

Review Article



Cytokines, Vascular Endothelial Growth Factors, and PlGF in Autoimmunity: Insights From Rheumatoid Arthritis to Multiple Sclerosis

Young eun Lee ¹, Seung-Hyo Lee ^{1,*}, Wan-Uk Kim ^{2,*}

¹Graduate School of Medical Science and Engineering (GSMSE), Biomedical Research Center, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Korea

²Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, Seoul 06591, Korea



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*Correspondence to

Wan-Uk Kim

Division of Rheumatology, Department of Internal Medicine, School of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea.
Email: wan725@catholic.ac.kr

Seung-Hyo Lee

Graduate School of Medical Science and Engineering (GSMSE), Biomedical Research Center, Korea Advanced Institute of Science and Technology (KAIST), 291 Daehak-ro, Yuseong-gu, Daejeon 34141, Korea.
Email: sl131345@kaist.ac.kr

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ORCID iDs

Young eun Lee

<https://orcid.org/0000-0003-2877-8845>

Seung-Hyo Lee

<https://orcid.org/0000-0003-0010-4072>

Wan-Uk Kim

<https://orcid.org/0000-0001-8224-8496>

<https://immunenetw.org>

ABSTRACT

In this review, we will explore the intricate roles of cytokines and vascular endothelial growth factors in autoimmune diseases (ADs), with a particular focus on rheumatoid arthritis (RA) and multiple sclerosis (MS). AD is characterized by self-destructive immune responses due to auto-reactive T lymphocytes and Abs. Among various types of ADs, RA and MS possess inflammation as a central role but in different sites of the patients. Other common aspects among these two ADs are their chronicity and relapsing-remitting symptoms requiring continuous management. First factor inducing these ADs are cytokines, such as IL-6, TNF- α , and IL-17, which play significant roles in the pathogenesis by contributing to inflammation, immune cell activation, and tissue damage. Secondly, vascular endothelial growth factors, including VEGF and angiopoietins, are crucial in promoting angiogenesis and inflammation in these two ADs. Finally, placental growth factor (PlGF), an emerging factor with bi-directional roles in angiogenesis and T cell differentiation, as we introduce as an "angio-lymphokine" is another key factor in ADs. Thus, while angiogenesis recruits more inflammatory cells into the peripheral sites, cytokines secreted by effector cells play critical roles in the pathogenesis of ADs. Various therapeutic interventions targeting these soluble molecules have shown promise in managing autoimmune pathogenic conditions. However, delicate interplay between cytokines, angiogenic factors, and PlGF has more to be studied when considering their complementary role in actual pathogenic conditions. Understanding the complex interactions among these factors provides valuable insights for the development of innovative therapies for RA and MS, offering hope for improved patient outcomes.

Keywords: Autoimmunity; Autoimmune disease; Cytokine; Vascular endothelial growth factor; Placental growth factor

INTRODUCTION

Autoimmune diseases (ADs) are characterized by the auto-reactive T lymphocytes and/or auto-Abs against their antigens leading to self-destructive immune responses. The progress of AD may take place in various organs or organisms systematically, such as rheumatoid

Conflict of Interest

The authors declare no potential conflicts of interest.

Abbreviations

AD, autoimmune disease; Ang, angiopoietin; BBB, blood-brain barrier; CIA, collagen-induced arthritis; CNS, central nervous system; CSF, cerebrospinal fluid; DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis; FLS, fibroblast-like synoviocytes; GM-CSFR, GM-CSF receptor; HIF-1, hypoxia-inducible factor-1; IBD, inflammatory bowel disease; IL-1Ra, IL-1 receptor antagonist; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; MS, multiple sclerosis; NRPI, neuropilin1; PlGF, placental growth factor; RA, rheumatoid arthritis; TIE, tyrosine kinase via Ig-like and EGF-like domains; TNFR, TNF receptor; VEGFR, VEGF receptor.

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arthritis (RA), multiple sclerosis (MS), inflammatory bowel disease (IBD), psoriasis, and systemic lupus erythematosus. According to the affected organ's characteristics, the mechanisms and the key players of the autoimmune pathology may differ (1-3). By default, the main cytokines and the intertwined relation between the pathologic cells are all differential among ADs. In the case of RA, multiple cells such as fibroblasts, osteoclasts, macrophages, lymphocytes, and fibroblast-like synoviocytes (FLS) are involved in the joint, while Th1 and Th17 cells take the leading role in the pathology of MS giving clues of which cytokines are essential in the disease (4,5). However, RA and MS share fundamental aspects, including inflammation, prolonged symptom duration, and a relapsing-remitting pattern, with overlapping cytokines playing a central role in their pathogenesis. According to up-to-date research, representative cytokines promoting these two ADs via pathogenic cell differentiation and functional maturation are IL-6, IL-1 β , IL-17, and TNF- α , and so on (Fig. 1). In another point of view, angiogenesis which is defined as the sprouting of new blood vessels from existing ones, may be a pillar of AD. Angiogenesis supplies fresh immune cells from the blood to the lesion, increasing cell infiltration. Rather angiogenesis as a potential target against AD is controversial, though various evidence of its impact on RA and MS are presented (6-8). It makes sense that angiogenic factors such as VEGF, placental growth factor (PlGF), and particular cytokines are crucial in the context of AD. By examining the commonalities and distinctions between RA and MS, it might be feasible to discern the factors that contribute to the unique characteristics of each AD, even as they share numerous immunological properties. Auto-Abs are another crucial factor in the field of AD, but in this review, we will focus on the cytokines and angiogenic factors. Considering their leading role in the pathology, a further comprehensive understanding of cytokines, vascular endothelial

