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REVIEW

Role of Chemokines and Chemokine Receptors in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is one of the most prevalent autoimmune diseases and a prototypic inflammatory disease, affecting the small joints of the hands and feet. Chemokines and chemokine receptors play a critical role in RA pathogenesis via immune cells recruitment. Several chemokines and chemokine receptors are abundant in the peripheral blood and in the local inflamed joints of RA. Furthermore, synthetic and biologics disease modifying anti rheumatic drugs have been reported to affect chemokines expression. Thus, many studies have focused on targeting chemokines and chemokine receptors, where some have shown positive promising results. However, most of the chemokine blockers in human trials of RA treatment displayed some failures that can be attributed to several reasons in their structures and binding affinities. Nevertheless, targeting chemokines will continue to be under development, in order to improve their therapeutic potentials in RA and other autoimmune diseases. In this review we provide an up-to-date knowledge regarding the role of chemokines and chemokine receptors in RA with an emphasis on their activities on immune cells. We also discussed the effects of drugs targeting those molecules in RA. This knowledge might provide impetus for developing new therapeutic modalities to treat this chronic disease.

Keywords: rheumatoid arthritis, chemokines, immunotherapy, immunotargets, chemokine receptors, drugs

Introduction

Rheumatoid Arthritis

Autoimmune rheumatic diseases, including systemic lupus erythematosus (SLE), Sjogren's syndrome (SS), and rheumatoid arthritis (RA), can be difficult to diagnose as they share multiple symptoms and are of complex nature. It would take years before clinical manifestations become apparent and that will probably happen after organ/tissue damage has occurred. Hence, early diagnosis and treatment would be crucial to preventing further damage.[1] Autoimmune diseases are manifestations of immune cells attacking normal tissues; however, the etiology of autoimmune diseases is not clearly defined.

Rheumatoid arthritis (RA) is one of the most prevalent autoimmune diseases (1–3% of the world's population). RA is a prototypic inflammatory disease, being characterized by an altered state of homeostasis, in which immunological stimulation and unwanted inflammation prevail. The disordered inflammation has painful and debilitating immediate effects while causing cumulative tissue damage, which could progress into symmetric polyarthritis thus leading to lifelong discomfort, disability and shortened life expectancy.[2–4] It has been reported that almost 50%

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of RA patients become disabled within 10 years of disease onset, and hence, their survival is lessened.[5–7] RA starts with a painful inflammation in the small joints of the hands and feet, especially in the metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints. Also, large joints can be involved such as the elbows, ankles, knees and shoulders.[4,8] Being a systemic autoimmune disease, RA also affects other organs and processes such as osteoclastogensis, angiogenesis and cardiovascular, pulmonary, and skeletal disorders. In clinical setting, RA can be diagnosed by the presence of physical knee inflammation (as per the ACR/EULAR 2010 criteria) along with the presence of a high-titer of rheumatoid factor and/or anticitrullinated peptide antibodies (ACPAs).[9]

The standard golden therapy for RA Patients is the disease-modifying anti-rheumatic drugs (DMARDs). These drugs act by ameliorating the signs of RA in order to inhibit further progression and damage of the joints.[10] The most commonly used DMARD is methotrexate. However, due to inefficacy, intolerance and side effects, there have been emerging therapeutic agents that can act on specific molecules associated with RA pathogenesis. Biologics DMARDs are prescribed only when treatment with DMARDs and/or NSAIDs failed. Currently, there are many specific biological DMARDs such as TNF-α inhibitors, IL-6R antibodies and JAK inhibitors, that are considered to be the most efficient therapeutic agents in RA.[11] The known anti-TNF therapies include etanercept, infliximab, adalimumab, certolizumab, and golimumab, while other cytokine receptor blockers include anakinra (IL-1R blocker) and tocilizumab (IL-6R blocker). Nevertheless, the therapeutic strategy for RA has to be monitored by continuous assessment of the disease activity in order to reach the clinical remission phase.[12,13]

RA is influenced by both genetic and environmental factors, where smoking, diet, obesity, microbiota and infections have been suggested to induce the disease in genetically susceptible individuals. The clinical representation of RA is the result of a cascade of responses and close interactions between immune and non-immune cells (e.g. endothelial and fibroblast-like synoviocytes), autoantibodies, soluble mediators such as cytokines and chemokines, as well as signal transduction pathways of the innate and adaptive immune system.[14] Various players of the immune system include neutrophils, macrophages, B cells, natural killer (NK) cells and T cells migrate to the synovial membrane and accumulate in the synovial fluid, leading to the release of mediators such as cytokines, chemokines, adhesion molecules, matrix metalloproteinases (MMPs) and reactive oxidative species (ROS) which consequently cause joint destruction.[8]

