence CXCR4 deficiency results in impaired neovascularization [117]. Elevated levels of CXCL12 are detected in RA synovial fluid [118]. Interestingly, CXCL12 expression in endothelial cells is induced by lymphotoxin alpha-1 beta-2 and LIGHT; however CXCR4 levels are modulated by pro-angiogenic factors such as VEGF and bFGF [119,120]. Similarly, ligation of CXCL12 to endothelial CXCR4 can also contribute to production of VEGF and bFGF, suggesting that activation of CXCL12/CXCR4 cascade can indirectly induce angiogenesis as well [121]. Others reported that the RA synovial fluid mediated blood vessel formation was inhibited by CXCL12 neutralization *in vivo* [116]. Consistently, earlier studies show that ligation of CXCL12 to CXCR4 is involved in angiogenesis observed in human glioblastoma [122] and pancreas cancer [123]. Blockade of CXCR4 by a non-peptide antagonist, ameliorated CIA by impairing the migration of CXCR4+MAC1+ myeloid cells, however; the effect of the treatment on joint neovascularization was not investigated [124].

In addition to being pro-angiogenic, CXCL1, CXCL5 and CXCL8/IL-8 can strongly attract neutrophils into the RA joint [7,41]. In RA synovial tissue fibroblasts and macrophages as well as experimental arthritis models, expression of CXCL1 and CXCL5 was shown to be associated with IL-17 mediated pathology [63]. Interestingly, while inhibition of CXCL1 function had no effect on IL-17 induced angiogenesis, blockade of CXCL5 could resolve IL-17 driven arthritis in part by reducing neovascularization through an IL-17 independent mechanism [63]. Moreover, it has been shown that CXCL16 can exert its pathogenic effect by attracting circulating monocytes and endothelial cells into the RA synovial tissue implanted into SCID mouse chimera model [125,68]. Corroborating with these findings, joint myeloid cell homing and neovascularization were impaired in CXCR6 (CXCL16 receptor) deficient mice provoked with K/BxN induced arthritis compared to wild type controls [68]. Taken together these results suggest that chemokines utilize multiple mechanisms to foster RA pathology.

CC chemokines—Similar to CXC chemokines, CC chemokines are predominately secreted from RA synovial tissue macrophages or fibroblasts that are stimulated by pro-inflammatory factors including TNF, IL-1β, IL-6, IL-8 and IL-17 [109,41]. The CC chemokines are chemotactic for monocytes and lymphocytes. CCL2, CCL3 and CCL5 are highly elevated in RA synovial tissue and can strongly attract monocytes and the blockade of their function alleviates experimental arthritis [126,127,2,128-130]. We have recently identified two CC chemokines in RA synovial tissues, namely CCL21 (binds to CCR7) (59, 112) and CCL28 (binds to CCR10) [76], that are integral for RA angiogenesis.

Notably the expression of CCR7 ligands, CCL19 and CCL21, is markedly increased in RA compared to normal synovial tissue endothelial cells as well as lining fibroblasts and macrophages [67]. Both CCL19 and CCL21 can bind to CCR7, however, only CCL21 can induce endothelial cell migration and capillary tube formation [67,131]. In RA peripheral blood differentiated macrophages and synovial tissue fibroblasts, CCL19 expression levels were upregulated by similar pro-inflammatory factors, whereas CCL21 concentrations were differentially modulated in these cell types [67]. Conversely, endothelial expression of CCR7 and CCL21 was similarly modulated by IL-17 and RA synovial fluid [67,131]. Despite, CCL19's lack of direct effect on RA angiogenesis, like CCL21, it is capable of promoting angiogenesis indirectly through VEGF, IL-8 and Ang-1 secretion from RA synovial tissue fibroblasts or macrophages [67].