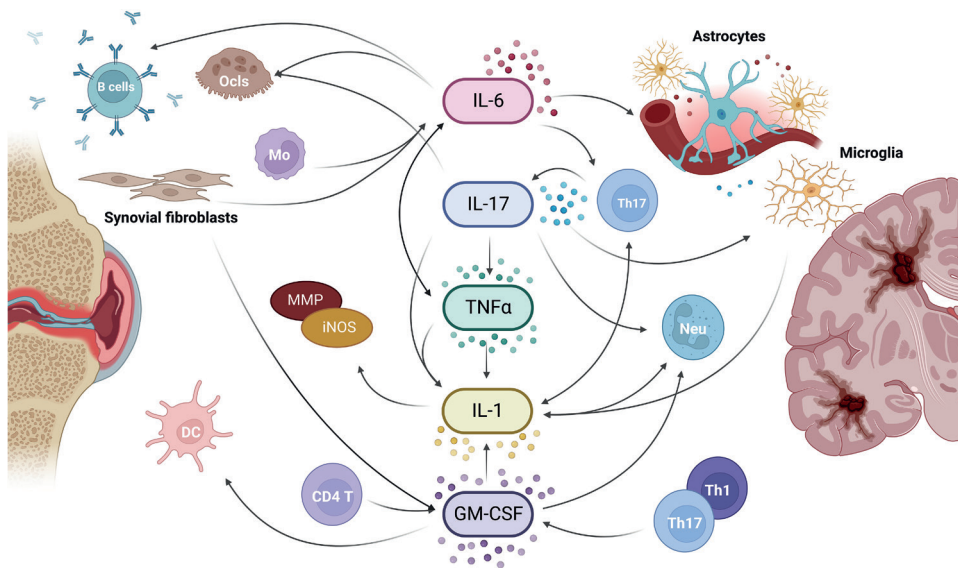


Figure 1. Role of cytokines in the pathogenesis of RA and MS (created with BioRender.com). RA and MS development is intertwined with multiple factors, especially cytokines. IL-6 works as a pleiotropic factor by differentiating naïve CD4 T cells to Th17 cells, inducing pathogenic B cells to produce auto-antibodies, and increasing the permeability of BBB. IL-17 mainly secreted by Th17 cells, functions to damage joints by indirectly activating osteoclasts, recruit neutrophils, and build an inflammatory environment in the CNS by stimulating resident cells such as astrocytes and microglia. TNF α is produced by multiple cells in inflamed joints. It activates osteoclasts, pannus formation, and MMP production playing as the central cytokine in RA and also inducing secretion of IL-1 and IL-6. TNF- α is a crucial cytokine in the pathogenesis of RA. A secreted form of IL-1, which is IL-1 β , induces the production of MMP and iNOS from synovial cells of RA. In MS, IL-1 β is mainly secreted by macrophages, but some minor portion is by Th17 cells. It promotes the activation of autoreactive T cells and the recruitment of CNS-infiltrated myeloid cells. GM-CSF binds to various types of cells expressing its receptors, which include epithelial cells and endothelial cells. In RA, it increases neutrophils in the inflamed joints, further worsening its symptoms by inducing inflammatory DCs. Secreted from Th17 and Th1 cells, GM-CSF also increases neutrophils in the CNS with higher infiltration of DCs and monocytes. Most of these cytokines cooperate with synergism, promoting higher secretion of each factor or aggravating inflammation together. (Ocls, osteoclasts; Mo, monocytes; Neu, neutrophils)

growth factors, and their relationship with AD might give insights into future therapeutics against RA and MS. In this review, we will highlight the functional roles of cytokines and angiogenic factors in the pathogenesis of ADs such as RA and MS broadening to their possibility as novel therapeutics.

CYTOKINES IN AUTOIMMUNITY

IL-6

RA

Although the exact mechanism of how the RA is triggered is yet known, a combination of genetic predisposition, environmental factors, and sex is considered a multiplicative factor. At the cellular level, the interaction of adaptive and innate responses takes place in the joints. These responses are intimately connected with cytokine secretion and related signaling events. For instance, IL-6 which is a pleiotropic cytokine inducing the pathology of RA, is mainly secreted by monocytes and fibroblasts in the joint and found in high levels in serum and synovial fluid (9). One of its main functions is to induce pathogenic B cell proliferation producing auto-Abs binding to cyclic citrullinated peptide-2, and carbamylated protein (10). Another type of Ab regarded as a precise biomarker of RA diagnosis is rheumatoid factor which is a type of IgM directed against the Fc region of IgG (11). This autoreactive IgM with high affinity protects autoantigens from degradation leading to the accumulation of autoantibodies occurring in AD (12). On the other hand, IL-6 is known to activate osteoclasts which induce bone destruction and suppress osteoblasts which oppositely repair the damaged bones of patients with RA (13). Besides activating osteoclasts, IL-6 attracts neutrophils which promote degradation of bone and cartilage by secreting enzymes (14). It also reveals synergism with TNF- α and IL-1 β leading to pannus maintenance and formation by inducing VEGFs (15). Lastly, IL-6 functions as the key cytokine of Th17 cell proliferation and differentiation. Th17 cells are also related to the pathogenesis and are pretty much detected in the inflamed synovium of patients with RA. Along with human cases, Th17 cells were engaged in various animal models such as collagen-induced arthritis (CIA) and SKG (point mutation in ZAP-70, W163C) mice, which emphasizes the indirect importance of IL-6 (16). Naturally, clinical trials aimed to inhibit its function have been conducted, and monoclonal Abs like Tocilizumab and Sarilumab, which target the IL-6 receptor, are employed for RA patients unresponsive to conventional treatments (17,18). Thus, IL-6 plays a multifaceted role in the pathogenesis of RA, influencing autoantibody production, inflammation, bone destruction, and the activation of immune cells. Targeting IL-6 with specific Abs has emerged as a promising therapeutic strategy for managing RA, especially in cases where traditional treatments are ineffective.