Each immune cell player can contribute to the pathogenesis of RA. For instance, M1 macrophages play a critical role in the production of several proinflammatory cytokines such as TNF-α, IL-6, IL-12, IL-23, IL-1β and IL-18,[15] which promote the production of other mediators from different cell types including endothelial cells and fibroblast-like synoviocytes.[16] Other innate immune cell players are neutrophils which release high levels of ROS, TNF-α, proteases, and defensins in RA joints. Various subtypes of T cells, including Th1, Th2 and Th17, take parts in immune-mediated inflammation of RA, where they become activated and then accumulate in the inflamed joints.[17–19] On the other hand, regulatory T cells (Tregs) have been described to suppress disease severity in collagen induced arthritis (CIA) animal models, and this could explain the finding that Tregs are decreased in the peripheral blood of RA patients.[20,21] One important arm in immune-mediated pathogenesis of RA includes B cells that react against citrullinated antigens and release antibodies that contribute to the initiation and persistence of the inflammatory process. The crosstalk among various immune cells whether via cell to cell contact or the release of mediators, is a critical aspect of the inflammatory process observed in RA. For example, activated Th17 cells are involved in the induction of inflammation by stimulating neutrophils, causing their chemoattraction into the joints.[22–24] Furthermore, neutrophils play a crucial role in the activation of NK cells, as their depletion has led to impairment in the function and homeostasis of NK cells.[25]

Chemokines

Chemokines are chemotactic cytokines that regulate the migration of immune cells in various physiological and pathological processes. They play a crucial role in homeostasis, generation of cellular and humoral immune responses, as well as pathologic immune contribution in various diseases. Chemokines consist of a large family of more than 50 chemokine ligands and receptors, that are classified based on the assembly of cysteine residues in their primary amino acid sequence.[26] Their nomenclature is based on the arrangement of the two cysteine residues dividing them into four subfamilies: CC, CXC, CX_3C, and XC.[27,28] In CC chemokines, the cysteine residues are next to each other, while CXC chemokines have one varying amino acid between them. On the other hand, the CX_3C chemokines have three variable amino acids

between these two cysteine residues, and the XC chemokines have only one cysteine amino acids.[26,29] Almost all chemokine ligands are secreted from the cells with the exception of CX_3 CL1 and CXCL16, that have a transmembrane domain to keep the chemokines at the surface, that can be later cleaved to release the chemokine portion into the extracellular space.[30,31]

Chemokine receptors are expressed on all leukocytes and can be classified into two groups: 1. serpentine G protein–coupled chemokine receptors (GPCRs), and 2. atypical chemokine receptors.[32] Many chemokine ligands can bind to multiple receptors, while some receptors have many ligands, especially with chemokines involved in inflammatory processes. Atypical chemokine receptors (ACKRs) are involved in regulating chemokine distribution and localization.[33] These receptors play a vital role in the regulation of hemopoietic stem and progenitor cells in addition to acting as chemokine scavengers that internalize and degrade chemokines.[34,35]

Chemokines have several functions primarily leukocyte migration, cell proliferation, survival, differentiation, degranulation, and cytokine production. Additionally, many chemokines were shown to possess angiogenic or anti-angiogenic activities.[36] Leukocyte migration is required and necessary for rapid employment of innate immune cells in order to kill pathogens, prevent microbial infection, and drive inflammation as an attempt to repair the damage.[37] Furthermore, chemokines help in the lymphoid organization, regulation of the adaptive immune response, and the consequent immune memory development.[38,39] Any imbalance in the chemokine system could lead to failure of immunosurveillance that can trigger diseases including autoimmunity, chronic inflammatory disease, allergy, cancer, and atherosclerosis.[40,41]

Chemokines in Rheumatoid Arthritis

Chronic inflammation represented in RA synovium is due to the release of a variety of mediators, including chemokines, cytokines, matrix metalloproteinases (MMPs), and growth factors, thus causing continuous activation of innate and adaptive immune systems, as illustrated in Figure 1. Extravasation of inflammatory T cells into the synovium is a crucial event in the pathogenesis of RA. Furthermore, chemokine receptors and ligands have been

