The Roles Of Sphingosine-1-Phosphate (S1p) On Arthritis: Review Article

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ABSTRACT

Arthritis is a pathological condition that results in degeneration of the joints. RA and OA are the most common types of arthritis. RA is a chronic joint inflammation caused by the immune system's self-attack on tissues. By contrast, OA is chronic joint inflammation caused by cartilage breakdown. Both illnesses cause joint discomfort, stiffness, and edema. One genetic factor in arthritis is sphingosine-1-phosphate (S1P). S1P regulates bone homeostasis and growth using 5 receptors: 1, 2, 3, 4, and 5. Thus, this literature review intends to investigate the impact of S1P on arthritis. Methods: The eligibility criteria comprised cross-sectional studies that were published in English until January 2024 and exclusively addressed the role of S1P in arthritis. Results and discussion: From 396 publications, 17 relevant articles were located, and 6 were chosen for the review.

The S1P/S1P2 signaling pathway releases osteoclasts to degrade cartilage in osteoarthritis. S1P also promotes bone growth by differentiating osteoblasts and forming blood vessels in the bone marrow. The miR-25 rs41274221 polymorphism may reduce osteoporosis risk. IL-6 is also produced by osteoblasts with S1P. Osteoarthritis is associated with elevated blood S1P and MMP-3 levels. Cyclic strain and inflammation increase Sphk1 upregulation and S1P release, suggesting a role in osteoarthritis. In conclusion, the expression of S1P by osteoclasts, osteoblasts, chondrocytes, and tenocytes is believed to play a crucial role in regulating cell migration and the production of cytokines or chemokines throughout the process of bone formation. Focusing on the S1P pathway may help treat bone and joint diseases.of 2020.

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Introduction

Arthritis and joint pain impact a significant number of elderly individuals, leading to decreased physical activity, heightened disability, and elevated incidence of sleep disturbances, anxiety, and despair. Presently, the primary focus of therapy for arthritis is on addressing the inflammatory cytokines, effector molecules, and oxidative stress that contribute to the condition. These medicines aim to provide temporary pain relief (1). Rheumatoid arthritis (RA) is the predominant autoimmune rheumatic disease characterized by persistent inflammation that gradually worsens and leads to irreversible joint destruction (2). The precise cause of RA is still uncertain, but it is understood that the development of this disease is a result of the interplay of genetic (internal) and environmental (external) variables. This connection triggers an immune process that is believed to have initiated several years before to the manifestation of clinical symptoms (3). Osteoarthritis (OA) is a degenerative joint disease that primarily affects the cartilage in joint structures such as capsules, ligaments, menisci, periarticular muscle, and synovium. Osteoarthritis is not only the most prevalent joint disease, but also a leading cause of disability in individuals over the age of 65. It is often accompanied by other medical diseases, higher mortality rates, and reduced quality of life. The primary risk factor for osteoarthritis is the process of aging (4).

Several genetic variables are believed to contribute to the development of RA, including HLA-DR4, HLA-DRB1, PTPN22 (5), PADI4, STAT4, TRAF1-C5, TNFAIP3, and Sphingosine-1-phosphate (S1P). Additional environmental factors that are believed to contribute include illness, smoking, and various other issues (6). In the recent years, several studies have emphasized the significance of sphingosine kinase (SphK)/ sphingosine-1-phosphate (S1P) metabolic pathway in numerous diseases such as RA, spondyloarthritis, OA, osteoporosis, and cancer-derived bone metastasis or calcification disorders like vascular calcification (7).