MS

MS is a heterogeneous disorder characterized by the involvement of various factors, particularly the dysregulation of immune cells, resulting in dysfunction of immune system. However, the exact etiology of this immune dysregulation still remains elusive. It is a chronic and inflammatory disease inducing demyelination of the central nervous system (CNS). During the progress of the disease, IL-6 is significantly elevated in the cerebrospinal fluid (CSF) and serum of patients with MS compared to other patients with non-inflammatory neurological disease (19). Along with this observation, IL-6 directly influences the integrity of the blood-brain barrier (BBB) by increasing the cell adhesion molecule, vascular cell adhesion protein-1 allowing T cells to pass through the endothelial cells (20,21). Another

significance of IL-6 is that the differentiation of auto-reactive Th17 cells, which play a critical role in the pathogenesis of MS, requires this cytokine (22). Targeting IL-6 in patients with MS has not been tried, but blockade of its receptor inhibits the function of auto-reactive CD4 T cells in animal models showing further possibility (23). Therefore, IL-6 appears to play a role in the pathogenesis of MS by influencing the integrity of the BBB, contributing to T cell differentiation, and potentially exacerbating the inflammatory responses within the CNS. Blocking IL-6 or its receptor may hold promise as a therapeutic strategy for MS, although further research and clinical trials are needed.

TNF- α

RA

TNF- α plays a central role in the progress of RA leading to inflammation and joint damage. It is a pro-inflammatory cytokine that is excessively secreted by multiple cells in the synovium promoting chronic inflammation in the joints. TNF- α works in many quarters as an activator of osteoclasts, pannus formation, and matrix metalloproteinase (MMP) production (16). It is also reported that polymorphisms of the TNF- α promoter gene reveal an association with susceptibility to RA (24). According to its pleiotropic role, a couple of therapeutics targeting TNF- α have already been prescribed to patients with RA such as Infliximab, a chimeric monoclonal Ab blocking TNFs, and Adalimumab, a humanized monoclonal Ab against TNF- α (25,26). By interfering with the effects of TNF- α , it is possible to primarily reduce joint inflammation by preventing its binding to TNF receptor 1 (TNFR1) and TNFR2, then secondarily decrease the secretion of other proinflammatory cytokines including IL-1 and IL-6. From this systemic downregulation of inflammatory status, infiltration of immune cells and activation of MMPs drop together (16). In the study of human PBMC, administration of Infliximab also leads to *de novo* differentiation of Treg cells for immune suppression (27). In conclusion, TNF- α is a crucial mediator of inflammation and joint damage in RA. Targeting TNF- α with monoclonal Abs like Infliximab and Adalimumab has become a standard therapeutic approach in managing RA, effectively reducing joint inflammation and potentially promoting immune regulation through Treg cell differentiation.

MS

Consideration of TNF- α as a significant factor in MS aligns with its recognized role in various ADs. However, the current contraindication of clinical treatments targeting TNF- α for MS treatment is paradoxical. While TNF- α is a pivotal cytokine in the pathogenesis of MS, therapies neutralizing its action present potential side effects, notably CNS demyelination and inflammation directly associated with symptoms of MS (28,29). This adverse outcome occurs from the opposing functions of its receptors, TNFR1 and TNFR2. TNFR1 contributes to demyelination and apoptosis, whereas TNFR2 promotes remyelination and neuronal protection. In response to these findings, researchers are directing their focus toward receptor-specific blockade targeting TNFR1 (30). Some studies have demonstrated successful preclinical amelioration using nanoparticle or monoclonal Abs. Unlike the concerns surrounding the current use of TNF- α blockade therapy in humans, these receptor-specific strategies have not exhibited neurological adverse effects, revealing meaningful therapeutic efficacy (31-33). These advancements instill optimism regarding the potential for human clinical trials targeting TNFR1.