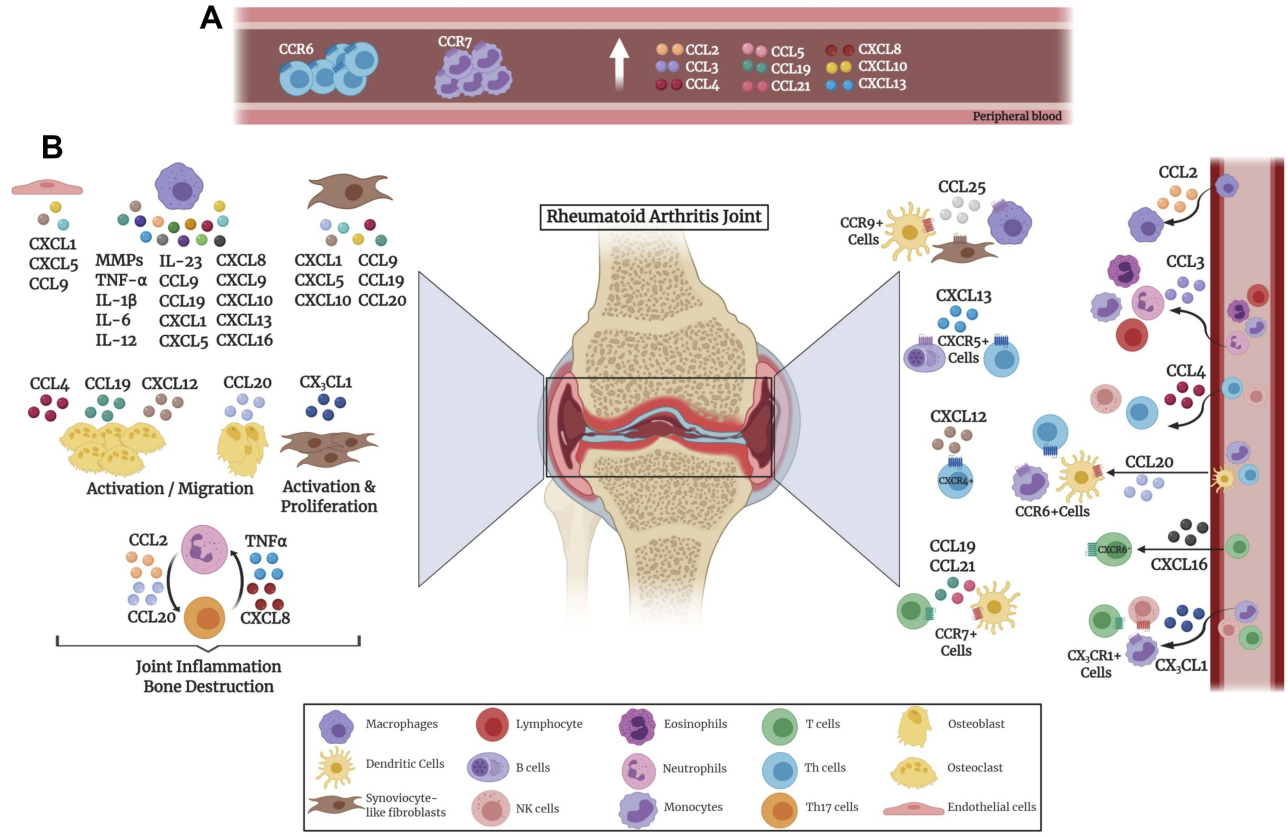

Figure 1 Chemokine involvement in the pathogenesis of rheumatoid arthritis. Various immune cells secrete chemokines that affect the joints. (**A**) Chemokines secreted in the peripheral blood by immune cells. (**B**) Chemokines secreted inside the joints by various immune and non-immune cells.

implicated in different processes of RA development including inflammation and angiogenesis.[42,43] Numerous studies have confirmed the critical role of chemokines for Th1 cell migration into the synovium where chemokine ligands are abundantly present.[39,44] Blocking these chemokine receptors has led to inhibition of inflammatory Th1 cells resulting in decreased synovitis. Neutrophils produce chemokines such as CXCL2 and CCL3 as well as trigger the production of chemokines including CXCL1, CXCL5 and CCL9 from fibroblast-like synoviocytes, endothelial cells, and macrophages.[45]

Chemokine production has been reported to vary at different stages of RA. At an early phase, CCL4, CXCL4, CXCL7 and CXCL13 were expressed, whereas CCL3 and CCL9 were released at later stages.[46,47] Other chemokines, including CXCL1 and CXCL5, promote inflammation and hence their levels keep escalating by persistent inflammation.[45] It is worth mentioning that citrullination of chemokines (e.g. CXCL5 and CCL2) occurs in RA and has been observed in synovial fluid of RA patients. Citrullinated chemokines possess an alteration in their activities which leads to reduction in chemotaxis.[48]

