The Role of CCL21/CCR7 Chemokine Axis in Autoimmune Diseases Progression

Le Han[1], Danlian Wu [1], and Lingling Zhang[2]

[1]Southeast University
[2]Anhui Medical University

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Abstract

Autoimmune diseases are diseases characterized by local or systemic abnormal inflammatory immune responses. With the in-depth exploration of the pathological mechanism of autoimmune diseases, it is found that occurrence and development of autoimmune diseases are largely related to the interaction between chemokine receptors and chemokines expressed at inflammatory sites. CCR7, one of Chemokine receptors members, binds to CCL21, which regulates lymphocyte homing, neovascularization and immune cells migration in autoimmune diseases. However, the underlying signaling pathways of CCL21/CCR7 need to be further explored. Despite the enormous advances in our knowledge of chemokines, research about the involvement of CCL21/CCR7 in autoimmune diseases progression is still limited. Thus, in this review, we summarize the essential role of CCL21/CCR7 in autoimmune diseases progression. Further studies are critical to illustrate the distinct roles of CCL21/CCR7 in autoimmune diseases progression, and are important significance for discovery of new biomarkers and drug targets of autoimmune diseases.

The Role of CCL21/CCR7 Chemokine Axis inAutoimmune Diseases Progression

Le HAN[1], Danlian WU[1], Lingling ZHANG[2, 3, 4 *]

[1] Department of Pharmacy, The Affiliated Jiangyin Hospital of Southeast University Medical College, Jiangsu Province, Jiangyin, China.

[2] Institute of Clinical Pharmacology, Anhui Medical University, Hefei,China

[3] Key Laboratory of Anti-inflammatory and Immune Medicine, Ministry of

Education, Hefei, China

[4] Anti-inflammatory Immune Drugs Collaborative Innovation Center, Anhui Province, Hefei, China

***Corresponding Author:**

Prof. Ling-ling ZHANG. Institute of Clinical Pharmacology, Anhui Medical University, Anhui, Hefei 230032, China

E-mail addres s: *ll-zhang@hotmail.com (L.L* . ZHANG);

Phone: +86-0551-6516-1206, Fax: +86-0551-6516-1208

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Abstract

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that occurrence and development of autoimmune diseases are largely related to the interaction between chemokine receptors and chemokines expressed at inflammatory sites. CCR7, one of Chemokine receptors members, binds to CCL21, which regulates lymphocyte homing, neovascularization and immune cells migration in autoimmune diseases. However, the underlying signaling pathways of CCL21/CCR7 need to be further explored. Despite the enormous advances in our knowledge of chemokines, research about the involvement of CCL21/CCR7 in autoimmune diseases progression is still limited. Thus, in this review, we summarize the essential role of CCL21/CCR7 in autoimmune diseases progression. Further studies are critical to illustrate the distinct roles of CCL21/CCR7 in autoimmune diseases progression, and are important significance for discovery of new biomarkers and drug targets of autoimmune diseases.

Key words: CCL21, CCR7, Cell Migration, Autoimmune Diseases, Signaling Pathway

Abbreviations

AS, ankylosing spondylitis; CDK, cyclin dependent kinase; CRP, C-reactive protein; DAG, diglyceride; DCs, endothelial cells; DMARDs, disease modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; FS, focal index; GPCRs, G-protein-coupled receptors; GSK3, glycogen synthase kinase 3; HMVEC, human vascular endothelial cells; NK, Natural killer; PI3K, phosphatidylinositol-3-OH kinases; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; VEGF, vascular endothelial grown factor.

Introduction

Autoimmune diseases are characterized by immune responses to self-antigens that result in tissue damage. Autoantibodies directed against normal host antigens are a common feature of many autoimmune diseases (Liang et al., 2017). Autoimmune diseases mainly include diffuse connective tissue diseases (such as rheumatoid arthritis, (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren Syndrom (SS), etc.), spondylitis-related arthritis (ankylosing spondylitis, AS) and infection-related arthritis, tenosynovitis and bursitis. Autoimmune diseases are the frequent disorder, however, its etiology and pathogenesis are still not completely understood (Han et al., 2020). The clinical manifestations and immune processes of affected tissues and organs are also different, but the common point is the deficiency of immune regulation. At present, treatment of autoimmune diseases has two goals: the first is to symptom relief and functional maintenance, and the second is to delay the process of tissue damage. Therapeutic drugs are mainly divided into non-steroidal anti-inflammatory drugs (NSAIDs), steroidal anti-inflammatory drugs (SAIDs) and disease modifying anti-rheumatic drugs (DMARDs) (such as chemical drugs, natural drugs and biological agents) (Zhang et al., 2020). With the further elucidation of the pathological mechanism of autoimmune diseases and the exploration of new drug targets, it has been found that cytokines, cell surface molecules and their mediated signal pathways are involved in immune cell dysfunction and the pathological process of autoimmune diseases (Xiao et al., 2021).

The chemokines comprise a large family of low molecular weight (8–10 kDa) cytokines, with chemotactic and pro-activatory effects on different leukocyte lineages (Griffith et al., 2014). It plays an important role in lymphocytes homing and cell differentiation, immune response, inflammatory response, wound repair and tumor cell metastasis ('Agostino et al., 2020). Chemokines are classified into 4 main families based on the position of conserved cysteine residues within their N-terminal region; CXC, CC, CX3C, and C chemokines. Chemokine receptors are GPCRs regulated by small protein ligands known as chemokines, which are 8–10 kDa proteins with a globular core structure stabilized by 1–2 conserved disulfide bridges1 (Wasilk et al., 2020). Chemokine receptors are a seven membrane-spanning domain, which regulates chemotaxis and effector functions of T-lymphocytes, macrophages, and dendritic cells. According to the types of chemokine binding, chemokine receptors can also be divided into four subfamilies: CXCR, CCR, XCR and CX3CR. Much of membrane signaling is mediated by ligand binding to specific receptors. These receptors bind to diverse ligands and evoke different effector systems (Worbs et al., 2020)(Figure 1).