IL-17

RA

IL-17 family comprises six members, IL-17A to IL-17F. The proinflammatory functions of IL-17 play a crucial role in safeguarding the host against microorganisms. However, aberrant

IL-17 production is linked to a spectrum of immunological disorders. Notably, IL-17A and IL-17F are considered critical factors in the pathogenesis of ADs (34). IL-17A (referred to as IL-17 from now) mainly secreted by Th17 cells, synergistically increases production of other proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6 (14). By upregulating the receptor activator of NK- κ B ligand of osteoclast precursors, IL-17 can induce bone destruction in the joints (35). Another mechanism of the disease progression is its chemotactic effect attracting neutrophils. Besides direct chemotaxis, IL-17 stimulates other surrounding cells to produce CXC chemokines, such as CXCL8 (IL-8) which is a potent chemoattractant for neutrophils (36). However, in addition to promoting inflammation and cell infiltration, the role of IL-17 in angiogenesis is controversial. Some studies in tumors have revealed contradictory results, but a study using synovial fluid from a mouse model of RA illustrates that IL-17 contributes to angiogenesis *in vitro* (37). Supported by abundant evidence in animal studies, a couple of clinical trials have been held with Secukinumab and Ixekizumab both of which are monoclonal Abs targeting IL-17A. Unfortunately, most of the trials are not statistically meaningful to the placebo group nor demonstrate clinical efficacy (38-40). Accordingly, IL-17, particularly IL-17A, plays a significant role in AD and inflammation. It can contribute to bone destruction, neutrophil chemotaxis, and potentially angiogenesis. Despite efforts to target IL-17 in clinical trials, the results have been mixed, highlighting the complex nature of IL-17's role in AD and the challenge of developing effective therapeutics.

MS

IL-17 which is mainly secreted from Th17 cells in the pathologically conditioned CNS, demonstrates the highest increase among genes expressed in the plaques of CNS and is also meaningfully higher in the serum of patients with MS (41). Besides its proinflammatory effect to synergize with other proinflammatory cytokines including TNF- α and IL-1 β , IL-17 activates resident cells in the CNS, such as astrocytes and microglia contributing to building the inflammatory environment and promoting demyelination. Th17 cells have been investigated to be the first initiator of CNS inflammation followed by other immune cells to induce further tissue damage (42). Experimental autoimmune encephalomyelitis (EAE) is preferred as the most common animal model representing human MS, but one of the differences between EAE and MS is the main sites of neuron demyelination. While EAE shows more damage in the spinal cord, pathologic lesions of MS are usually more spread in the brain cortex. Another difference is that MS possesses more CD8 T cells as CNS infiltrates, but CD4 T cells are primarily dominant in EAE (43). Besides CD4 T cells, it is reported that IL-17-producing CD8 T cells contribute to the symptoms of MS and EAE (44). Along with IL-17, IFN- γ ⁺ Th17 or GM-CSF⁺ Th17 cells are highly pathogenic for the induction of the main symptoms of the disease (41,45). The role of IL-17 and IFN- γ co-expressing cells demonstrate the importance of Th1 cells as well as Th17 cells, though a couple of studies show controversial results of IFN- γ from its protective action in EAE and development of EAE symptoms in IFN- γ or IFN- γ -receptor deficient mice (46,47). Research in targeting IL-17 in MS is ongoing, however, the efficacy of IL-17 blocking therapy has been variable. Human monoclonal Abs against IL-17A like Secukinumab or targeting both IL-17A and IL-17F, Afasevikumab have gone through clinical trials but were discontinued (48). These disappointing consequences may come from the heterogeneous and complex characteristics of MS or the mistiming of IL-17 blockade. Since IL-17 may act as the key player in an earlier stage of disease onset, it might be more effective when administered in the early stage of the disease. Therefore, IL-17 is a central player in the pathogenesis of MS, along with various immune cells contributing to the development of the disease. Developing effective IL-17-targeted therapies for MS remains a challenge and understanding the timing and context of IL-17 blockade is critical for potential therapeutic success.

IL-1

RA

The IL-1 family is a group of 11 cytokines that mostly act in inflammation. Among them, IL-1 β and IL-1 α are the most well-studied cytokines and play significant roles in the pathogenesis of RA. Unlike IL-1 β , IL-1 α is expressed as a cell-associated form, activating nearby cells or released upon cell death. An endogenous inhibitor called IL-1 receptor antagonist (IL-1Ra) regulates the activity of these two cytokines. Secreted by monocytes, fibroblasts, and B cells, IL-1 induces the production of cytokines from synovial fibroblasts, chemokines, inducible nitric oxide synthase (iNOS), and MMPs. Taking charge of multiple inflammatory factors, an imbalance of IL-1 leads to AD, and a high concentration of soluble IL-1 β is detected in plasma and SF of RA patients. Consequently, synovial lymphoid organization, cartilage and joint destruction, and bone erosion are mediated by activated immune and non-immune cells (14,16). IL-1 blocking agents have already been through clinical trials and approved for RA therapeutics. Anakinra is a recombinant human IL-1Ra, utilized as a secondary treatment for RA patients who failed to respond to disease-modifying antirheumatic drug. It competitively inhibits IL-1 α and IL-1 β from binding to their receptors (49). Thus, IL-1 α and IL-1 β are key players in the inflammatory processes of RA, and their imbalance can lead to AD. Therapeutic interventions that block IL-1, such as Anakinra, have been developed and approved for the treatment of patients with RA, offering a means to modulate the immune response and reduce inflammation in those who do not respond adequately to other treatments.