CCL28 and CCR10 expression levels are accentuated in synovial tissue/fluid of RA patients compared to normal controls and this chemokine and its receptor were predominately co-expressed in RA myeloid and endothelial cells [76]. We found that protein expression of CCL28 and CCR10 is modulated by TNF and TLR4 ligation in RA peripheral blood monocytes and endothelial cells, and by IL-6 stimulation in RA peripheral blood *in vitro* differentiated macrophages [76]. Antibody neutralization of CCL28 in RA synovial fluid or the use of anti-CCR10 antibody in human endothelial progenitor cells (EPC)s significantly reduced synovial fluid induced endothelial cell migration and capillary tube formation, demonstrating that ligation of CCL28 to CCR10+ endothelial cells participates in RA angiogenesis [76]. We conclude that while CCL2, CCL3, and CCL5 are important for joint monocyte infiltration, CCL21 and CCL28 can highly impact RA angiogenesis.

CX3C Chemokines—Fractalkine (CX3CL1) is expressed in RA peripheral blood monocytes and RA synovial tissue macrophages, fibroblasts and endothelial cells [132]. TNF, IL-1β, IFN-γ and LPS stimulation can enhance fractalkine expression in endothelial cells [133,134]. Levels of fractalkine are highly elevated in RA compared to osteoarthritis (OA) synovial fluid, and neutralization of fractalkine results in compromised monocyte and endothelial cell migration [132,135].

Matrix metalloproteinase and adhesion molecules

MMPs—MMPs are a family of zinc containing, calcium-dependent proteinases, that break down the basement membrane and the extracellular matrix components [136]. The collagenases (MMP-1, 8, 13), the gelatinases A and B (MMP-2 and 9), the stromelysins (MMP-3, 10, 11), the matrilysins (MMP-7, 26), and the MT-MMPs (membrane-type MMPs)

are expressed at low levels in normal joint tissue; however their expression is highly elevated in arthritic joints [137-139]. MMP-2 is constitutively expressed in RA joints, however expression levels of MMP-1, MMP-3, MMP-9, MMP-8, and MMP-13 are accentuated by IL-1β, TNF or hypoxia [140-142]. MMP-2 and MMP-9 are expressed from RA synovial tissue myeloid cells, fibroblasts and endothelial cells, and together with MMP-1 and MMP-13 participate in RA angiogenesis [143]. Synovial fluid levels of MMP-9 and MMP-13, but not MMP-1 or MMP-2, correlated with those of VEGF suggesting that certain class of MMPs may play an important role in RA angiogenesis [144]. In animal models of RA, MMP-2, MMP-9 and MMP-13 deficient mice demonstrated compromised joint vascularization or bone growth; however mice deficient in MMP-3 and MMP-7 had no altered phenotype, further highlighting the importance of specific MMPs in RA pathogenesis [145].

Adhesion molecules

JAMs—Junctional adhesion molecule (JAM)-C is highly expressed in RA synovial fibroblasts [146]. JAM-C is also cleaved from the surface of endothelial cells by ADAM10 and ADAM17 or can be released from endothelial cells in response to IL-1β, IL-17, LPS, MIF, TNF, or PMA stimulation [147]. JAM-C is shown to promote adhesion of myeloid cells to the endothelium as well as facilitating myeloid cell retention and angiogenesis in RA [146,147]. In acute models of preclinical arthritis, treatment with anti-JAM-C antibody ameliorated antigen induced arthritis (AIA) by reducing synovial neutrophil migration and delayed the onset of K/BxN serum induced arthritis [148]. However in the AIA model, blockade of JAM-C had no significant impact on myeloid or endothelial cell migration [148]. Conversely, in JAM-C deficient mice, tumor micro-vessel formation was impaired compared to wild type mice [149]**,** suggesting that chronic arthritis models may be more appropriate for assessing the impact of inflammatory factors on joint neovascularization.

CAMs—Soluble intracellular adhesion molecule (sICAM)1, sICAM3 and soluble vascular cell adhesion molecule (sVCAM)1 are primarily expressed by RA synovial tissue macrophages and/or fibroblasts and their expression is modulated by TNF stimulation [150,151]. Elevated levels of sICAM1, sICAM3 and sVCAM1 were also detected in RA synovial fluids [152-154]. In streptococcal cell wall induced arthritis and CIA models, treatment with anti-ICAM1 antibody reduced ankle edema and neutrophil infiltration without affecting joint vascularization [155,156]. In contrast, RA joint angiogenesis was markedly reduced by neutralization of sVCAM1 in RA synovial fluid [154]. Despite the lack of direct effect of ICAM1 on RA angiogenesis, earlier studies document that serum concentrations of sICAM1 and sVCAM1 closely correlate with serum levels of VEGF, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the number of swollen joints [157], suggesting an indirect role for ICAM1 on neovascularization.