Chemokines interact with chemokine receptors in a promiscuous network, such that each receptor can be

activated by multiple chemokines. Actions of chemokines through chemokine receptor signaling leads to an array of diverse functions in different tissue compartments (Cardona et al., 2008, Hons et al., 2018). Under the regulation of chemokines and their receptors system, immune cells are involved in a variety of physiological and pathological processes, such as the reconstruction of the cytoskeleton structure, migration and infiltration into target organs, mediated stress response, infection, wound healing, T cells differentiation, lymphoid organ development, angiogenesis, tumor cells metastasis and DCs maturation (Ridiandries et al., 2018). Different cells express the different types of chemokines and receptors. Thus, they have different functions on different cells. When chemokine binds to their receptor, various combinations of intracellular signaling pathways are activated. Receptor-ligand interaction leads to signal transduction involving G-proteins which promotes the release of intracellular second messengers such as calcium, cyclic adenosine monophosphate (cAMP) and phosphoinositides (Laufer et al., 2018). This results in the expression of several genes and activates a signaling cascade that, depending on the context, can stimulate cellular growth, migration, pseudopodia formation, adhesion, as well as angiostasis. Some chemokine systems have been reported to promote or inhibit tumors by driving immune cells or directly participating in tumor activities. Additionally, the chemokine/receptor systems also play a key role in the pathogenesis of autoimmune diseases by regulating the biological functions of immune cells. Chemokines and their receptors not only regulate the migration of immune cells during inflammation, but also closely related to the formation of lymphoid tissues, maturation and transport of immune cells (Comerford et al., 2013). Altogether, chemokines and their receptors are not only abnormally expressed in tumors, but also closely related to the pathological process of autoimmune diseases (Tripathi et al., 2020). This article reviews the research progress of chemokines and their receptors in autoimmune diseases. The aim is to provide the new insights and find new targets for the treatment of autoimmune diseases.

Biological characteristics of CCL21/CCR7chemokine axis

Construction, source, distribution and expressionof CCL21/CCR7 chemokine axis

CCL21,one of the chemokines of CC family, is a small molecular protein with the function of chemotactic cell migration. CCL21 is one of the only two ligands of CC-Chemokine receptor 7 (CCR7) (the other being CCL19) (Salem et al., 2021). The distribution positions of these two ligands is overlaping and distinct. Both of them are expressed in stromal cells of T-cell-rich lymph node regions, and mainly perform cell migration function (Forster et al., 2008). CCR7 is a GPCR commonly expressed by T-cell subset centra memory cells, thymic T-cells, B cells, mature DCs and other rare cell subsets such as $CD4^{+}CD25^{+}$ splenocytes. CCL21/CCR7 chemokine axis plays a vital role in the homing of lymphocytes to secondary lymphoid tissues. CCL21 have chemotactic effect on a variety of immune cells, including DCs, T/B cells and Natural killer (NK) cells (Stone MJ et al., 2017, Nagarsheth et al., 2017). Like other chemokine receptors, CCR7 is a seven-fold transmembrane G-protein-coupled receptor with seven a-helical transmembrane structures rich in hydrophobic amino acids. The N-terminal is located on the outside of cell, which determines the specificity of ligand binding. CCR7 was expressed on the surface of B cells, naive T cells, memory T cells, activated NK cells and DCs. In addition, the expression of CCR7 could also be detected in various lymphoid tissues (Tutunea-Fatan et al., 2015, Cai et al., 2017).

The chemotactic effect of CCL21 is realized through its receptor CCR7, and the intensity of the effect is determined by the expression level of CCR7 on immune cells (Goto et al., 2017). When CCL21 binds to CCR7 expressed on target cell, it promotes the aggregation of integrin on the cell surface, activates the cytoplasmic conjugated G protein. GDP is replaced by GTP that binds to the a subunit, which forms a free $\beta\gamma$ dimer. $\beta\gamma$ dimer activates enzymes in two main signaling pathways: phospholipase Cβ2, phospholipase Cβ3 (PLCβ2 and Cβ3) and phosphatidylinositol-3-OH kinases (PI3K). Activated by PLC, inositol hexaphosphate on the cell membrane is hydrolyzed to produce inositol triphosphate (IP3) and diglyceride (DAG). IP3 promotes the release of intracellular stored calcium which causes a rapid increase in intracellular calcium ion concentration, thereby inducing rapid $Ca2^{+}$ mobilization of tyrosine kinases (such as MAPK, FAK(including PI3K and JAK, etc.)), PKC, and GTPase phosphorylation (Shi et al., 2015, Mollica et al., 2019, Singh et al., 2017, Hauser et al., 2016). Signal transduction could be stimulated in various ways to change the recombination of

intracellular skeletal proteins, such as actin polymerization. With the extension and retreat of pseudopodia, it can cause the movement of target cells which produces efficient chemotaxis. A considerable body of evidence suppoorts that the high-affinity binding of CCL21 and CCR7 regulates a series of signal transducments that exert a strong chemotactic effect on B cells, T cells, NK cells and DCs (Vanden , 2014).

CCL21/CCR7 chemokine axis was also reported to be highly expressed on the surface of various tumor cells. While the over-expression of CCR7 is correlated with the metastasis of cancer cells from non-small cell lung cancer, breast cancer, squamous cell carcinoma of the head and neck, colorectal cancer, prostate cancer, esophageal squamous cell carcinoma and gastric cancer to lymph nodes (Zhong et al., 2017). The specific binding of CCL21 and CCR7 promotes the migration, proliferation and anti-apoptosis of tumor cells, thus affecting the occurrence and development of tumors. Previous studies have proved that CCL21/CCR7 chemokine axis can not only promote the proliferation and metastasis of tumor cells, but also promote the differentiation and migration of immune cells (Park et al., 2015, Joutoku et al., 2019, Xiong et al., 2017, Chen et al., 2015). CCL21/CCR7 chemokine axis is also widely expressed in non-lymph node tissues such as fibroblasts and smooth muscle nuclear endothelial cells, and is closely related to biological effects such as inflammation, smooth muscle cell proliferation and matrix remodeling. The specific binding of CCL21 and CCR7 can also promote the migration of naive T cells and effector T cells to inflammation and infection sites and promotes the interaction of memory T cells, naive T cells and DCs in lymph nodes, which enhances the effective activation of DCs to antigen-specific T cells. In addition to inducing chemotaxis, CCL21 can also stimulate the proliferation of $CD4^+/CD8^+$ T cells and promote Th1 cell polarization (Luo et al., 2016, Stacer et al., 2016). These studies show that CCL21 can not only chemotactic T cells to the lesion sitee, stimulate the proliferation and differentiation of T cells, but also mediate lymphatic metastasis. Taken together, the CCR7-mediated cell migration underlies a broad range of immune system activities and therefore it is important to understand its mechanism. CCL21/CCR7 chemokine axis may provide a new perspective for clinical treatment (Dong et al., 2017, Xia et al., 2015)(Figure 2).