MS

In the case of MS, IL-1 β is the primary protagonist in EAE induction. Including IL-1 α , other cytokines of the IL-1 family, such as IL-18 and IL-33 are not essential in this animal model (50). It is reported to be elevated in the serum and CSF of MS patients, mainly secreted by monocytes, macrophages, and neutrophils but still how IL-1 impacts neuroinflammation has a lot to be researched. Several studies have reported that neutrophils also play an important role in EAE induction and the severity of symptoms. IL-1 β can be activated through inflammasome-independent maturation by neutrophil-derived serine protease (51). Along with this route, classical IL-1 β activation via inflammasomes in the innate immune response is newly considered to be related to MS (52). Other than myeloid cells, Th17 cells are also known to produce IL-1 β . The amount of IL-1 β from Th17 cells is less than that produced by macrophages and dispensable for Th17 differentiation in the EAE model, but still promotes reactivation and expansion of myelin-specific autoreactive CD4 T cells and aggravates the pathogenic symptoms (53,54). Because IL-1 receptor 1 is expressed in endothelial cells of CNS, IL-1 β has been shown to stimulate the primary endothelial cells to produce GM-CSF, G-CSF, IL-6, CXCL1, and CXCL2. Furthermore, a study has reported that IL-1 β from CNS-infiltrated neutrophils and monocyte-derived macrophages seems to recruit more myeloid cells in a paracrine manner (55). Direct and indirect inhibition of IL-1 β via caspase inhibitor and IL-1Ra both attenuated disease symptoms in animal models, but meaningful efficacy in patients with MS has not been reported (56,57). Thus, IL-1 β plays a significant role in the pathogenesis of MS, particularly in the context of EAE induction. While therapeutic interventions targeting IL-1 β have shown promise in animal models, their efficacy in MS patients has been less clear, highlighting the complexity of the disease and the challenges of translating research findings into effective treatment for patients with MS.

GM-CSF

RA

GM-CSF, also called colony-stimulating factor 2, is a cytokine acting as a leukocyte growth factor. It promotes bone marrow cells to differentiate into monocytes and granulocytes such as neutrophils and eosinophils, but also interacts with various types of cells expressing GM-CSF receptor (GM-CSFR) such as epithelial cells, endothelial cells, and alveolar macrophages. In the case of AD, GM-CSF is one of the early detected cytokines in synovial fluid of patients with inflamed joints showing a correlation with the pathogenesis of RA. Besides its well-known function to differentiate and mature neutrophils, eosinophils, and macrophages, GM-CSF and its receptor are highly detected in the serum, synovial fluid, and synovial tissue (58). The receptor is composed of a high-affinity heterodimeric receptor composed of α subunit (GM-CSFR α) and a signal transducing subunit, common β chain (59). Its main source is regarded as synovial fibroblasts and macrophages, but GM-CSF is also secreted from the synovial CD4 T cells of RA patients, showing an ability to induce inflammatory dendritic cells (DCs) subset aggravating RA (60). Preclinical trials against GM-CSF and its receptor have shown promising results and have completed phase II or III clinical trials with monoclonal Abs such as Namilumab, Otilimab, and Mavrimumab (61).

MS

In terms of MS, GM-CSF is reported to be elevated in the serum of MS patients, and mainly produced by both Th1 and Th17 cells. Utilizing the animal model of MS, GM-CSF or its receptor knock-out mice has revealed strong resistance to EAE induction showing variations depending on the strain of mice (62,63). A couple of studies prove that GM-CSF is dispensable in disease initiation, but independently recruits neutrophils even in the absence of IL-17 (64). Besides neutrophil recruitment to the CNS, GM-CSF has a meaningful effect on the infiltration of DCs and monocytes to CNS and proinflammatory cytokine production (62,65). GM-CSF also shows a synergic effect increasing the production of IL-1 β from neutrophils and monocytes, sustaining chronic inflammation in CNS (50). Unlike inhibition of IL-17, treatment with anti-GM-CSF Abs significantly reduces disease severity in MS animal models (66). In human patients, pathogenic CD4 T cells produce higher levels of GM-CSF, and it is also observed that GM-CSF-producing T cells diminished after treatment (67). From this strong evidence, the first clinical trial of a human Ab to GM-CSF, called Otilimab, has held and has well been tolerated without immunogenicity (68). This approach targeting GM-CSF may be promising but still needs more validation. As referred above, multiple cells are GM-CSF responsive, and total inhibition of GM-CSF may affect alveolar macrophage leading to pulmonary problems (67). Therefore, GM-CSF plays a significant role in the pathogenesis of MS and is implicated in disease severity. Targeting GM-CSF through therapeutic interventions, such as anti-GM-CSF Abs, has shown promise in preclinical studies and early clinical trials.

VASCULAR ENDOTHELIAL GROWTH FACTORS IN AUTOIMMUNITY

VEGF

RA

In normal physiological conditions, angiogenesis is well-regulated with pro-angiogenic and anti-angiogenic factors. However, in the induction of chronic synovitis of RA, angiogenesis promotes immune cell recruitment, synovial hyperplasia, and pannus formation leading

to joint destruction. Persistent influx of inflammatory factors in the synovium expands volume and weight leading to increased requirement of nutrients and oxygen. Then, chronic ischemia and hypoxia activate as a strong signal for *de novo* vessel formation. The augmented capillary network accelerates tissue inflammation and immune imbalance (69). VEGF, the most well-known angiogenic factor managing neovascularization, comprises seven members from VEGF-A to VEGF-F, and PlGF. VEGF-A is one of the most important pro-angiogenic factors which is primarily secreted by synovial fibroblasts and macrophages. Th17 cells and chondrocytes are also sources of VEGF contributing to both inflammation and angiogenesis. Lastly, endothelial cells themselves produce VEGF in a positive feedback mechanism. Correlated with the abnormal angiogenesis, a high concentration of VEGF is detected in serum and SF of RA patients manifesting the clinical symptoms of RA (2,70) VEGF targeting therapy using Abs or small molecular drugs has been already utilized in oncology and is currently being tested in animal models of arthritis (71). Thus, angiogenesis, particularly driven by VEGF, is a significant contributor to the pathogenesis of RA. Targeting VEGF through therapeutic interventions has shown promise in other medical contexts and is now being explored for its potential in the treatment of RA. This approach holds the potential to modulate the abnormal angiogenic processes and alleviate the clinical symptoms associated with RA.