RA patients exhibit increased levels of CCL2, CCL3, CCL4, and CXCL10 in plasma as well as synovial fluid.[49–53] On the other hand, CCL5 showed an increased level in the plasma but a reduction in synovial fluid of RA patients.[49] CCL2 is a potent chemoattractant for macrophages, while CCL3 recruits various lymphocytes, monocytes, and eosinophils.[54] Elevated CCL2 level in RA has been strongly associated with an increase in joint infiltration by immune cells, specifically macrophages.[55] Moreover, high levels of CCL3 were found in neutrophils isolated from synovial fluid.[56] CCL4 has been found to be an important regulator for osteoclast migration indicating that it is a potential therapy target for bone resorptive diseases.[57] A study reported that CXCL10, CCL5 and CXCL8 chemokines were elevated in the plasma of patients with active RA similar to Th1 associated proinflammatory cytokines TNFα, and IL-6.[58] CXCL10 is primarily secreted by fibroblast-like synoviocytes and infiltrating macrophages in the synovium. Another study reported that there is a strong association between serum CXCL10 and disease activity scores (DAS) indicating that this chemokine can be a possible biomarker and diagnostic aid in monitoring disease progression in RA patients.[59] CXCR3 is expressed primarily on NK cells[60] and activated T lymphocytes especially the inflammatory Th1 cells, that secrete high levels of IFN-gamma.[60,61] It has been stated that CXCR3 knockout mice would be more resistant to inflammatory autoimmune diseases.[62] The interaction between CXCR3 and its ligands CXCL9, CXCL10 and CXCL11, would lead to migration of these Th1 cells such as those present in the synovial tissues of RA patients.[63–65]

As mentioned earlier, the interplay between immune cells consists of key players involved in the pathogenesis of RA, including neutrophils, B cells, T cells and macrophages. Th17 cells are known to generate cytokines and chemokines such as TNF-α and CXCL8 that attract neutrophils.[22,24] Mutually, neutrophils further activate Th17 cells through the secretion of CCL2 and CCL20 chemokines.[66] M1 macrophages secrete proinflammatory cytokines and chemokines such as TNFα, IL-1β, IL-6, IL-12, IL-23, CXCL5, CXCL8, CXCL9, CXCL10, and CXCL13 which recruit more leukocytes thus promoting RA and leading to joint destruction (Figure 1).[22,67]

It is well known that leukocyte migration to the joints is one of the main causes of RA pathogenesis. CCR7 was found to aid in the guidance of antigen presenting dendritic cells and T cells to the inflamed synovium and thus contributing to RA pathogenesis. This infiltration in the synovial tissues is partially attributed to CCL21 and its receptor CCR7, where their blockage led to prevention of the migration.[68] It has been reported that plasma CCL19 level and monocyte CCR7 surface expression were higher in RA patients.[69,70] Likewise, CCL19 and CCL21 were reported to be higher in RA patients in comparison to osteoarthritis individuals.[69,71] Also, CCL19 has been found at high concentrations in the synovium where it was reported to be expressed by fibroblasts and macrophages.[69,70] In addition, inflammatory molecules such as lipopolysaccharide, TNF-α and IL-1β were found to promote CCR7 expression.[71] Moreover, CCL19 and CCL21 stimulated osteoclast migration as well as bone resorption by osteoclasts in an animal model of RA,[71] and CCL21 drives osteoclastogensis in RA through M1 macrophage polarization of Th17 cells as well as neovascularization.[68] CCL25 and its receptor CCR9 were both detected in the RA synovium. CCR9 was reported to be expressed on dendritic cells, macrophages, and fibroblast-like synoviocytes. In addition, stimulation with CCL25 led to the secretion of proinflammatory cytokines IL-6 and TNF-α from peripheral blood monocytes.[72]

A subgroup of T helper cells expressing CCR6 was detected in the peripheral blood, synovial fluid and inflamed synovial tissue of RA patients.[73] These $CCR6^{+}$ Th cells can be further classified to Th17, Th22, and

Th17.1 which were identified to be pathogenic as they lead to the progression of chronic arthritis.[74–78] A proportion of peripheral T memory cells were reported to be $CCR6^+$, highlighting the significance of CCR6-CCL20 axis in cell migration to synovium in RA.[79,80] It has been reported that the presence of the rheumatoid arthritis risk variant: dinucleotide polymorphism in the CCR6 gene (CCR6DNP genotype) is linked to RA susceptibility.[81,82] CCL20 has been reported to be secreted by chondrocytes, synoviocytes and Th17 cells in the joints, as well as being able to activate osteoblasts.[73,83–85] Also, CCL20 works in synergy with RANKL leading to bone resorption and destruction.[83] Additionally, CCL20 contributes to T cells, monocytes and $CD1a^+$ dendritic cells chemotaxis towards the joints.[79,80,84,86]