Biological functions of CCL21/CCR7 chemokine axis

Chemotaxis of CCL21/CCR7chemokine axis

Chemotaxis is the most important function of CCL21/CCR7 chemokine axis in adaptive immunity (Nomiyama et al., 2013). The specific binding of CCL21 to its receptor CCR7 can mediate the homing of DCs and T lymphocytes to the secondary lymphoid tissues, and guide the directional movement and aggregation of T cells in the secondary lymphoid. CCL21/CCR7 chemokine axis can promote the migration of mature DCs from peripheral tissues to regional lymph nodes, and enhance the phagocytosis of mature DCs to different antigens (Ruytinx et al., 2018). DCs are a powerful antigen presenting cell. Immature DCs are highly active, can effectively absorb and process antigens, and locate the processed antigens to non-lymphoid tissues. After exposure to active signals, DCs mature and enter lymphatic tissues. Because CCL21 plays a vital role in the migration and functional maturation of DCs (Ruez et al., 2018, Antonelli et al., 2014). Additionally, CCL21 was highly espressed in lymphatic epithelial cells, which combined with CCR7 to facilitate the entry of mature DCs into lymphatic vessels. Mature DCs entering the lymphatic vessels can be located in the T lymphocyte area under the action of CCL19. Nevertheless, CCL21 has chemotactic effect only on mature DCs and has no chemotactic effect on immature DCs. CCL21 binds to CCR7 expressed on mature DCs, which exerts biological effects by inducing the mobilization of calcium ions in mature DCs (Averbeck et al., 2017). Previous studies have reported that the combination of CCL21 and CCL19 with CCR7 is both different and competitive. Physiological concentration of CCL21 shows chemotactic effect on peripheral blood T cells, but CCL19 does not. This is due to the different affinity of CCL21 and CCL19 with CCR7. In the presence of CCL21, T cells move away from CCL19 and toward CCL21, which reflects the competitive relationship between CCL21 and CCL19. However, both of these ligands can induce the migration of B cells and tumor cells through different signal transduction (Yu et al., 2015).

Cell adhesion and integration capabilities of CCL21/CCR7 chemokine axis

CCL21/CCR7 chemokine axis has the ability to promote cell adhesion and affinity to varying degrees.

Previous studies have found that CCL21/CCR7 chemokine axis can enhance the adhesion properties of glomerular mesangial cells through mediating glycogen synthase kinase 3 (GSK3) and Akt pathways (Li et al., 2011). CCL21/CCR7 chemokine axis can also promote the metabolism, adhesion and anti-apoptotic processes of various tumor cells. In metastatic squamous cell carcinoma of the head and neck, CCL19/CCR7 chemokine axis promotes the migration of tumor cells by regulating β_1 integrin expression. Subsequently, studies have also discovered that integrin $\alpha v\beta 3$, a new signaling molecule, is involved in the process of tumor cell migration through CCL19/CCR7 chemokine axis. These signaling molecules initiate the process of cell adhesion and migration through the interaction with the CCL21/CCR7 chemokine axis (Zhang et al., 2018).

Effect of CCL21/CCR7 chemokine axis on cell growth

CCL21/CCR7 chemokine axis can affect cell proliferation by mediating different signaling pathways. Early studies have shown that CCL21 can affect the biological activity of hematopoietic progenitor cells by inhibiting their proliferation. Additionally, CCL21/CCR7 chemokine axis can also affect the proliferation of glomerular mesangial cells, $CD4^+$ T cells, $CD8^+$T cells and $CD34^+$cells in bone marrow through different signals (Zhang et al., 2016). It was also proved that CCL21/CCR7 chemokine axis inhibits T cell proliferation by slowing down the degradation of cyclin dependent kinase (CDK) inhibitors and down-regulating the activity of CDK1 (Kuwabara et al., 2012). A recent investigations found that CCL21/CCR7 chemokine axis stimulated the proliferation of DCs in bone marrow through phosphorylating NF-B65. These results provide a new entry point for studying the function of CCL21/CCR7 chemokine axis in terms of proliferation (Korbecki et al., 2020, Li et al., 2020).

Other functions of CCL21/CCR7 chemokine axis

In addition to the above functions, CCL21/CCR7 chemokine axis has a certain effects on cell differentiation, survival, endocytosis, migration rate and invasion ability. Studies have suggestted that the binding of CCL21 and CCR7 can significantly affect the internal structure and migration rate of renal DCs and blood T cells (Luo et al., 2020, Legler et al., 2016). And different concentrations of CCL21 produced different chemotactic rates for renal DCs and blood T cells. The functional diversity of CCL21/CCR7 chemokine axis in the immune process also provides the basis for participating in the occurrence and development of autoimmune diseases. With the continuous in-depth study of CCL21/CCR7 chemokine axis, the role of CCL21/CCR7 chemokine axis has attracted more and more attention from domestic and foreign scholars in autoimmune diseases (Rong et al., 2017, Zlotnik et al., 2012, Sokol et al., 2015).

CCL21/CCR7 chemokine axis regulates the pathological process of autoimmune diseases

CCL21/CCR7 chemokine axis and RA

The pathogenesis of RA is related to the abnormal activation of T and B cells. Activated $CD4^+$ T cells differentiate into special effector cells, which plays a essential role in specific immune responses. A large number of activated $CD4^+$ T cells infiltrate the synovial tissues and secrete inflammatory cytokines, causing synovial inflammation in RA. The pathological manifestations of RA are synovitis, vasculitis and pannus formation (Zhao et al., 2019, Klammt et al., 2015). Chemokines are one of the important factors of lymphocyte infiltration in the synovial tissue of RA patients. In the pathogenesis of RA, chemokines regulate the selective recruitment of lymphocytes to the site of inflammation. The synergistic effect of chemokines and their receptors with adhesion molecules determines the invasion and proliferation ability of immune cells (Aldahlawi et al., 2015).

Genome-wide association studies (GWAS) study showed that CCL21 is a susceptibility gene for RA and has a variety of genetic polymorphisms related to RA. Studies have shown that CCR7 is highly expressed in DCs in animal models of collagen-induced arthritis (CIA), nevertheless, administration of CCR7 monoclonal antibody can prevent the occurrence of CIA. Injection of CCR7 monoclonal antibody into the successfully established CIA mouse model can significantly delay the progress of CIA. Moreover, it is reported that immune neutralization or knockout of CCR7 can also reduce the number of $CD3^+$ naive T cells and increase the number of Treg cells, which protects against the joint destruction of CIA mice. The CCL21 knockout