S1P plays a crucial role in regulating bone homeostasis and development. Multiple cells in bone possess the capability to produce, release, and react to S1P via its 5 receptors, S1PR1–5, and influence different cellular activities in bone balance (6). Prior research has demonstrated a direct correlation between levels of S1P in individuals with osteoporosis and the occurrence of fractures, low bone mineral density, indicators of bone resorption, and inadequate response to bisphosphonates (8).S1P plays a potential role in angiogenesis, cancer, and autoimmune diseases. S1P stimulated the transcriptional activity of S1PR1,3, leading to the upregulation of cyclooxygenase2 (COX2) expression and generation of prostaglandin E2 (PGE2). S1P recruited and activated PTX-sensitive Gi or -insensitive Gq protein-coupled S1P receptors. This activation subsequently increased the PKCα-dependent phosphorylation of p42/p44 MAPK, p38 MAPK, and janus kinase (JNK)1/2. As a result, the activating transcription factor NF-κB was activated (9). Cytokine production stimulates the expression of matrix metalloproteinases (MMPs) and triggers the activation of osteoclasts, leading to the breakdown of bone and injury to soft tissues. Osteoclasts also produce S1P, which promotes the movement of osteoblasts and mesenchymal stem cells (MSC) (10). Thus, S1P produced by osteoclasts can serve as a chemotactic signal to attract osteoblasts to sites of bone resorption, initiating the initial stages of bone regeneration in injured areas (11). S1P plays a significant role in arthritis and bone health, which has piqued the curiosity to investigate its impact on arthritis. Thus, this study aimed to enhance the current understanding of the studies on S1P in different forms of arthritis and explore the potential of employing S1P and the S1P receptor for future arthritis treatments.

Methods

The data search process involves the collection of secondary data, which is gained from the findings of earlier researchers. The secondary data sources acquired consisted of selected papers or journals, with data extracted from publications available on Science Direct, Pubmed, and Google Scholar. This systematic review, done in April 2024, adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.

Searching for data in research journals involves utilizing certain keywords to facilitate the search process and identify the most relevant articles or publications. The research focuses on the terms sphingosine-1-phosphate AND arthritis AND chondrocyte AND osteoclast. The term modification used in the searching is : sphingosine-1-phosphate OR S1P AND arthritis OR inflammatory disease OR derivation OR rheumatic OR creacky OR rheumatoid OR arthritis OR rheumatism OR arthropic OR osteogout OR gouty urspondyl OR rheumatoid degenerative joint disease AND chondrocyte AND osteoclast OR bone cell.

Inclusions and Exclusions Criteria

The inclusion criteria in searching for research data used are:

1. The search for research data is limited to research articles published within the timeframe of the last 5 years (2019-2024).
2. Research publications are available full text for access.
3. An article analyzing the impact of S1P on arthritis.

The criteria for excluding research data throughout the search process are as follows:

1. Articles from non-research journals.
2. Research articles are either presented in abstract format or are inaccessible.
3. Explore research publications written in languages other than English.
4. Explore research articles that lack comparable elements related to S1P and athritis.

Results

The auathors discovered literature on Pubmed, Google Scholar, and Science Direct. The literature gathering approach involved the careful selection of publications or articles from a total of 396 to a final selection of 6 international journals (Figure 1) after undergoing a rigorous process of inclusion and exclusion. The literature search methods were conducted using indexed electronic resources. Table 1 provides a summary of the findings from the review of six journals.

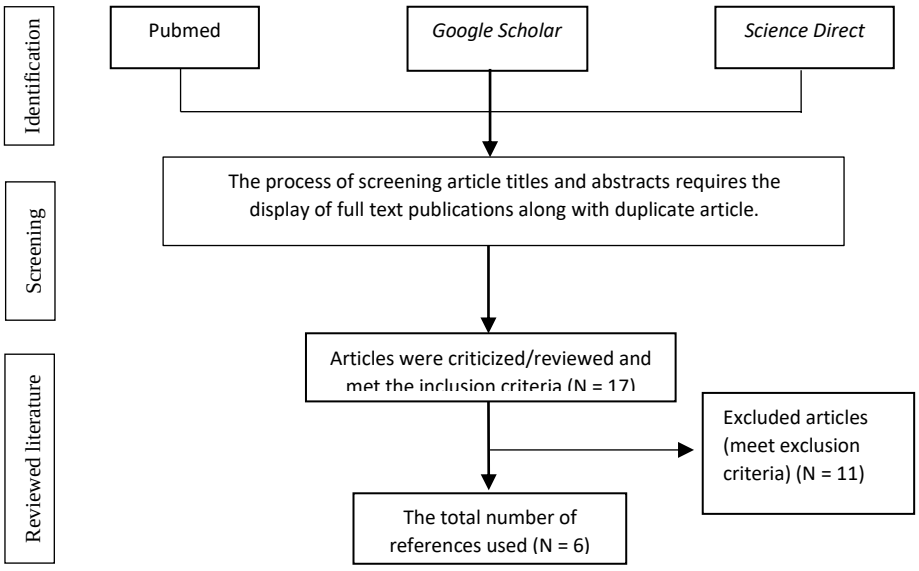

Figure 1. Flowchart depicting the PRISMA method for selecting articles.