T cells

TH-17 cells—The frequency of TH-17 cells is significantly higher in RA synovial fluid compared to RA and normal peripheral blood [158]. Our group recently uncovered that differentiation of TH-17 cells is fostered by ligation of TLR5 in RA peripheral blood

mononuclear cells. Further, we demonstrate that TLR5 mediated angiogenesis is in part due to TH-17 cell development and IL-17 production [159].

We documented that the *in vitro* RA synovial fluid mediated endothelial migration was reduced by neutralization of IL-17 or by blockade of IL-17RC on endothelial cells [62]. Moreover, IL-17 contributes to matrigel plugs blood vessel formation and joint vascularization in preclinical arthritis models [62,63]. IL-17 driven joint angiogenesis can be impaired in CIA by IL-27 administration at early onset [160]. However, others determined that IL-17 can indirectly induce angiogenesis, by promoting production of pro-angiogenic factors such as VEGF, bFGF and HGF from RA synovial tissue fibroblasts [54]. We demonstrate that in addition to the direct effect of IL-17/IL-17R on angiogenesis, joint IL-17 mediated CXCL5, but not CXCL1, plays a key role in IL-17 induced arthritis and vascularization [63] (Fig. 3).

Endothelial Cells

Selectins—Members of selectin family include soluble E-, L- and P-Selectins. While sE- and sP- Selectins are produced from endothelial cells, sL-Selectin is mainly secreted from circulating leukocytes [150]. Elevated levels of sE-Selectins and sP-Selectins have been also detected in RA sera and synovial fluid [150]. Within few hours of TNF, IL-1β and LPS stimulation expression of sE-Selectins is highly accentuated on vascular endothelial cells [161-163]. sE-Selectin is the only member of the family that is involved in RA angiogenesis as it can contribute to a dose dependent endothelial migration while its depletion significantly reduces RA synovial fluid mediated endothelial migration [154]. Whereas, previous studies have shown that sP-Selectins is responsible for adhesion of neutrophils and monocytes to endothelial cells [164,150].

Future directions for anti-angiogenic therapy in RA

RA therapeutics targeting angiogenesis include the use of anti-cancer therapies-as well as blockers of angiogenic pro-inflammatory factors of which a few are FDA approved and others are under development [165]. Current cancer treatments which have been studied in RA preclinical models include VEGF inhibitors, Taxol, CPT, Vitaxin and FTY720 [165]. Approved RA treatment strategies that may function in part through inhibiting angiogenesis include TNF, IL-1β, and IL-6 inhibitors, Thalidomide, and Cox-2 inhibitors. Pro-inflammatory mediators that promote RA angiogenesis and can be evaluated as future therapeutic targets include cytokines (IL-17, IL-18 and MIF), chemokines (CXCL12), growth factors (Ang1 and Ang2), proteases (MMPs) and adhesion molecules (ICAM1 and VCAM1) (Table 1).

Post onset treatment of CIA mice with a neutralizing anti-IL-17 antibody markedly reduced the disease severity and serum IL-6 levels as well as IL-1β and RANKL positive cells [166]. Ixekizumab and Secukinumab, are both monoclonal neutralizing anti-IL-17 antibodies, that can significantly reduce RA serum CRP levels and DAS28 scores and are currently being evaluated in phase II and III clinical trials [167,168]. Additionally, Brodalumab, an anti-IL-17 RA monoclonal antibody, was examined in phase II clinical trials and psoriatic arthritis patients that received treatment for 24 weeks had markedly improved response rates

compared to the placebo group [169]. However, the effect of Ixekizumab, Secukinumab and Brodalumab has not been assessed on RA synovial angiogenesis.