MS

In the case of MS, even though some abnormal barrier functions of blood vessels are observed, accurate association with CNS pathology is unclear. Representative immune cells infiltrating the CNS are confirmed to secrete inflammatory factors worsening the disease symptoms but also angiogenic factors in both MS and EAE along with endothelial cells (72,73). Demyelinated neurons and the gathering of inflammatory cells may increase the energy demand leading to potent angiogenic responses. BBB disruption and vascular remodeling are regarded as pre-symptomatic actions providing evidence as to why VEGFs are detected in the lesions of the brain of the early stage and then reduced in the late phase (7). VEGF can bind to three main types of surface receptors, VEGF receptors (VEGFR), and an additional co-receptor called neuropilin, especially VEGFR2, also called human kinase insert domain receptor or mouse fetal liver kinase 1 is mainly expressed in vascular endothelial cells of CNS consisting of BBB (74). Along with VEGFs, hypoxia-inducible factor-1 (HIF-1) acting in hypoxic conditions is another important regulator highly expressed in MS lesions and blood. Even though a couple of reports claim that the inducible subunit of HIF-1, called HIF-1 α has a role in AD including MS, its gene polymorphism does not show a significant relevance in MS induction, unlike VEGF. Still, it indirectly militates by activating VEGF secretion from other cells (75-77). Other than immune cells and endothelial cells, activated microglia and astrocytes also secrete VEGF affecting BBB permeability during neuroimmune disease providing clues for VEGF as a meaningful target to treat MS patients (78,79). There has not been a human clinical trial, but at least in the EAE various attempts to inhibit VEGF itself, its receptor, or signaling pathway have significantly ameliorated systemic symptoms (80-82). From these results, targeting VEGF with current anti-VEGF Abs, especially VEGF-A such as Bevacizumab or Ramucizumab, may be a promising attempt to manipulate MS symptoms. Thus, VEGF and its associated pathways may play a significant role in the pathology of MS, and targeting VEGF could be a promising avenue for potential treatments. However, it is important to note that further research and human clinical trials are needed to validate these findings and assess the safety and efficacy of VEGF-targeted therapies in MS.

Angiopoietin (Ang)

RA

Ang is a member of the vascular growth factor corresponding to angiogenesis. Ang1 primarily promotes vessel maturation and stabilization, while Ang2 destabilizes blood vessels to initiate angiogenesis with VEGFs. These two types of vascular growth factors bind to their receptor, associated with tyrosine kinase via Ig-like and EGF-like domains (TIE), leading to the TIE pathway mainly mediating angiogenesis signaling (75,83). Although Ang1 and Ang2 reveal each unique function in blood vessels, there have been certain numbers of observations that both factors increase in the serum, synovial fluid, and synovial cells of RA patients (84,85). In verification with animal models of RA, Ang1, and Ang2 stimulate intracellular signaling via the TIE2 pathway and induce inflammatory macrophages and IL-6 production. Neutralization of Ang2 suppresses the disease onset of RA, suggesting its possibility to be implicated in the pathogenesis of RA along with its single nucleotide polymorphism in the gene of RA patients (86-88). Blockade of Ang2 has been preclinically verified in the field of cancer for inhibition of angiogenesis, but still, there's more to be studied in AD especially RA (89).

MS

As mentioned before, Ang1 matures existing blood vessels and has been reported to ameliorate inflammation-induced leakage in rat models of MS. Overall disease symptoms, blood leakage reflected from Evans Blue staining, and immune cell infiltration are reduced by Ang1 injection (90). On the other hand, Ang2 displays opposing effects from those of Ang1 after spinal cord injury, as Ang2 is observed to be induced after artificial CNS damage. Induced by perivascular and non-vascular cells, it contributes to the recovery activity of CNS (91). Derivable from this study, Ang2 blockade is beneficial in animal models of MS. After anti-Ang2 Ab injection, novel vessel sprouting, adhesion molecules of endothelial cells, and infiltration of leukocytes decrease simultaneously improving BBB integrity (92). According to these results, it is plausible to develop novel therapeutics by targeting Ang. By utilizing the two conflicting functions of angiogenic factors, Ang1 itself could be tested as an effective treatment to regain BBB permeability while anti-Ang2 Abs as a potent therapy to block the angiogenesis of MS. Thus, there is a dual role of Ang in angiogenesis and their potential as therapeutic targets in MS. Further research and clinical trials would be necessary to determine the effectiveness and safety of targeting Ang1 and Ang2 in MS treatment.