Table 1. Literature Search Results

No	References	Purpose	Methods	Results
1.	Cherifi, et. al., (2021) (12)	Observed the function of the osteoclast secretome and the lipid mediator S1P in regulating chondrocyte metabolism in OA.	The murine osteoclast secretome's effects on chondrocyte metabolism were examined in SphK1LysMCre and wild-type (WT) mice. Mmp gene and protein expression in chondrocytes and explants was evaluated by RT-qPCR and Western blots. Analyses of OA score and immunohistochemistry were performed on SphK1LysMCre or WT mice treated with JTE013 or sphingomab.	The absence of S1P in myeloid cells and the targeted neutralization of S1P in the affected area effectively relieves osteoarthritis in mice. The data presented here establish S1P as a viable therapeutic target for OA.
2.	Yang et. al., (2023) (13)	Conducted an in vitro and clinical study to examine the association between the miR-25 rs41274221 polymorphism with osteoporosis in postmenopausal women.	To study the miR-25 rs41274221 polymorphism in osteoporosis, a total of 300 patients and 320 healthy controls underwent genotyping using the polymerase chain reaction (PCR) method. This study also examined how the miR-25 rs41274221 polymorphism affected miR-25 and its target gene S1PR1 using luciferase reporter gene, qRT-PCR, and Western blot. Dual-luciferase activity and TargetScan database predictions imply miR-25 targets S1PR1. S1PR1 mRNA and protein are downregulated by MiR-25.	The single nucleotide polymorphism (SNP) rs41274221 in miR-25 may operate as a protective factor in the development of osteoporosis in postmenopausal women by interfering with the modulation target of S1PR1. Nevertheless, because of the constraints imposed by the locality and the limited number of participants, we are of the opinion that additional study with bigger populations is necessary to confirm the correlation and evaluate the functions of this polymorphism.
3.	Hu et. al., (2020) (14)	Examined alterations in the levels and clinical relevance of MMP-3 and S1P in individuals diagnosed with OA.	Thirty-six early-stage OA patients and thirty-two late-stage OA patients were recruited, along with 72 healthy volunteers of the same age undergoing physical examination as a control group. Different S1P and MMP-3 levels in the three groups were also evaluated by ELISA to determine the association.	The levels of S1P and MMP-3 in the serum of patients with OA exhibited an elevation. Furthermore, an increase in S1P levels leads to a subsequent increase in MMP-3 levels, ultimately contributing to the development of OA. This effect is particularly pronounced in patients in the advanced stages of the disease.
4.	Hu et. al., (2020) (15)	Investigated the impact of S1P on IL-6 production in osteoblasts. The data obtained from the gene expression omnibus database clearly indicate that patients with RA have significantly elevated levels of IL-6 compared to individuals with osteoarthritis.	This study conducted cell culture of osteoblast-like cell lines, MG-63 and MC3T3-E1. The proteins phosphorylase (p)-PI3K, p-ERK, p-p65, PI3K, MEK, p-MEK, ERK, p65, and β-actin were analyzed by western blot analysis, PCR, and ELISA experiment.	S1P enhances the synthesis of IL-6 and promotes an inflammatory response in osteoblasts through the activation of the PI3K, MEK/ERK, and NF-κB signaling pathways. S1P is a promising new target for treatment in RA.
5	Jamal, et. al., (2019) (3)	Analyzed the production of sphingosine 1-phosphate induced by cytokines and stretching in entesis. Cells may facilitate abnormal ossification in spondyloarthritis.	Spondyloarthritis patients provided synovial fluid for this investigation. Cell culture was followed by histological analysis. Both PCR and Western blot were used to evaluate the cells.	S1P serves as a therapeutic target for treating spondyloarthritis. S1P metabolism is involved in the development of bone-related disorders and is targeted in the treatment of Spondyloarthritis.