IL-18 can impact RA disease activity through both direct and indirect effects on inflammation and angiogenesis. Adenovirally expressed IL-18bp/IL-4 fusion protein reduces the secretion of pro-angiogenic mediators such as TNF, IL-6, IL-8 and IL-18 from RA synovial tissue fibroblasts [170]. In a more recent phase I clinical trial, up to 10 mg/kg i.v. injection of the humanized neutralizing antibody to IL-18 (GSK1070806) was well tolerated in healthy subjects [171]. Consistently, the use of recombinant human IL-18bp (rhIL-18bp) in a Phase I clinical trial demonstrated a dose dependent pharmacokinetics with no adverse effect in moderate to severe RA patients [172]. However, the impact of GSK1070806 and rhIL-18bp therapies was not determined on human angiogenesis.

Neutralization of MIF relieves joint swelling in experimental arthritis and suppresses vascularization in tumors and arthritic mice [173,105]. MIF can be targeted through numerous approaches which include anti-MIF neutralizing antibodies, anti-MIF receptor blocking antibodies or soluble small molecule antagonists of MIF [174,175]. An anti-MIF antibody is in phase I clinical trials for the treatment of solid tumors (clinicaltrails.gov). Additionally, Milatuzumab (anti-CD74 monoclonal antibody) which targets CD74, a part of the MIF receptor, is currently in phase I clinical trials for the treatment of SLE (clinicaltrails.gov). Yet, the anti-angiogenic properties of these therapeutic approaches have not been tested in the clinical trials.

In CIA, treatment with an antagonist that targets CXCL12 ligation to CXCR4 (Plerixafor; AMD3100) relieves joint inflammation, although the significance of the therapy was not examined on synovial vascularization [124]. Plerixafor is currently FDA approved for the treatment of non-Hodgkins lymphoma and multiple myeloma and is in several clinical trials for the treatment of other cancers [176]. A fully human anti-CXCR4 antibody, BMS-936564, that impairs CXCL12-induced cell migration by disrupting its binding to CXCR4, is currently in phase I clinical trials for the treatment of multiple myeloma [177]. Despite the use of Plerixafor and MBS-936564 in cancer therapy, their effect on human angiogenesis remains to be determined.

Trebananib, a neutralizing peptibody to Ang1 and Ang2, has a strong binding affinity to Ang1 and Ang2 and as a result can prevent their ligation to Tie2 [178,179]. Hence, Trebananib is currently being tested in clinical trials for the cancer treatment [179]. Double anti-angiogenic protein (DAAP), a dimeric decoy receptor with strong binding affinity to Ang1, Ang2 and VEGF [180], could markedly reduce CIA joint vascularization. However, the effect of Trebananib and DAAP on RA patients remains undetermined.

MMPs have been the target of many clinical trials for different diseases with little success. Two clinical trials studying MMP inhibitors, Apratastat and Cipemastat Trocade, in RA were discontinued after reaching phase II [181,182].

Future treatments targeting adhesion molecules will need to advance from the previous attempts to target CD11a, a ligand of ICAM-1 [183,184]. An anti-CD11a monoclonal antibody, Efalizumab, was FDA approved for the treatment of psoriasis until it was later

removed from the market for adverse reactions [183,184]. Another anti-CD11/CD18 monoclonal antibody, Rovelizumab, was earlier shown to not be efficacious in the treatment of several disease states including multiple sclerosis (MS) [185]. An anti-ICAM1 monoclonal antibody was in clinical trials for the treatment of RA, unfortunately it was determined that repeated treatments had reduced efficacy [186-188]. More recently, a monoclonal antibody targeting the VCAM1 receptor α4 integrin, Natalizumab, has been FDA approved for the treatment of MS and has been in clinical trials for RA [189]. Interestingly, studies performed *in vitro* and in animal models of cancer have shown that Natalizumab has an impact on VEGF expression and angiogenesis [190]. Another anti-α4 integrin monoclonal antibody, Vedolizumab, which specifically targets α4β7 integrin, is approved for the treatment of Crohn's disease and ulcerative colitis. Vedolizumab has not been studied in models of arthritis however it blocks lymphocyte α4β7, an integrin important for RA pathogenesis [191].

Overall there are many therapeutic approaches that have successfully resolved arthritic joint vascularization in RA preclinical models. However, it is less likely that targeting one specific cascade will have a critical effect in ameliorating RA angiogenesis. Hence, discovering novel strategies to target multiple pathways or selecting an upstream cascade that modulates numerous pro-angiogenic factors may be utilized in future RA therapies.