PlGF AS AN ANGIO-LYMPHOKINE IN AUTOIMMUNITY

PlGF is one of the six family members of VEGF. It is a homologous form of VEGF inducing angiogenesis by activating endothelial cells via binding to VEGFR1 and neuropilin1 (NRP1). As inferable from its designation, PlGF was originally discovered in the human placenta, promoting the development and maturation of the placental vascular system (93). Therefore, unlike other types, it is mostly undetectable in normal physiologic conditions, but highly upregulated in pro-angiogenic status such as tumor and AD (94). PlGF may have been less studied compared to VEGF because it does not bind to VEGFR2, which is considered more important than VEGFR1 in angiogenesis signaling but still, it can stimulate various types of cells by affecting vessel growth and maturation (95). For example, PlGF can promote endothelial cell and mural cell growth, indirectly recruit pro-angiogenic cells, proliferate fibroblasts and smooth muscle cells, and attract macrophages to release angiogenic and lymphangiogenic molecules (96). From this pleiotropic role of PlGF, it has already been

targeted for anti-angiogenesis therapy against cancer with other VEGFs. For instance, Aflibercept (Zaltrap) is a recombinant fusion protein with VEGFR1 and VEGFR2 to bind with VEGF-A, B, and PlGF proved to be effective in metastatic colorectal cancer (97). Owing to its various roles in pathogenic conditions, further studies about the association of PlGF with other diseases are possible.

Recently our group has reported PlGF and its role in connecting angiogenesis and AD (Fig. 2). Th17 cells, but not other Th cell subsets, secrete PlGF to promote angiogenesis and induce the differentiation of pathogenic Th17 cells. From this novel finding, we denominate PlGF as ‘angio-lymphokine’ from its dual function of angiogenesis and T cell differentiation. We have observed PlGF acting as a Th17-polarizing cytokine, able to replace the function of IL-6 via phosphorylation of STAT3. *In vivo* confirmation with animal models of AD also reveals a decrease in disease symptoms when tested with PlGF-deficient mice. Multiple animal models mediated by Th17 cells, the delayed-type hypersensitivity model, CIA, and EAE have been utilized revealing a consistent reduction in Th17 cells and pro-inflammatory cytokines. From these results, PlGF could be re-examined as an effective target against AD (98). Thus, based on these findings, PlGF is suggested as a potential target for the treatment of AD. Further research and clinical studies would be necessary to explore the therapeutic potential of PlGF in AD and other diseases associated with angiogenesis and T cell responses.

RA

Other than Th17 cells, PlGF is known to influence FLS, which are the main effector cells having promigratory and invasive characteristics causing chronic inflammation and joint destruction in RA. FLS produces abundant MMPs, proinflammatory cytokines, and angiogenic factors including IL-1, IL-6, VEGF, and PlGF itself. PlGF activates FLS in an autocrine and paracrine manner by binding to VEGFR1 and NRP1 leading to increased migration and invasion simultaneously inducing anti-apoptotic molecules. Therefore,

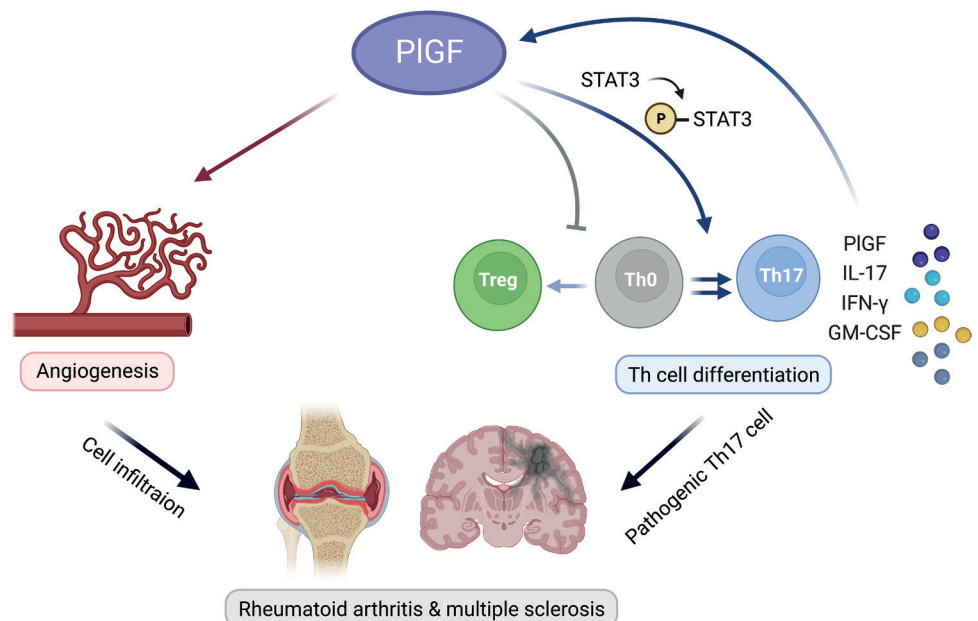


Figure 2. Multi-function of PlGF acting as an angio-lymphokine (created with BioRender.com). PlGF, as an angio-lymphokine, plays an important role in the pathogenesis of ADs by promoting angiogenesis (i.e., inflammatory responses) and phosphorylation of STAT3 (replacing the effect of IL-6). In addition, Th17 cells produce large amounts of PlGF to form double positive loop to further enhance its effect.

targeting PlGF as a novel therapeutic is effective not only in inhibiting angiogenesis and Th17 cells but suppressing FLS activity in patients with RA (99).