6	Wille et. al., (2024) (16)	Discovered a new mechanism, mediated by S1P, that connects osteoblasts to the specialized bone vasculature, promoting bone growth.	The in vivo analysis utilized male C57Bl/6J mice, aged 16-20 weeks, that were genetically modified to have Sgpl1flox/flox and actb-CreERT2 genes activated. In order to remove Sgpl1, tamoxifen injections of 40 mg/kg/d were administered for a duration of 5 days, following the previously established protocol. The involvement of S1P receptors was investigated by utilizing S1pr3tm1Rlp mice with the S1P3−/− genotype, along with S1P3+/+ controls that were genetically matched. The in vitro analysis employed primary mouse brain microvascular endothelial cells (BMECs) that were obtained from C57BL/6 mice. Immunohistochemistry, flow cytometry, enzyme-linked immunosorbent assay (ELISA), and reverse transcription polymerase chain reaction (RT-PCR).	S1P-dependent bone regeneration involves several separate positive feedback loops between osteoblasts and the bone vasculature. The identification of this hitherto unknown component of osteoanabolic S1P signaling could have substantial implications for the maintenance of proper bone equilibrium and for comprehending conditions that affect the bone microvasculature, such as age-related osteopenia and post-traumatic bone regeneration.

Table 2. Review of the role of S1P in arthritis

No.	Type of the disease/defect	Role of S1P	Related biomarker	Citation
1	Osteopenia associated with aging and bone regeneration after trauma	S1P	VEGF	(16)
2	Osteoarthritis	S1P2, SphK1	MMP3, MMP13	(12)
3	Osteoarthritis	S1P	MMP3	(14)
4	Osteoporosis	S1P1	miR- 25 rs41274221	(13)
5	Rheumatoid arthritis	S1P	PI3K, MEK/ERK, NF-κB	(15)
6	Spondyloarhritis	S1P, SphK1	TNF-α and IL-17	(3)

Discussion

Arthritis is characterized by the presence of acute or chronic inflammation in the joints (1). Arthritis can arise from a number of symptoms, such as pain, stiffness, limited range of motion, and joint deformity. Arthritis encompasses various forms, each requiring specific therapies. The history and physical examination are crucial for identifying the specific form of arthritis, although additional laboratory tests and imaging may be required to confirm the diagnosis (12). The cause of arthritis differs based on the specific form of arthritis. Arthritis is frequently linked to other disorders such as inflammatory bowel disease, psoriasis, celiac disease, Sjogren's syndrome, systemic sclerosis, dermatomyositis, mixed connective tissue disease, and various others (16).

The review findings indicate that S1P analysis is conducted on several forms of arthritis and bone diseases, including OA, RA, spondyloarthritis, osteoporosis, age-related osteopenia, and posttraumatic bone regeneration (Table 2). The primary etiological variables in OA include advancing age, female sex, joint injury, and obesity. Various genetic variables have been identified, including mutations in the genes responsible for collagen types II, IV, V, and VI (7). Osteoarthritis is a chronic and advancing condition marked by the wearing down of joint cartilage and the uneven growth of new bone on the joint surfaces. The first symptom that arises is pain, which is then accompanied by a reduction in the range of motion in the joints. This can lead to impairment and hinder one's ability to do daily activities (17). RA is a condition characterized by the body's immune system incorrectly attacking its own tissues, leading to widespread inflammation throughout the body. The interplay of multiple hereditary genes and environmental factors, such as smoking, leads to the activation and impairment of the immune

system, resulting in inflammation in RA. RA commonly occurs in patients with different autoimmune disorders and is a prevalent clinical characteristic in individuals with systemic lupus erythematosus (18).

RA is characterized by persistent inflammation of the synovial membrane and progressive deterioration of cartilage in the joints (1). Chronic inflammation in RA is controlled by many networks of cytokines. The causative reasons behind the initiation of deterioration and loss of articular tissue remain mostly unidentified. An increase in the expression of S1P has been observed in the synovial tissue of mice with collagen-induced arthritis (14). Nevertheless, there is limited knowledge regarding the involvement of S1P in the regulation of the crucial inflammatory cytokine IL-6 and the progression of RA. In this study, it was discovered that S1P stimulated the synthesis of IL-6 in human osteoblasts through the activation of the phosphoinositide-3-kinases (PI3K), MEK/ERK, and NF-κB signaling pathways. IL-6 possesses numerous biological functions, and prior research has demonstrated elevated levels of IL-6 in the blood and joint fluid of individuals with RA. This study provides confirmation that the levels of IL-6 in the synovial fluid of individuals with RA were higher compared to patients with OA (15).