CONCLUSION

In this review we have discussed the potential impact of growth factors, hypoxia induced factors, cytokines, chemokines, matrix metalloproteinase and adhesion molecules on RA angiogenesis. The majority of these pro-angiogenic factors are released from cells in the lining layer to foster pannus formation and leukocyte infiltration. To relieve disease progression and RA bone destruction, many of these pro-angiogenic regulators have been evaluated in RA preclinical studies. In many cases because of the complexity and heterogeneity of the human disease, promising results obtained from the experimental arthritis models could not be translated into successful treatment strategies in RA. This could in part be due to activation of multiple pro-angiogenic factors that are in crosstalk with each other; hence targeting a single player may not impact disease severity or bone destruction. Therefore the recent innovative approaches to target several pro-inflammatory factors through bispecific antibodies may be effective in blocking RA angiogenesis. Regardless of the approach, emerging evidence based on ultrasonographic vascular imaging and expression of pro-angiogenic biomarkers strongly support the indispensable role of neovascularization in RA pathology, thus implicating that inhibition of synovial angiogenesis may provide a promising therapeutic strategy.

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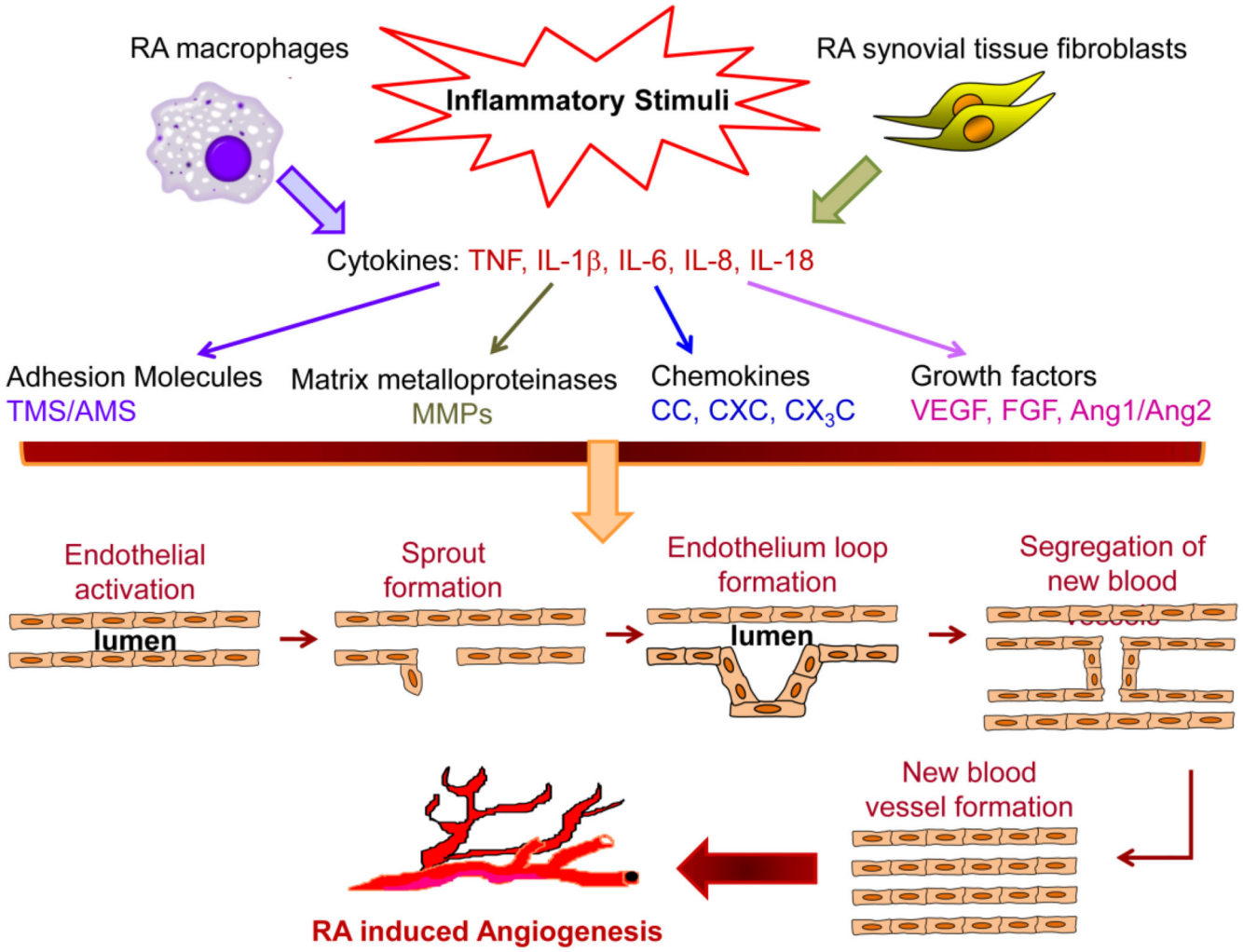