mice had a weakened response to infection. Preliminary researches shown that CCL21 is mainly responsible for the pathological function of CCR7 and increases cell chemotaxis (Aldahlawi et al., 2016). The recruitment of DCs, T/B cells to the specific sites in the lymph nodes is mediated by the actions of CCL21 and CCR7 , which have also been widely linked to RA progression. In plt/plt (lymph node T cell deficiency) mice lacking CCL21 expression, DC and T cells were unable to migrate to draining lymph nodes, and the T cell area tissues were altered. In addition to chemotactic activity, CCL21/CCR7 chemokine axis may also be closely related to the lymphoid follicular tissue in the RA synovium. Expression of CCL21 and CCR7 was higher in RA samples with germinal centers than that RA in samples without germinal centers, indicating that CCL21/CCR7 chemokine axis may contribute to the formation of germinal centers. The expression of CCL21 and CCR7 was significantly higher in RA patients than that in normal controls and patients with osteoarthritis, and CCL21 was found to increase the migration ability of osteoclasts and the activity of bone resorption, which depended on the effect of CCR7. These results suggest that the CCL21/CCR7 chemokine axis may play a crucial role in the occurrence and development of RA by regulating osteoclasts function (Pickens et al., 2011). Immunohistochemical examination found that $CD45RA^+$ naive T cells infiltrated around the vessels of RA patients, and the expression of CCL21 was abnormally increased in the lesions. This suggests that CCL21 may be involved in the process of abnormal aggregation of naive T cells to inflammation sites in RA patients. The co-expression of CCR7 and CD95 in peripheral blood $CD4^+$ T cells of patients with active RA was significantly higher than that of patients inactive RA and normal controls, and this expression level was positively correlated with the level of plasma IL-6 and the disease activity of RA, suggesting $CCR7^+CD95^+CD4^+$ T cells are an important cell subset in the pathogenesis of RA. Meanwhile, it was also found that the expression of transcriptional CCR7 in RA monocytes and macrophages was closely correlated with patient's disease activity score (DAS28). Immunohistochemical and ELISA results showed that CCL21 was also highly expressed in the synovial tissues of RA patients, and these highly expressed CCL21 was produced by fibroblasts and macrophages. CCR7 was also highly expressed in macrophages and the lining and sublining of endothelial cells in the synovial tissue of RA patients. Activation of $CCR7^+$ endothelial cell migration can promote angiogenesis. Pannus formation is one of the important pathological manifestations of RA (Pickens et al., 2012). Studies have shown that CCL21 can induce the migration of human vascular endothelial cells (HMVEC) by combining with CCR7 at the joints of RA, which directly promotes angiogenesis. While antagonism of CCL21 or CCR7 inhibits HMVEC migration and reduce angiogenesis. Altogether, CCL21 indirectly triggers angiogenesis by activating RA fibroblasts and macrophages to secrete pro-angiogenic factors (such as vascular endothelial growth factor, angiopoietin-1 and interleukin-8), providing favorable evidences that CCL21/CCR7 chemokine axis mediates synovial angiogenesis. CCL21 has been reported to promote the proliferation and antigen presentation of bone marrow DCs in RA. $CCR7^+$ DCs and T cells can be recruited into lymphoid and non-lymphoid tissues. These findings indicate that CCL21 stimulates immune cell migration and new blood vessel formation to synergistically accelerate the progression of RA disease (Li et al., 2017).

In addition to regulating immune cell infiltration, studies have shown that CCR7 is highly expressed on the surface of monocytes in the early stages of RA. With the development of RA, the level of CCR7 in RA synovial tissue macrophages was significantly increased. During RA progression, infiltrating macrophages are remodeled into M1-type macrophages, producing IL-6 and IL-23, and polarizing naive T cells into pathogenic Th17 cells. CCL21 promotes M1-driven Th17 cell differentiation, which promotes osteoclast production and initiates the destructive phase of the disease. Interestingly, IL-17 secreted by Th17 cells regulates CCR7 expression in RA fibroblasts and endothelial cells, indicating that there may be a feedback regulation between CCL21-induced Th17 polarization and the reactivity of RA fibroblasts and endothelial cells to CCL21. The combination of CCL21's ability to mediate T cell accumulation, recruit bone marrow cells and activate the transcription of IL-6 and IL-23 can achieve crosstalk between macrophages and T cells, which is a necessary condition for CCL21 to drive Th17 polarization. Ultimately, this inflammatory environment cultured by CCL21 promotes osteoclast production (Van et al., 2020, Jiang et al., 2015). In summary, locally expressed CCL21 causes erosive arthritis by driving M1 and Th17 cells, while angiogenesis and progressive immune cell influx further accelerate the disease course of RA. Nevertheless, blocking the function of CCL21 eliminates monocyte infiltration in the early stage of RA and prevents M1 and Th17 cross-talk, which prevents the

progression of joint inflammation and bone destruction in RA. Studies have shown that CCL21 is also highly expressed in RA synovial fluid, attracting circulating monocytes. CCL21 plays a vital role in the recruitment of $CCR7^+$ monocytes in RA synovial fluid. CCR7 level on monocytes correlated with C-reactive protein (CRP) level. These findings not only indicate that CCL21 actively attracts monocytes to joints, but also that synovial macrophages remain key effector cells in CCL21-induced arthritis mice. These results suggest that CCL21/CCR7 chemokine axis may be a new target for the treatment of RA (Moschovakis et al., 2019).

CCL21/CCR7 Chemokine Axis and SS

The main pathological manifestations of SS are dry eyes and xerostomia caused by the infiltration of lymphocytes into lactear and salivary glands. The pathogenesis of SS is based on the dysfunction and infiltration of lymphocytes, accompanied by the production of auto-antibodies and hypergamma globulinemia. The study found that the expression of CCR7 was detected on the surface of $CD4^+$ and $CD8^+$ T cells in the peripheral blood of patients with SS. Compared with the $CD4^+$ and $CD8^+$T cells in the normal control, the expression of CCR7 was significantly increased in SS. Compared with peripheral blood T cells in SLE patients, $CD4^+$ T cells in SS patients express more CCR7, suggesting that $CCR7^+$ $CD4^+$ T cells may play a key role in the pathogenesis of SS (Argyropoulou et al., 2018). Transwell showed that under the action of CCL21, the migration number of $CD4^+$ T cells in peripheral blood of SS patients was significantly higher than that of the normal control, and the number of $CCR7^+CD4^+$ T cells was significantly higher than that of $CCR7^+CD8^+$ T cells, indicating that CCL21 can significantly improve the migration ability of $CD4^+$ T cells in SS patients, and the chemotaxis ability of CCL21 to $CD4^+$ T cells may be stronger than $CD8^+$ T cells. This is because the combination of CCL21 and CCR7 induces actin aggregation and pseudopodia formation in CCR7-expressing cells and promotes the migration of $CCR7^+$ cells along the ligand concentration gradient, which leads to the increase of CD4+T cell migration in the peripheral blood of SS patients. This may be the mechanism by which the CCL21/CCR7 chemokine axis in SS participates in the migration and infiltration of a large number of lymphocytes, especially $CD4^+$ T cells. Previous studies have been reported that the chemotaxis index of $CD4^+$ T cell in SS patients decreased significantly after anti-CCR7 monoclonal antibody treatment. Correlation analysis showed that there was a significant correlation between the chemotactic index and CCR7 expression on $CD4^+$ T cells in peripheral blood of SS patients. These results further confirm that CCR7 plays a crucial role in the migration of CCL21 chemotactic lymphocytes to specific tissues (Rischmueller et al., 2016). Analysis of $CD4^+$ T cell migration in SS patients and clinical data showed that the chemotactic index of $CD4^+$T cell was positively correlated with disease activity index, but there was no significant correlation with the disease damage index. The results indicated that the increased expression of CCR7 on the surface of $CD4^+$ T cells in the peripheral blood of SS patients promoted the migration and infiltration of $CD4^+$T cells to inflammatory sites. $CCR7^+$ T cells migrate to specific tissues under the action of CCL21, which inhibits cell apoptosis, prolongs cell survival time and participates in the occurrence and development of SS by activating corresponding signal transducting pathways (Barone et al., 2005).