Prior research analysis also shown elevated levels of IL-6 in RA tissue compared to OA tissue. The SIP signaling pathway, which controls the inflammatory response in RA illness, has been found to target the protein IL-6. These findings emphasize the significance of IL-6 as a molecular target in the treatment of rheumatoid arthritis. S1P, a growth factor derived from cells, is the ultimate product of the sphingolipid pathway and is synthesized from SphK and S1P lyase (7). S1P interacts with G protein-coupled receptors situated on the external surface of cells, specifically the S1P1–5 receptors. This relationship is essential for controlling various important physiological processes, such as cell differentiation, survival, proliferation, migration, invasion, as well as angiogenesis and trafficking. Derived from immunological cells. Although S1P1–3 is widely distributed in several organs, the expression of S1P4 and S1P5 is limited to immune cells and cells in the central nervous system (13).

Osteoclast secretion led to an increase in the production of MMP3 and MMP13 in the chondrocytes and cartilage of mice. This secretion also activated the JNK signaling pathway, resulting in the breakdown of the matrix. JTE013 inhibited the breakdown of chondrocytes by osteoclasts and provided protection against OA in rats. This indicates that the S1P produced by osteoclasts contributes to cartilage destruction in OA through the S1P/S1P2 signaling pathway. The level of SphK1 activity was found to be higher throughout the process of osteoclast formation. Additionally, the expression of SphK1 was elevated in the subchondral bone of mice with OA. The levels of MMP3 and MMP13 in chondrocytes were reduced when exposed to the secretome of osteoclasts lacking Sphk1. $SphK1^{LysMCre}$ mice exhibited a notable decrease in cartilage injury, however synovial inflammation remained unaffected. Ultimately, the introduction of sphingomab directly into the joint effectively prevented cartilage degradation and reduced inflammation in the synovial tissue (12).

The S1P/S1P receptor axis regulates a range of biological processes, such as tumor invasion and progression, vasculogenesis, angiogenesis, as well as degeneration of skeletal muscle and the nervous system. Curiously, the removal of the S1P2 receptor enhances the movement of murine embryonic fibroblasts towards S1P and platelet derived growth factor (PDGF), which in turn stimulates the creation of S1P. Additionally, the deletion of S1P2 leads to a rise in the expression and activity of SphK1, the enzyme responsible for generating S1P (6).

The signaling pathway involving S1P/S1P1 is known to control the interaction between the immune system and bone health. Studies have shown that there is an increase in the expression of S1P receptors in the synovial tissue of animal models with collagen-induced arthritis. Nevertheless, the precise involvement of S1P in the production of IL-6 and the

development of RA is still unclear. This study elucidates the role of S1P in upregulating IL-6 expression in human osteoblasts. Additionally, it investigates the participation of PI3K, MEK/ERK, and NF-κB signaling pathways in the promotion of IL-6 production by S1P1 (15).

It has been suggested that S1P may play a role in the process of angiogenesis, as well as in cancer and autoimmune illnesses like rheumatoid arthritis. It has been demonstrated that S1P promotes an increase in the expression of PGE2 and COX-2 in rheumatoid arthritis synoviocytes in response to proinflammatory cytokines, specifically TNF and IL-1. The synthesis of these cytokines causes the development of MMPs and the activation of osteoclasts, which ultimately leads to the resorption of bone and the destruction of soft tissue. It is also the case that osteoclasts themselves express S1P, and this molecule is responsible for stimulating the migration of osteoblasts and MSCs. Consequently, osteoclast-derived S1P may be able to recruit osteoblasts to sites of bone resorption, which is one of the initial steps in the process of rebuilding lost bone in places that have been injured (13).

The S1P signaling pathway, which is mediated by S1P1, is responsible for regulating the formation of T cells and enhancing synoviocyte proliferation, inflammatory cytokine production, and osteoclastogenesis in bone stability. During this time, it was discovered that osteoclasts that had their cathepsin-K gene removed had a higher level of SphK1 expression. It was also observed that these osteoblasts exhibited a larger RANKL/OPG ratio, which is in line with the presence of a greater number of osteoclasts (16).