Fig. 1. RA angiogenesis is driven by pro-inflammatory cytokines released from the cells in the synovial tissue-lining layer

In response to inflammatory stimuli, RA synovial tissue macrophages and fibroblasts produce pro-inflammatory cytokines that can modulate expression of adhesion molecules, MMPs, chemokines and growth factors which are all important in different stages of angiogenesis. There are several steps involved in angiogenesis; which consist of endothelial cells migration, endothelial cell proliferation into vascular tubules, separation of the newly formed blood vessels that mature and become interconnected to the circulatory system.

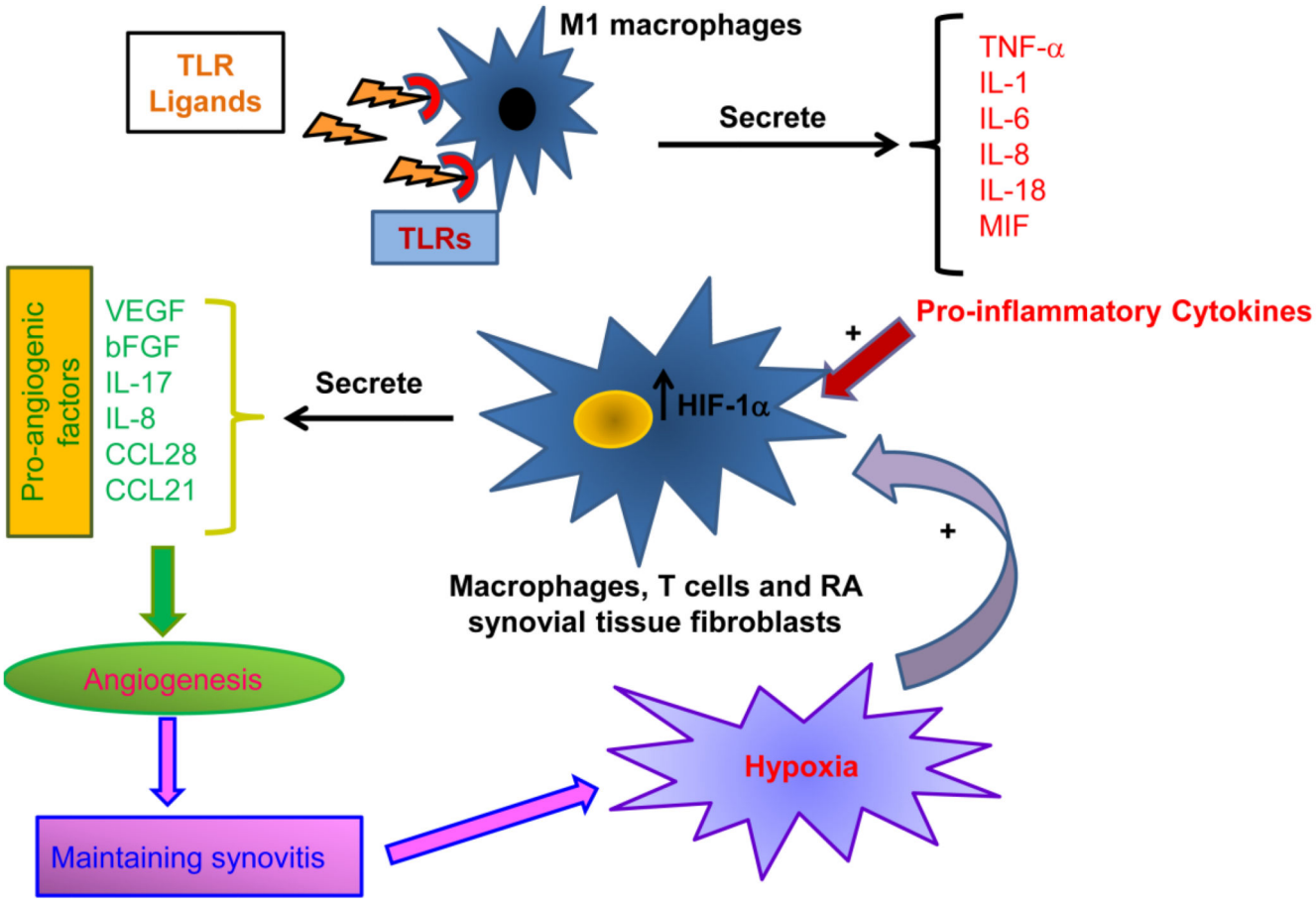

Fig. 2. Ligation of TLRs fosters angiogenesis indirectly through induction of pro-inflammatory cytokines and pro-angiogenic factors

Potentially, TLR endogenous ligands can bind to the RA joint macrophages and activate the production of pro-inflammatory factors such as TNF, IL-1β, IL-6, IL-8, IL-18 and MIF. Excessive leukocyte migration in the RA joint increases the oxygen demand resulting in hypoxia and the subsequent accumulation of the hypoxia inducible factor-1α (HIF-1α). The pro-inflammatory cytokines released into the joint space together with the increased intracellular levels of the HIF-1α can then activate the production of pro-angiogenic factors from the RA synovial tissue macrophages, T cells and fibroblasts. The pro-angiogenic factors increase the joint neovascularization process (Angiogenesis) in order to maintain synovitis.