The prominent manifestation of abnormal humoral immunity in SS is hyperglobulinemia, which occurs in more than 90% of patients. The increase of IgG level was the most obvious. Meanwhile, hyperglobulinemia can promote erythrocyte sedimentation rate (ESR), and the levels of ESR and IgG are closely related to the degree of disease activity in SS. Studies have shown that the expression of CCR7 on $CD4^+$T cells in SS patients is positively correlated with the levels of ESR and serum IgG. The expression of CCR7 on $CD4^+$ T cells and the clinical manifestations in SS patients showed that the expression of CCR7 was positively correlated with the disease activity index. These results further demonstrate that the expression of CCR7 on $CD4^+$ T cells is closely related to the disease activity of SS, and it is expected to be a new indicator for monitoring the disease activity of SS (Bombardieri et al., 2012). However, there is no significant correlation between the CCR7 level and the disease injury index, indicating that although CCR7 plays an important role in the pathogenesis of SS, but it is not a key factor in assessing disease severity. Taken together, the abnormally increased expression of CCR7 on $CD4^+$T cells in SS peripheral blood may play a key role in the abnormal accumulation of lymphocytes to the affected glands to form lymphocytic infiltrating foci. Some scholars reported that high expression of CCL21 was detected in the salivary glands of SS patients, and the expression of CCL21 was related to lymphocyte infiltration. The expression of CCL21 was also

correlated with the increased level of ESR, IgG, rheumatoid factor (RF), anti-SSA antibody and anti-SSB antibody. The focal index (FS) and disease activity index of SS were also correlated with the expression of CCL21. CCL21/ CCR7 chemokine axis is expected to be a new indicator for monitoring SS disease activity and predicting prognosis (Lee et al., 2017). However, the expression of CCR7 on $CD4^+$ T cells was not associated with the degree of impairment of salivary and lacrist gland function. This also indicated that the pathological changes of a large number of $CD4^+$ T cell infiltration in SS exocrine glands may be related to the abnormal expression of CCR7 on T lymphocytes of SS patients, which indirectly proved that CCR7 plays an important role in the abnormal aggregation of T cells into diseased tissues. T cells accumulate to the inflammation site, and the apoptosis of infiltrating T cells is inhibited under the regulation of CCR7, leading to the continuous and gradual enhancement of the inflammatory response, which may partly explain the reason why the high expression of CCR7 T cells are closely related to disease activity. In conclusion, the CCL21/CCR7 chemokine axis may be one of the momentous links in the pathogenesis of SS, and blocking the interaction of CCL21-CCR7 may have positive significance for the control of SS disease progression. Therefore, monoclonal antibodies against CCR7 and small molecule compounds that inhibit the binding of CCL21 to CCR7 are highly likely to be new therapeutic approaches for SS in the future (Psianou et al., 2018).

CCL21/CCR7chemokine axis and SLE

The main characteristics of SLE are auto-antibodies formation, multiple organs damage and multiple clinical inflammatory manifestations. Increasing evidences suggest that the infiltration of T cells and white blood cells into inflammatory tissues may play a key role in organ involvement of SLE (Fanouriakis et al., 2021). Chemokines and their receptors can migrate white blood cells to inflammatory sites, initiate T cell immune response and regulate the differential recruitment of Th1 and Th2 cells. At present, many studies have shown that the abnormal expression of CCL21 and CCR7 is closely related to SLE (Odler et al., 2017). The expression of CCL21 in peripheral blood may be a biomarker of lung involvement in SLE patients, as CCL21 and CCR7 have been identified as key participants in the progression of pulmonary fibrosis. CCR7 is expressed on lung fibroblasts and is important for the activation, survival and proliferation of lung fibroblasts (Watanabe et al., 2008). Moreover, It was found that CCL21 could not induce the migration of $CD4^+$ and $CD8^+$ T cells in normal body, could induce moderate migration of $CD4^+$ and $CD8^+$ T cells in inactive SLE patients, and could induce strong chemotactic movement of $CD8^+$ T cells in active SLE patients. The expression of CCR7 on $CD8^+$ T cells in the peripheral blood of active SLE patients was significantly higher than that of inactive SLE patients and normal control. The level of CCR7 mRNA on $CD8^+$ T cells of active SLE patients was significantly increased, and was significantly positively correlated with SLE disease activity index score (Wieczorek et al., 2010).

The number of $CD4^+CD95^+CCR7^+$cells in active and inactive SLE patients was significantly higher than that in normal control, the number of $CD4^+CD95^+CCR7^-$cells in active SLE patients was higher than that in the inactive SLE patients and normal control, the number of $CD4^+CD95^-CCR7^+$cells in SLE patients was lower than that in normal control, indicating that $CD4^+CD95^+CCR7^+$cells were associated with auto-antibody reactions, while $CD4^+CD95^+CCR7^-$cells were closely related to were inflammatory response. However, CCR7 monoclonal antibody can completely block the chemotaxis of $CD8^+$ T cells induced by CCL21 in active SLE patients, suggesting that high expression of CCR7 on $CD8^+$ T cells may be related to SLE activity. In summary, these results demonstrate thatCCL21/CCR7 chemokine axis plays a crucial role in the pathogenesis of SLE, and can provide an important reference for monitoring the disease activity of SLE (Xu et al., 2012).