Regarding its pathogenic role in RA, CXCL12 was described to provoke osteoclastogensis by upregulating RANKL expression in synovial fibroblasts and $CD4^+$ T cells, via TNF-α.[87] CXCL12 receptor CXCR4 was correlated with the presence of synovial $CD4^+$ T cells and thus could be associated with T cell migration and joint destruction.[88,89] CXCL13 activates CXCR5 that is present on B cells and T helper cells attracting them to the follicles. CXCL13 which is known to play a critical role in RA pathogenesis, has been reported to be a novel biomarker for RA disease severity.[46,90] It was found to be significantly higher in early compared to established RA. Moreover, its serum level significantly correlated with DAS28 score as well as RF and ACPAs.[91] Therefore, CXCL13 can aid in the diagnosis of early RA with an enhanced diagnostic performance compared to rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP).[91] Serum baseline levels of both CXCL10 and CXCL13 were found to be elevated in RA patients, especially those that are RF and anti-CCP positive individuals.[46,70,90,92,93] Additionally, serum CXCL13 was associated with inflammation, synovitis, RF and DAS28, which could be a predictor of high RA severity. Several studies have shown that CXCL16 is highly expressed in RA synovia, causing the recruitment and accumulation of $CXCR6^+$ T cells in RA joints, which is highly associated with RA pathogenesis.[94,95] It has been suggested that CXCL16 is released and expressed by synovial macrophages, where the expression was elevated by inflammatory TNF-α.[95]

CX_3CL1 "Fractalkine", that is present in RA synovium,[96] was found to play a crucial role in monocyte chemotaxis and angiogenesis in the rheumatoid synovium. The interaction of CX_3CL1 and its receptor CX_3CR1 contributes to the recruitment of various immune cells including T cells, monocytes and NK cells causing inflammatory autoimmune diseases such as RA and SLE.[96–99] Moreover, stimulation by CX_3CL1 was found to trigger the proliferation of fibroblasts and atherosclerosis as well as leading to an increased MMPs and further inflammation in RA joints.[100–104]

Multiple studies in RA have been carried out with antagonists and/or neutralizing antibodies against chemokines including CCR1, CCR5, CXCR4, CXCR7, CCL19, CXCL10, CXCL12, and CXCL13, where they revealed potential to be future targets.[105,106] However, further understanding of the role of these chemokines in RA is quite essential.

Effect of Chemokines in RA Therapy

It has been noted that chemical and biologic DMARDs affect chemokine expression in RA. Many studies have shown that NSAIDs, glucocorticoids and DMARDs (sulfasalazine, sulfa pyridine, methotrexate, and leflunomide) hinder the production of numerous chemokines in various clinical setups,[107–111] as summarized in Figure 2. RA patients treated with biological DMARDs such as infliximab, etanercept and tocilizumab exhibited a significant reduction in serum CCL20 levels compared to before treatment.[112] Furthermore, the expression of CCR7 and CCL19 chemokines reversed to normal baseline levels after 1 year of DMARD methotrexate and cyclosporine A therapy.[69] Similarly, levels of CCL5 and CCL19 were reported to be decreased by rituximab and anti-TNF therapies, respectively.[69,70,113] Hence, blocking CCR7 and its ligands CCL19 and CCL21 could be a therapeutic approach targeting inflammation and bone destruction in RA. Besides, serum CCL19 was reported to be a promising predictive diagnostic tool for effective response to rituximab therapy.[70]

Additionally, RA patients that responded to IL-1 receptor antagonist (IL-1Ra) therapy had significantly lower mean changes in the serum CCL2 and CCL3 levels compared to non-responders or placebo. This indicates that CCL2 and CCL3 may be convenient markers for IL-1Ra efficient treatment.[51] Likewise, chemokine ligands such as CXCL10, CCL2, and CCL4 levels decreased significantly upon treatment with infliximab along with a reduction of chemokine receptors CCR2 and CXCR1 on T cells.[52] Furthermore, RA patients that responded to TNF inhibitors had higher baseline serum levels of CXCL10 and CXCL13, that were reduced after therapy.[46,92,106] Another class of therapy, Janus kinase (JAK) inhibitor