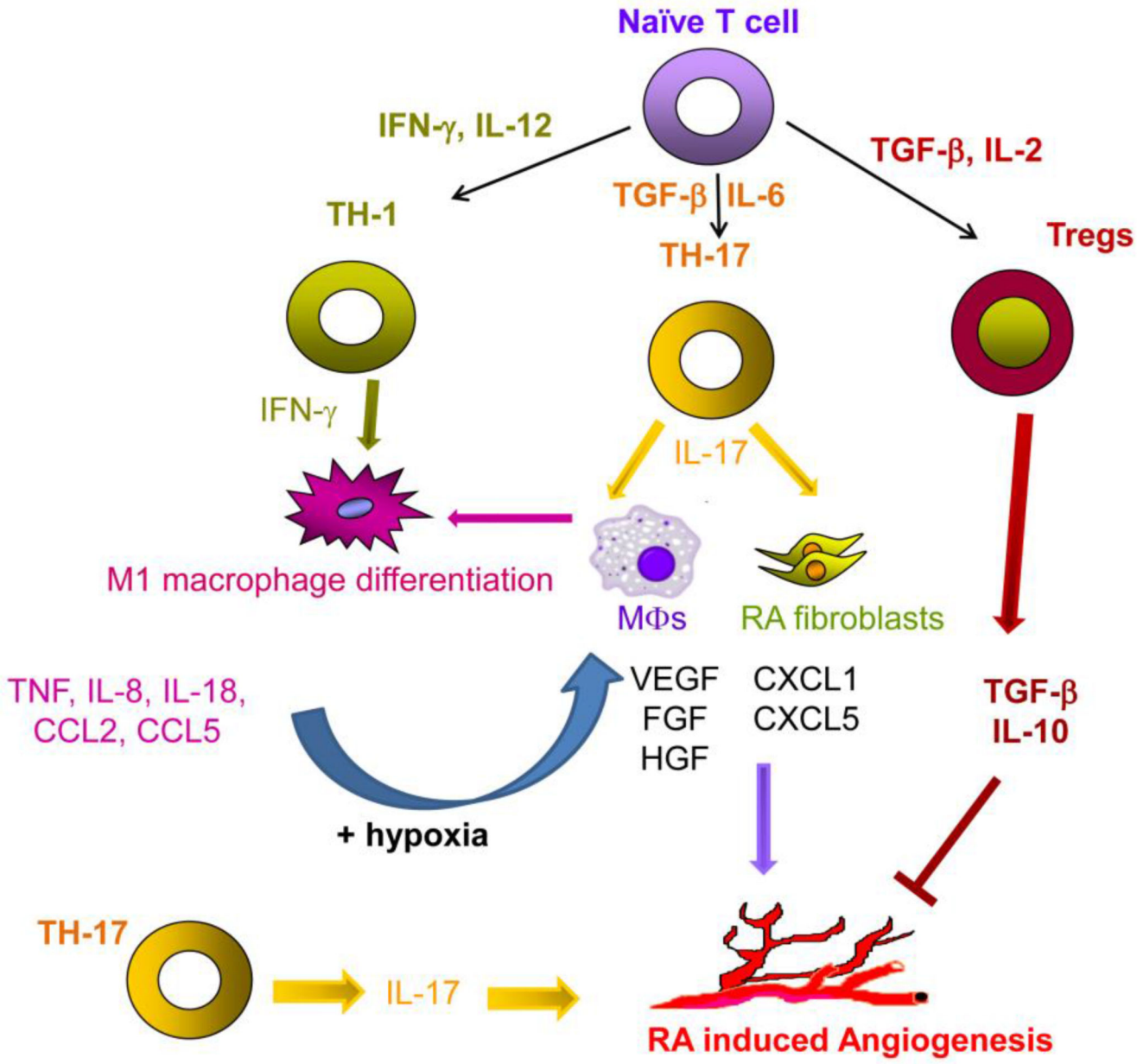

Fig. 3. Differentiation of TH-1 and TH-17 cells can foster RA angiogenesis

In RA joint, IFN-γ and IL-12 drive the polarization of naïve T cells into TH-1 cells that promote angiogenesis indirectly through inducing the production of TNF, IL-8, IL-18, CCL2 and CCL5 by M1 macrophages. Whereas, TGF-β and IL-6 differentiate naïve T cells into TH-17 cells. TH-17 cells can provoke angiogenesis both directly through the production of IL-17 and indirectly by inducing the secretion of pro-angiogenic factors from RA macrophages and fibroblasts. In contrast, inducible T regulatory cells (iTregs) are differentiated from naïve T cells through the effect of TGF-β and IL-2 and release TGF-β and IL-10 that has an inhibitory effect on RA angiogenesis.

Table 1

Angiogenic pro-inflammatory mediators in RA that may be future therapeutic targets.

Target	Drug	Nature/Mode of action	Status	References
Cytokines				
IL-17	Secukinumab	Humanized monoclonal neutralizing anti-IL-17	In phase III clinical trials.	167
	Ixekizumab	Humanized monoclonal neutralizing anti-IL-17	In phase III clinical trials.	168