MS

Not much has been studied about the relationship between PlGF and MS, but our previous study provides meaningful evidence of its potential as a future immunotherapy target. In animal models of MS, PlGF does not only perform as an inducer of Th17 cells but also increases pathogenic Th17 cells, regarded as GM-CSF⁺ Th17 cells. Along with these *in vitro* results, systemic portions of Treg cells from wild-type and PlGF-deficient mice differ showing a statistically high percentage in the latter group (98). It is well documented that the balance of Th17 and Treg cells is correlated with the severity of MS (100). From these bidirectional effects, PlGF has a sufficient impact on MS pathology qualified as a novel target for MS therapy.

CONCLUSIONS

In this review, we explore the intricate roles of cytokines and angiogenic factors in AD, with a specific focus on RA and MS as described in **Table 1**. Cytokines like IL-6, TNF- α , and IL-17 contribute significantly to joint inflammation, immune cell activation, and tissue damage in RA. Therapies targeting these cytokines have shown promising prognoses in managing RA. In MS, IL-6 and IL-17 influence the BBB and T cell differentiation, while GM-CSF exacerbates disease severity. Another important factor in AD, the vascular growth factors, including VEGF and Ang, play vital roles in promoting angiogenesis and inflammation in both RA and MS. PlGF, a lesser-explored factor in immunology, emerges as a potential therapeutic target due to its bi-directional involvement in angiogenesis and T cell differentiation. From this discriminatory role illustrated in **Fig. 2**, we call it 'angio-lymphokine'. Understanding the complex interactions between these factors offers valuable insights for the development of innovative therapies for AD. Targeted therapies at specific points within these factors hold the potential to revolutionize the treatment for RA and MS, and offer hope for improved outcomes and quality of life for suffering patients.

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Table 1. Role of soluble factors in the pathogenesis of AD

Name	Main cellular sources	Receptors	Type of AD	Functions	Utilized in therapy
IL-6	T cells, B cells, fibroblasts, monocytes, macrophages, endothelial cells, keratinocytes, chondrocytes	IL-6Ra, IL-6Rβ	RA	Stimulation of reactive oxygen intermediates, proteolytic enzymes, osteoclast differentiation, production of VEGF, MMPs	Tocilizumab (anti-IL-6 receptor antibody) Sarilumab (anti-IL-6 receptor antibody)
	Macrophages, microglia	IL-6Ra, IL-6Rβ	MS	Differentiation of T cells, increase of cell adhesion molecules and VAM-1 in endothelial cells	Tocilizumab (anti-IL-6 receptor antibody)
TNF-α	Monocytes, macrophages, fibroblasts, mast cells, NK cells	TNFR1, TNFR2	RA	Stimulates production of collagenase, MMPs, GM-CSF, pro-inflammatory cytokines, induction of ICAM-1, T, B, NK cells differentiation	Infliximab (anti-TNF antibody), Adalimumab (anti-TNF-α antibody)
IL-17	Th17 cells, neutrophils, CD8+ T cells, lymphoid tissue inducer cells	IL-17RA, IL-17RC	RA	Increases production of pro-inflammatory cytokines, MMPs and iNOS, induction of cell infiltration and neovascularization	Secukinumab (phase III clinical trial, anti-IL-17 antibody), Ixekizumab (phase II clinical trial, anti-IL-17 antibody)
	Th17 cells, γδT cells, NKT cells	IL-17RA, IL-17RC	MS	Activation of astrocytes and microglia to inflammatory status, initiation of inflammation, tissue damage	Secukinumab (phase II clinical trial, anti-IL-17 antibody)
IL-1	Monocytes, fibroblasts, B cells, chondrocytes	IL-1RI, IL-1RII	RA	Induction of cytokines, chemokines, MMPs, iNOS, osteoclast activation, induction of cell adhesion molecule expression	Anakinra (recombinant IL-1 receptor A)
	Monocytes, macrophages, neutrophils	IL-1R1	MS	Stimulation of endothelial cells to produce pro-inflammatory cytokines, chemokines, cell recruitment	Not reported
GM-CSF	Synovial fibroblasts, CD4 T cells	GM-CSFR	RA	Induction of inflammatory DCs, increase of neutrophils in the joints	Namilumab (phase II clinical trial, anti-GM-CSF antibody), Otilimab (phase III clinical trial, anti-GM-CSF antibody, MOR103)
	T cells, endothelial cells, epithelial cells, mast cells,	GM-CSFR	MS	Stimulates neutrophils to produce ROS, survive, and secrete pro-inflammatory cytokines, DC maturation, monocyte differentiation	Otilimab (phase I clinical trial, anti-GM-CSF antibody)
VEGF-A	Synovial fibroblasts, macrophages, endothelial cells, chondrocytes, Th17 cells	VEGFR2, neuropilin	RA	Neovascularization	Not reported
	Th17 cells, endothelial cells, microglia, astrocytes	VEGFR2, neuropilin	MS	Neovascularization, increasing the permeabilization of BBB	Not reported
Angiopoietin1	Pericytes	TIE	MS	Blood vessel maturation, stabilization	Not reported
Angiopoietin2	Endothelial cells	TIE	MS	Destabilization of blood vessels to initiate angiogenesis	Not reported
PlGF	FLS, Th17 cells, endothelial cells, osteogenic cells, chondrocytes	VEGFR1, neuropilin1	RA	FLS activation, Th17 differentiation, direct and indirect induction of angiogenesis	Not reported
	Th17 cells, endothelial cells, neurons, astrocytes	VEGFR1, neuropilin1	MS	Th17 differentiation, direct and indirect induction of angiogenesis	Not reported

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