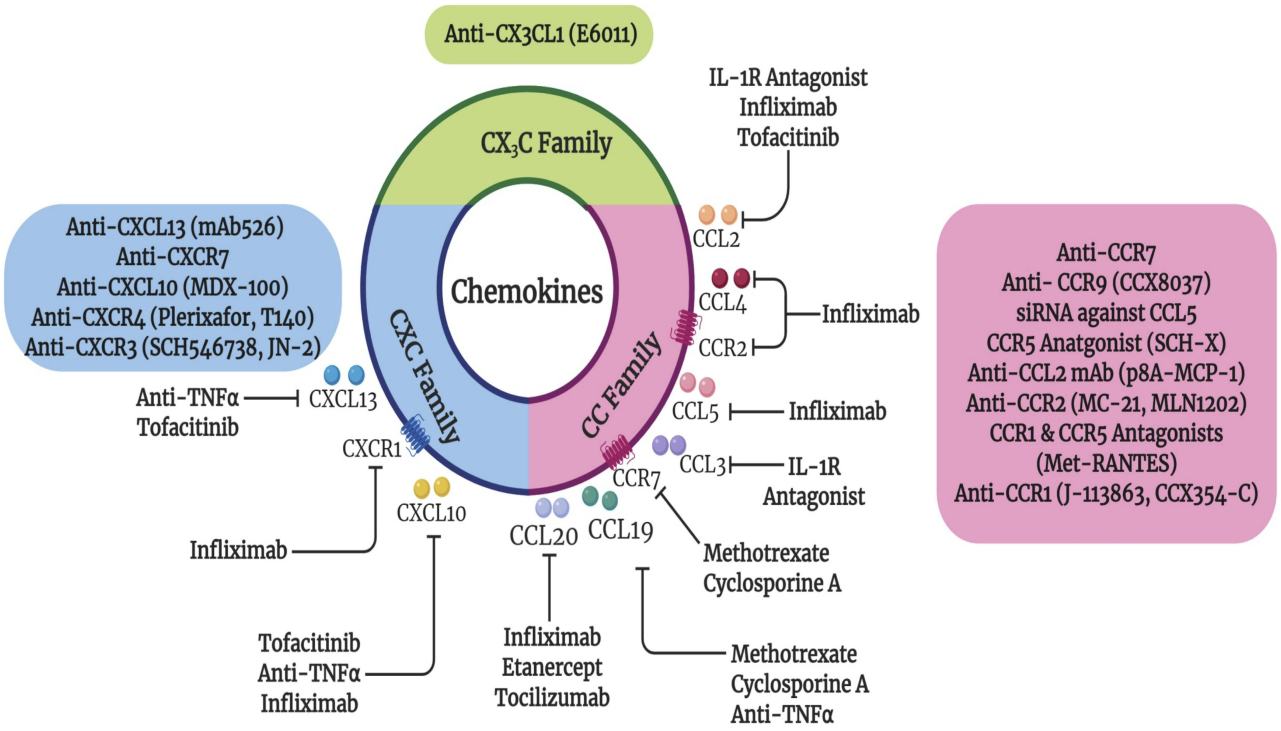

Figure 2 Effect of current RA therapies on chemokines as well as the current chemokine targeted therapies in RA. Closed arrows indicate antagonism.

Tofacitinib caused a significant reduction of synovial mRNA chemokine expression of CCL2, CXCL10 and CXCL13.[114] Therefore, levels of CXCL10 and CXCL13 could be used as prognostic tools for biological TNF and JAK inhibitor therapy.[46] Also, serum baseline levels of CCL2 and CXCL8 were found to be higher in the tocilizumab responders compared to non-responder RA patients. A closely related chemoattractant, macrophage migration inhibitory factor (MIF) level was reduced after tocilizumab treatment in RA responders, highlighting the importance of MIF in RA.[115]

Numerous chemokine inhibitors targeting CC or CXC receptors have been investigated, with controversial outcomes, especially in autoimmune diseases.[116–120] For instance, CXCR4 antagonist Plerixafor and the CCR4 monoclonal antibody Mogamulizumab, have been utilized in the mobilization of stem cells in the treatment of non-Hodgkin lymphomas and T cell leukemias, respectively.[105] Additionally, CCR5 antagonists Aplaviroc, Maraviroc and Vicriviroc have been utilized for the treatment of HIV infection.[121] Another CCR9 antagonist Vercirnon, displayed promising results in Crohn's disease.[72] Interestingly, antibodies against CXCL12 and CXCL13 showed beneficial effects in vitro and in animal models of cancer and inflammatory diseases including collagen induced arthritis (CIA).[122,123] Currently, many studies and clinical trials have investigated chemokine targeting in autoimmune diseases including RA (Figure 2).[118,124–131]