CCL21/CCR7chemokine axis andpolymyositis

The self-invasive of $CD8^+$ T cells is the basis of polymyositis (PM), and the main clinical manifestations are muscle damage in the proximal extremities. The number of activated T cells in the peripheral blood of PM patients increased significantly and moved to the local area of myositis (Cerezo et al., 2020). A large number of infiltrating cells, mainly $CD8^+$ cytotoxic T lymphocytes and macrophages, were found in myocytes and subintima of PM. $CD4^+$T cells were found in the perineal and perivascular regions. Immunohistochemistry

and RT-PCR tests showed that the expression of CCL21 was found in the muscles of PM, and CCR7 expression was detected in infiltrating monocytes in the endomysium of PM.

Around the non-necrotic muscle tracts, more than half of $CD8^+$ T cells expressed CCR7, and the phenotype of these cells was mostly $CD45RO^+CCR7^+CD^+8$ T cells. A few monocytes, muscle fibers and vascular endothelium showed the immune activity of CCL21. These results suggested that the interaction between CCL21 and CCR7 may play a vital role in the pathogenesis of PM (Kuwabara et al., 2009). Since CCL21 mRNA is only weakly expressed in normal muscle tissues, while CCR7 mRNA is not expressed in normal muscle tissues, suggesting that the expression of CCL21 and CCR7 may be pathologically up-regulated in PM. Double immunostaining showed that a large number of $CD8^+$ T cells in the endomysium expressed CCR7, and $CCR7^+$memory T cells may infiltrate the endomysium of PM. Studies have found that $CCR7^+$ memory T cells closely surrounded the muscle fibers expressing MHC I class. There could be multiple explanations for these findings. The first possibility is that CCR7 may be expressed on auto-invasive $CD8^+$ T cells in PM. The second possibility is that $CCR7^+$ memory T cells may respond to the antigens presented by muscle fibers, or some $CCR7^+$ T cells may be naive T cells that are sensitized for the first time at the lesion (Lv et al., 2018).

Studies have found that the immunohistochemical expression of CCL21 in inclusion body myositis and dermatomyositis is different from that in PM, which may be a different pathological mechanism of the disease. Low-intensity expression of CCL21 and CCR7 was also detected by immunohistochemistry or RT-PCR in control diseases without inflammation (Rider et al., 2016). Like other chemokine systems, CCL21/CCR7 chemokine axis is multifunctional and may not only participate in immune cell recruitment, but may also participate in tissue homeostasis. Further study of the effect of chemokines on muscle fibers may help us understand the pathogenesis of PM and develop specific immunomodulatory therapies (Chen et al., 2015). A series of research results have indicated that the CCL21/CCR7 chemokine axis plays an important role in the pathogenesis of PM. These findings, together with our data on the up-regulation of CCL21/CCR7 chemokine axis, strongly suggest that CCL21/CCR7 chemokine axis may play an important role in monocytes recruitment and muscle tissue damage in PM (De et al., 2009, Miller et al., 2013).

CCL21/CCR7 chemokine axis and other diseases

In addition, CCL21/CCR7 chemokine axis are is closely related to autoimmune diseases such as SSc, vasculitis and osteoarthritis (OA) (Ciccia et al., 2017). Studies have found that CCL21/CCR7 chemokine axis can affect the connective tissue immune disorders of heart, lung, kidney and digestive tract in SSc. In early studies, the differences between children and adults with SSc showed that the number of resting regulatory T cells was decreased and the number of $CD45RA^+CD4^+$T cells was increased in children compared with adults, but $CD45RA^+CD4^+$T cells were characterized by high expression of CCR7. This change in T cell expression is conducive to initiating the activation of $CCR7^+CD4^+$ effector T cells in adolescent SSc (Gonzalez et al., 2019). In vasculitis, CCR7 has attracted much attention as a marker of B cells and memory T cells differentiation. Moreover, CCR7 was also found to be expressed in synovial tissues and synovial fibroblasts, which provided the basis for CCCL21/CCR7 chemokine axis and local lesions (Hoffmann-Vold et al., 2018). OA is also a major category of autoimmune diseases, and immune dysfunction plays a crucial role in the pathogenesis of OA. Therefore, the role of CCCL21/CCR7 chemokine axis in OA should not be ignored (Favero et al., 2019)(Figure 3).

CCL21/CCR7 chemokine axis participates in the occurrence and development of autoimmune diseases by regulating related signal pathways

CCL21/CCR7 chemokine axis participates in the pathological process of RA through regulating the PI3K signaling pathway

Angiogenesis is one of the main pathological features of RA, which depends on the activation, migration and proliferation of endothelial cells. Accordingly, inhibition of angiogenesis may provide a new therapeutic approach for RA (MacDonald et al., 2018). Studies have found that CCL21 and CCR7 were co-expressed on the endothelial cells of synovial tissue. CCL21 can induce fibroblasts, macrophages and synovial lining

cells to produce pro-angiogenic factors in RA. Altogether, the expression of CCL21 and CCR7 in RA blood vessels was linearly correlated, suggesting that the CCCL21/CCR7 chemokine axis plays a vital role in RA angiogenesis. Some studies have also shown that the combination of CCL21 and CCR7 can induce HMVECs migration in the joints of RA patients, but CCL19 has no effect on HMVECs migration. It may be that CCL21 and CCL19 mediate different signal pathways (Hayashi et al., 2009).

CCL21 was found to promote neovascularization at detectable concentrations in RA joints. However, CCL21 promotes angiogenesis by recruiting the accumulation of endothelial cells and endothelial progenitor cells in RA synovial fluid and tissues. Further studies have revealed that the binding of CCL21 to CCR7 regulates HMVEC migration and angiogenesis by mediating the activation of PI3K pathway. In vitro studies found that ERK, AKT1 and PI3K were the first to be phosphorylated by CCL21 in HMVEC treated with CCL21 for different durations, while JNK was activated last. However, blocking the ERK and JNK pathways had no effect on the chemotaxis of CCL21-induced HMVEC. Blocking the PI3K and AKT1 pathways can reduce the chemotaxis of CCL21 (Jiang et al., 2008, Van et al., 2020). Blocking PI3K pathway can also reduce CCL21-mediated angiogenesis by 35-40%, while blocking ERK and JNK pathways had no effect on angiogenesis. These results indicate that CCL21 may induce HMVEC chemotaxis through mediating PI3K and AKT1 pathways, and blocking PI3K pathway can reduce the regulatory effect of CCL21 on HMVEC chemotaxis and angiogenesis. In conclusion, blocking PI3K pathway can inhibit endothelial cells migration and angiogenesis induced by the CCCL21/CCR7 chemokine axis in RA. These findings suggest that inhibition of angiogenesis may provide a new idea for the treatment of RA, and CCL21/CCR7 chemokine axis may also be a new target for the treatment of RA (Cuesta-Mateos et al., 2010, Calabresi et al., 2018)(Figure 4).