	Brodalumab	Humanized monoclonal neutralizing anti-IL-17 receptor	In phase III clinical trials.	169
IL-18	GSK1070806	Humanized monoclonal neutralizing antibody to IL-18	In phase I clinical trials.	171
	rhIL-18bp	Recombinant human IL-18 binding protein	In phase I clinical trials.	172
MIF	anti-MIF	Anti-MIF neutralizing antibody	In phase I clinical trials.	(clinicaltrials.gov)
	Milatuzumab	Anti-CD74 (part of MIF receptor) monoclonal antibody	In phase I clinical trials.	(clinicaltrials.gov)
Chemokines				
CXCL12	Plerixafor	CXCR4 (CXCL12 receptor) antagonist	FDA approved for treatment of certain cancers. In clinical trials for other disorders.	176
	BMS-936564	Fully human anti-CXCR4 antibody	In phase I clinical trials.	177
Growth Factors				
Ang1 and Ang2	Trebananib,	Neutralizing peptibody to both Ang1 and Ang2	In phase I, II and III clinical trials.	178
	Double anti-angiogenic protein (DAAP)	A dimeric decoy receptor with strong binding affinity to Ang1, Ang2 and VEGF	In preclinical trails.	179
Adhesion Molecules				
VCAM-1	Natalizumab	Fully human anti-α4 integrin (VCAM-1 receptor) antibody	FDA approved for treatment of MS. In phase II clinical trials for RA.	189