Another autoimmune disease, Sjögren's Syndrome (SS), occurs when the immune system attacks exocrine glands. Similar to RA, SS is a debilitating progressive disease. CXCL13 expression was found to be increased in salivary tissue and associated with disease progression in SS mouse model.[132] In addition, CXCL13 was described to be elevated in the serum and saliva of SS patients, highlighting its importance in SS.[132] Studies have reported that blockage of CXCL13 reduced glandular inflammation and hence could be an effective therapeutic strategy in SS mouse model as well as in SS patients.[132,133] Besides, mAb 526, an anti-CXCL13 antibody, has shown therapeutic efficacy in various autoimmune diseases including mice models of RA or CIA as well as multiple sclerosis model (experimental autoimmune encephalomyelitis or EAE).[134] In addition, inhibition of CXCR7, another receptor for CXCL12, decreased inflammation in the joints and reduced angiogenesis in CIA model.[135]

A recent study reported engineered nanobodies that target CCR7 which can be used for therapeutic and diagnostic purposes.[136] Another study indicated that both prophylactic and therapeutic treatments of CIA-humanized

CCR7 mice with anti-human CCR7 monoclonal antibody led to complete resistance to CIA and arrested progression, thus highlighting that CCR7 could be a potential therapeutic target in RA.[136]

One potential therapeutic target in RA is CX_3CL1 which has been blocked in a clinical trial using a monoclonal antibody as a treatment for RA.[137] The humanized anti-CX_3CL1 monoclonal antibody E6011 was found to be safe, well tolerated, and exhibited efficacy for 52 weeks in active RA patients who were non-responders or intolerant to MTX or TNF inhibitor therapies.[138,139] Moreover, E6011 was found to hinder the migration of CX_3CR1^+ macrophages as well as blocking joint destruction via reducing inflammatory cytokines and suppressing osteoclastogenesis.[139,140] All of these data support the utilization of anti-CX_3CL1 monoclonal antibody in Phase 2 clinical trials for further assessment.

Different CXCR4 antagonists have shown positive results in tempering synovitis in animal models of arthritis including Plerixafor and T140.[141,142] Previously, SCH546738, a synthetic compound targeting CXCR3, was found to weaken the development of CIA in mice.[143] Furthermore, a CXCR3 antagonist JN-2, was reported to improve arthritis symptoms in a CIA animal model.[144] This was suggested to be due to inhibiting cell migration and pro-inflammatory cytokine expression from macrophages and $CD4^+$ T cells.[144] A study by Broeren et al reported that CXCR3 ligand, CXCL10 increases inflammatory mediators which are present in the serum of patients with RA.[145] The CXCL10 promoter-regulated IL-10 overexpression was described to lead to a reduction in inflammatory cytokine production. For that reason, this vector was suggested to provide a possible gene therapy approach for RA.[145] Additionally, the use of blocking monoclonal antibody against CXCL10 as therapy for arthritis led to halting its progression.[146,147] Clinical trials using anti-CXCL10 monoclonal antibody (MDX-1100) for RA patients with an ineffective response to methotrexate showed that blocking CXCL10 significantly improved the response rate, suggesting a possible therapeutic use in humans.[148] This has been supported by a decrease in the levels of C-reactive protein and disease activity score (DAS) as well as an improvement in the ACR20 (i.e. 20% improvement in RA symptoms) and physical function.[148]

CCR9 antagonist, CCX8037 or knockdown of CCR9 repressed arthritis symptoms in mice.[72] A neutralizing mAb against CCL2 was shown to reduce ankle swelling along with a decrease in the number of monocytes/macrophages recruited to the joints.[149] While the treatment with a small-molecule inhibitor of endogenous CCL2 (p8A-MCP-1) displayed a positive clinical efficacy on adjuvant-induced arthritis (AIA),[150] its receptor CCR2 is expressed by $CD14^+$ monocytes, demonstrating a vital role in monocyte recruitment during CIA.[149] Consequently, low doses of a monoclonal antibody against CCR2, the MC-21 showed some improvement in CIA.[151] On the other hand, administration of an anti-CCR2 antibody (MLN1202) was implemented in humans with no observed reduction in the numbers of inflammatory cells.[126,152] Another possible chemokine target was a highly abundant chemokine in RA synovium, i.e. CCR5 that is expressed by inflammatory Th1 cells and tissue-resident macrophages.[107,153,154] Local injection of small interfering RNA (siRNA) against CCR5 in a rat model of adjuvant-induced arthritis was found to repress joint inflammation and swelling, highlighting that CCR5 inhibition may be a promising target for therapy.[155] Additionally, CCR5 antagonist SCH-X was found to hinder the development of CIA.[156] A single nucleotide polymorphism of CCR5 influenced RA severity and immune infiltration to joints where individuals bearing the unfunctional Δ32-CCR5 variant, were more likely to develop less severe RA symptoms.[157] However, CCR5 antagonists such as Maraviroc and AZD5672 did not exhibit any clinical efficacy in RA patients in terms of ACR20 response.[158] Dual antagonists have been under development, where dual targeting of CCR1 and CCR5 via Met-RANTES caused prevention of arthritis in CIA and AIA animal models.[159,160]