CCL21/CCR7 chemokine axis participates in the pathological process of SS by regulating the JNK and p38MAPK signaling pathways

The migration and continuous infiltration of lymphocytes are closely related to the destruction of SS exocrine glands. A large number of lymphocytes are focally infiltrated around the ducts of exocrine glands, and the infiltrating lymphocytes are mainly T cells (Aiyegbusi et al., 2021). Studies have found that CCR7 is highly expressed on the surface of $CD4^+$ and $CD8^+$ T cells in the peripheral blood of SS patients, and the chemotactic effect of CCL21 on $CD4^+$ T cells is stronger than that of $CD8^+$ T cells, indicating that the pathological changes of a large number of $CD4^+$ T cell infiltration may be related to the abnormal expression of CCL21 and CCR7 in SS. This suggests that CCL21/CCR7 chemokine axis may play an important role in the pathogenesis of SS and participate in the immune response of SS. It was reported that the migration of $CD4^+$ T cells in the peripheral blood of SS was significantly increased under the action of CCL21, indicating that CCL21 can significantly increase the migration of $CD4^+$ T cells in SS (Mircheff et al., 2019). As shown above, the expression of CCR7 on $CD4^+$ T cells in peripheral blood of SS patients was significantly increased, which was due to the combination of CCL21 and CCR7 to induces actin agglutination and pseudopodia formation in CCR7-expressing cells, promoting the directed transfer of $CCR7^+$ cells along the CCL21 concentration gradient, leading to an increase in the migration of $CD4^+$ T cells. This may be the mechanism of migration and infiltration of $CD4^+$ T cells in SS. However, after treatment with CCR7 monoclonal antibody, the chemotactic index of $CD4^+$ T cells was significantly reduced, and there was a significant positive correlation between the chemotactic index of $CD4^+$ T cells and the expression of CCR7 in SS patients. The high expression of CCL21 was detected in the salivary glands of SS patients, and the expression of CCL21 was correlated with lymphocyte infiltration, suggesting that there may be a positive feedback regulation mechanism in the pathogenesis of SS. That is, under the action of the CCL21/CCR7 chemokine axis, a small amount of early lymphocytes migrate and infiltrate to the salivary gland lobules, while the migrated lymphocytes are activated and continue to express CCL21 and CCR7, which greatly increases the number of infiltrated lymphocytes, thereby promoting the development of SS (Tandon et al., 2017, Bunting et al., 2013, Carubbi et al., 2014).

Previous studies reported that $CD4^+$ T cells in different groups were stimulated by CCL21 in vitro, and SP600125 and SB203580, the specific blockers of JNK and p38MAPK signaling pathways, were used to intervene on $CD4^+$ T cells in peripheral blood of SS patients. It was found that under the condition of

no stimulating factors, compared with the normal group, p-JNK and p-P38MAPK were highly expressed in SS group, suggesting that there were abnormally active p-JNK and p-P38MAPK signal transduction in $CD4^+$T cells of SS patients, which may be related to the pre-activation state of $CD4^+$ T cells or the presence of certain cytokines in plasma that can cause their activation in SS patients. These two signaling pathways may be involved in mediating the occurrence and development of SS. In $CD4^+$ T cells stimulated by CCL21, the expression of p-JNK and p-P38MAPK was significantly increased in SS group compared with normal control group, suggesting that CCL21/CCR7 chemokine axis can can rapidly activate JNK and p38MAPK. This effect is more obvious in SS patients. After adding CCR7 monoclonal antibody to block the interaction between CCL21 and CCR7, the expression of p-JNK and p-P38MAPK on $CD4^+$ T cells in pSS patients was significantly decreased. These results further demonstrated that the activities of JNK and p38MAPK were related to the regulation of CCL21/CCR7 chemokine axis. The chemotactic index of $CD4^+$ T cells was significantly decreased in JNK pathway blocking group and p38MAPK pathway blocking group of SS, suggesting that blocking these two pathways can significantly inhibit the chemotactic effect of CCL21/CCR7 chemokine axis on the $CD4^+$ T cell in SS patients. These results suggest that JNK and p38MAPK pathways may mediate lymphocyte migration induced by CCL21/CCR7 chemokine axis in SS. Moreover, it was also found that the chemotactic index of p38MAPK pathway blocking group was lower than that of JNK pathway blocking group in SS, suggesting that the inhibitory effect of p38MAPK blocker on CCL21/CCR7-induced lymphocytes migration was stronger than that of JNK blocker in SS. This may be due to "cross talk" between JNK and p38MAPK pathways. In conclusion, CCL21/CCR7 chemokine axis, as an extracellular signaling molecule, can activate JNK and p38MAPK pathways in peripheral blood lymphocytes, and blocking the activity of two pathways can significantly reduce the migration of $CD4^+$ T cells in SS, suggesting that JNK and p38MAPK pathways play a crucial role in the signaling transmission process of CCL21/CCR7 chemotactic $CD4^+$ T cells, and opens up new ideas for controlling the occurrence and development of SS (Mircheff et al., 2015)(Figure 4).

""Λ21/""P7 ςηεμοκινε αξις παρτιςιπατες ιν τηε πατηολογιςαλ προςεσς οφ αστημα τηρουγη ρεγυλατινγ ΝΦ-κΒ σιγναλινγ πατηωαψ

The pathogenesis of asthma is very complex. Chemokines and their receptors, inflammatory cytokines and inflammatory signaling pathways play different important roles in different pathological stages of asthma (Alwarith et al., 2020). The combination of CCL21 and CCR7 regulates the activity of DCs or macrophages, presenting antigens and activating naive T cells. T cells secrete a large number of inflammatory cytokines when regulated by DCs, which directly or indirectly induce or aggravate the inflammatory immune response in asthma (Feng et al., 2021). Studies have also found that the number of $CCR7^+$ T cells in the BALF of allergic asthma patients is significantly increased, and the expression of CCR7 is closely related to the pathological process of allergic asthma. Therefore, inhibiting the activity of CCL21 and CCR7 may help reduce the inflammatory response in asthma. The level of CCL21 was also significantly increased in BALF of asthma model mice, and the expression of CCR7 mRNA and CCR7 in lung tissue was significantly increased, indicating that CCL21/CCR7 chemokine axis may be one of the important factors of airway inflammation in asthma (Qi et al., 2018).