Several studies suggested that CCR2 and CCR5 are not as critical as CCR1 for the migration of monocytes towards the synovial compartment in RA.[127,131] As mentioned earlier, CCR1 levels are elevated on several leukocytes present in the RA synovium, along with its multiple ligands.[130,161] This has been supported by immunohistochemistry findings reporting the presence of $CCR1^+$ cells promoting inflammatory monocyte infiltration into RA synovial tissue.[162] The CCR1 antagonist J-113863 displayed a positive clinical efficacy in murine CIA.[163] However, in the past, Phase II clinical trials using oral CCR1 antagonists, such as CP-481,715 (Pfizer), MLN3897 (Millennium), BMS-817399 (Bristol-Myers Squibb) and c-4462 failed to induce noticeable activities in RA patients.[118,124,164–166] This could be attributed to persistent high level of receptor blockage which may be necessary to inhibit monocyte migration in the synovium. Another possibility could be that CCR1 ligands can interact with multiple receptors including CCR2 and CCR5,[164] mediating their effects in RA. However, a recent clinical trial using an oral CCR1 antagonist, CCX354-C was performed to evaluate

its safety and efficacy in RA patients.[167] The clinical trial so called CARAT-2 reported that CCX354-C revealed good safety and tolerability profiles that can be implemented in clinical aspects in RA.[167] A slight elevation in the ACR20 was observed in RA patients using CCX354-C but the difference was not significant. Nevertheless, treatment with CCX354-C revealed more than 90% receptor occupancy that was required for effective blockade of infiltration of inflammatory cells.[131,168]

Targeting chemokines as a therapeutic approach has shown several obstacles that might hinder their development and approval in various diseases. One of the main reason for the failure is that chemokine receptors are not cell-specific and can be shared by several inflammatory and anti–inflammatory cells, making their blockage difficult to reach reasonable therapeutic effects.[169,170] Furthermore, many chemokines are engaged in physiological and developmental processes where any intervention could lead to undesirable adverse effects.[54,94,107,171,172] It is worth mentioning that single targeting is not quite effective as the binding affinities are much limited in vivo compared to in vitro studies.[173–175] Additionally, the use of animal models could create difficulties, as the affinity of a compound for a rodent chemokine receptor can differ noticeably from its affinity for the equivalent human chemokine. Also, as mentioned earlier, chemokines could become citrullinated in RA and hence, they might not be inhibited by chemokine blockers that are designed for unmodified chemokines.[48] Therefore, it is vital to find the appropriate chemokine targets in order to be able to succeed in blocking pathogenic lymphocyte recruitment to the RA synovium.

Conclusions

Chemokine signaling has shown to be critical in RA pathogenesis, as several chemokines and their respective receptors contribute to immune cell recruitment in arthritic joints. Therefore, targeting chemokines could be a suitable therapeutic approach in the treatment of RA. Nevertheless, many studies with antagonists and antibodies directed against chemokines and chemokine receptors failed upon translation into clinical trials. Currently, the development of more effective chemokine therapies is underway, where it would provide new opportunities for clinical trials for the treatment of RA and similar autoimmune diseases. We aim from this article to shed some lights on the importance of chemokines and chemokine receptors in RA disease. This information should provide a solid background for developing new drugs or other therapeutic modalities to target chemokine or their receptors due to their vital importance in disease initiation, progression and development.

Abbreviations

ACKRs, Atypical chemokine receptors; ACPAs, Anti–citrullinated protein antibodies; ACR20, American College of Rheumatology 20; CCP, Cyclic citrullinated peptide; CD, Cluster of Differentiation; CIA, Collagen-induced arthritis; DAS, Disease Activity Score; DMARDs, Disease Modifying Anti Rheumatic Drugs; DNP, Dinucleotide polymorphism; EAE, Experimental Autoimmune Encephalomyelitis; GPCRs, G-protein Coupled Receptor; IL, Interleukin; JAK, Janus Kinase; MIF, Migration inhibitory factor; MMPs, Matrix Metalloproteinases; MTX, Methotrexate; NK, Natural Killer; RA, Rheumatoid Arthritis; RANKL, Receptor activator of nuclear factor kappa-B ligand/ tumor necrosis factor ligand superfamily member 11; RF, Rheumatoid Factor; ROS, Reactive Oxygen Species; siRNA, Small interfering RNA; SS, Sjogren's Syndrome; SLE, Systemic Lupus Erythematosus; Th, T helper; TNF-α, Tumor Necrosis Factor alpha; Tregs, Regulatory T cells.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors report no conflicts of interest in this work.

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