NF-κB plays a vital role in the regulation of inflammation and immune response. P65 and P50 are important members of the NF-κB family, which binds to their inhibitor protein IκB in inactive form in resting cells. Chemokines, cytokines and oxidative stress can activate and phosphorylate them, thus activating transcription and mediating inflammation response (Liu et al., 2016, Wei et al., 20168). The studies found that the expression of p-IκB and p-P65 in the lung tissue of mice in asthma model group was significantly increased, while the expression of p-IκB and p-P65 in the lung tissue of mice in asthma model group was significantly down-regulated by blocking NF-κB pathway. In addition, reports have shown that the interaction between CCL21/CCR7 and NF-κB can activate IκB, leading to NF-κB entry into the nucleus and enhancing its DNA-binding ability. Stimulation of DCs by CCL21 also leads to the activation of NF-κB, which mediates inflammation response. Taken together, these results suggest that CCL21/CCR7 chemokine axis may participate in the pathological process of asthma by regulating the NF-κB pathway. CCL21/CCR7 chemokine axis may also provide a new research direction for asthma prevention and treatment (Lou et al., 2021, Zhang

et al., 2018)(Figure 4).

CCL21/CCR7 chemokine axis participates in the pathological process of ankylosing spondylitis by regulating Smads/Runx2 and Smads/osterix signaling Pathways

The main pathological features of ankylosing spondylitis (AS) are tendon attachment point lesions and ligament ossification. The blood macrophages of AS patients can produce high level of IL-23, and IL-23 plays a great role in promoting the systemic inflammation of AS. IL-23 can attachment point inflammation symptoms in Spondyloarthropathy by acting on T cells in AS attachment point. Additionally, IL-23 over-expression can cause infiltration of macrophages, T cells and neutrophils at the attachment point (Voruganti et al., 2020, Yu et al., 2020). Studies found that the mRNA expression of CCL21 was significantly increased in the ligament tissue of AS, suggesting that the macrophages and Th cells in the blood of AS as well as the macrophages and ligament fibroblasts in the tissue of the attachment point may be the source of CCL21. Secondly, the binding of CCL21 and CCR7 mediated the migration of synovial vascular endothelial cells and angiogenesis in RA, and the disorder of angiogenesis and heterotopic ossification are manifestations of AS attachment point lesions. IHC results showed that CCL21 and CCR7 were mainly expressed in the capillary wall of AS, and CCR7 was also highly expressed in ligament fibroblasts, suggesting that CCL21 might migrate to ligament tissue through capillaries. In addition, the capillary density in the ligament tissue of AS is much higher than that in the normal tissue, and combined with the function of CCL21 to promote angiogenesis, it is speculated that the high expression of CCL21 in the ligament tissue may be a vitalfactor that promotes the disorder of vascular formation in AS ligament. Taken together, these results suggest that CCL21/CCR7 chemokine axis may be involved in AS attachment point lesions and accelerate the process of angiogenesis disorder and heterotopic ossification (Sulicka et al., 2017).

Alkaline phosphatase (ALP) and integrin-binding salivary protein (IBSP) are early markers of ossification. Studies have found that different concentrations of CCL21 have different effects on ALP transcription level, but no significant change in IBSP expression. Osteocalcin (OCN), as a mid-stage marker of osteogenesis, was significantly up-regulated after 48h of treatment with CCL21, and the level of osteocalcin in the culture medium supernatant was also significantly increased on the sixth day of treatment. Meanwhile, the expression of Runx2 and osterix, the upstream regulators of ALP and OCN, was also increased significantly. These results suggested that CCL21 might promote osteogenic activity by regulating Runx2 and osterix expression. Additionally, studies have found that CCL21 can stimulate the synovial fibroblasts of RA and OA to secrete vascular endothelial grown factor (VEGF), and similar effects have been found in the ligament fibroblasts of AS. VEGF plays an momentous role in the ossification process and is also regulated by osterix. These resulte suggested that CCL21 might contribute to the occurrence of ossification through regulating Runx2 and osterix signaling pathway. At the same time, it was found that CCL21 level in serum and ligament tissues was increased in AS patients, and CCL21 could promote the ossification ability of ligament fibroblasts, which provided a basis for further studies on the roles of CCL21/CCR7 chemokine axis in AS (Qin et al., 2014)(Figure 4).

Conclusion and future perspective

In summary, the specific combination of CCL21 and CCR7 significantly promotes the activity of immune cells, induces immune cell homing and promotes immune cell migration and angiogenesis during the process of immunity and inflammation. The migration of immune cells is a crucial part of the autoimmune response. Accordingly, the pathological role of CCL21 and CCR7 has attracted more and more attention from domestic and foreign scholars in autoimmune diseases (Rizeq et al., 2020)(Figure 5). With the in-depth exploration of CCL21/CCR7 chemokine axis, it was found that CCL21 and CCR7 regulate the expression of downstream proteins through the activation of intracellular signaling pathways to promote the migration of immune cells to inflammatory and infectious sites, which participates in the occurrence and development of autoimmune diseases (McHugh, 2019). Therefore, understanding the signaling transduction mechanism of CCL21 and CCR7 in autoimmune diseases is essential for the discovery of potential diagnostic biomarkers and therapeutic targets, providing a deep foundation and new insights for the development of new drugs. Therefore, it is of great significance to elucidate the important role of CCL21/CCR7 chemokine axis in inflammatory response

for reveal the pathological mechanism of autoimmune diseases and discovering new biomarkers and new drug targets.

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Conflict of interest

The authors have declared no conflicts of interest.

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Figure legends

Figure 1: The ligand-binding patterns of the seven-transmembrane domain G-protein-coupled chemokine receptors.

Figure 2: Biological functions of CCL21/CCR7 chemokine axis.

Figure 3: Regulation of CCL21/CCR7 chemokine axis on immune cells. CCL21/CCR7 chemokine axis has been found to regulate the functions and activities of immune cells, to balance immune cell subsets, which could further reduce inflammation and tissue damage in autoimmune diseases.

Figure 4: Effects of CCL21/CCR7 chemokine axis on MAPKs signaling pathway, PI3K/AKT signaling pathway and Smads signaling pathway in autoimmune diseases. MAPKs, PI3K/Akt and Smads signaling mediated by CCL21/CCR7 chemokine axis participates in the occurrence and development of autoimmune diseases.

F igure 5: Effect of CCL21/CCR7 chemokine axis on autoimmune diseases-related indicators. CCL21/CCR7 chemokine axis is widely involved in the pathological process of autoimmune diseases, including RA, SS, SLE, PM, AS and so on, through regulating inflammatory cytokines and disease-related indicators, and mediating signaling pathways.

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