As was revealed in earlier experiments involving Runx2 expression and alkaline phosphatase activity, osteoclast development and maturation are dependent on the transmission of signals through the SphK1/S1P/S1P3 pathway. In addition, it has been demonstrated that the signaling pathway of transforming growth factor (TGF)/Smad3 can affect cartilage homeostasis by altering the signaling pathway of S1P/S1P receptors and encouraging chondrocyte migration (19, 20). On the other hand, it was discovered that the SphK1/S1P/S1P3 signal axis was the only one that played a significant role in the deterioration of the mandibular condyle in mice that had chondrocytes that were defective in Smad3 (20). The migration of osteoclast precursor cells from bone tissue into the blood circulation is regulated by the S1P/S1P1 signaling axis, which is also responsible for the development of synovial hyperplasia in RA (13). It was discovered that stimulation with RANKL led to a reduction in the expression of S1P1 in a manner that was dependent on NF-κB, but which did not depend on NFATc1. Furthermore, the production of RANKL during osteoclastogenesis, which is promoted by the SphK1/S1P1 signaling axis, is the result of interactions between bone marrow stromal cells and macrophages (2, 15).

The study investigates the impact of the S1P-related miR-25 rs41274221 polymorphism on osteoporosis risk by altering its interaction with S1PR1. This polymorphism shows potential as a new biomarker for early detection of osteoporosis (13). A newly discovered pathway, regulated by S1P, connects the bone microvasculature with the osteoblast compartment. This pathway supports and enhances the pro-osteogenic functions of both the microvasculature and the osteoblast compartment. The process involves an autocrine loop, in which S1P/S1PR3 signaling triggers the synthesis of VEGFa in osteoblasts to enhance differentiation. Additionally, there is a paracrine loop, where VEGFa produced by OBs promotes bone marrow endothelial cells to create osteogenic H-type capillaries (16).

The production of VEGFa in primary osteoblasts is strongly influenced by S1P stimulation. This production plays a crucial role in promoting osteoblast differentiation and the formation of blood vessels in the bone marrow. Based on the evidence obtained, it has been determined that the S1PR3 receptor is responsible for mediating these effects (16). In vitro, the production of VEGFa was prevented by blocking S1PR3, and this effect was also observed in S1Plyase-

inhibited S1PR3-deficient mice in vivo. In vitro, the mineralization of osteoblasts mediated by S1P was inhibited by a neutralizing antibody against VEGFa, while in vivo, the osteoanabolic and angiogenic effects of S1P lyase inhibition were suppressed by blocking VEGFR signaling with axitinib (16).

In a different study, it was discovered that the expression of Sphk1 and S1P1 in the mandibular condyle of MRL/lpr mice was up, and this elevation was followed by an increase in Rac1 activity (2). As a consequence, the administration of S1P1 led to a substantial reduction in inflammation and joint damage, which is in line with the anticipated effect of agonistin on the preservation of osteoclast precursor cells (2, 11).

Taking all of these data into consideration, it appears that targets that stimulate the S1P/S1P1 signaling axis could be a possible therapeutic for RA. During the course of RA, it is believed that the expression of S1P and S1P1–5 by osteoclasts, osteoblasts, chondrocytes, and MSCs plays a significant role in the regulation of cell migration, cell survival, and the production of cytokines or chemokines during bone formation. It is therefore essential for future research to investigate the function that the S1P/S1P receptor system plays among the cell–cell interactions that are responsible for bone homeostasis in the pathophysiology of temporomandibular joint-related arthritis (11).

Conclusion

Arthritis is a multifaceted and varied illness marked by joint inflammation. Various types of arthritis, including osteoarthritis and rheumatoid arthritis, have distinct causes and mechanisms that play a role in their formation. The presence of S1P/S1P1-5 in osteoclasts, osteoblasts, chondrocytes, and MSC is believed to play a crucial role in regulating cell migration, cell survival, and the production of cytokines or chemokines throughout the process of bone formation. The S1P signaling system, S1P/S1P1 axis, has a vital function in controlling inflammation, cell movement, and the release of cytokines in arthritis. Directing attention towards this pathway may offer possibilities as a treatment strategy for controlling arthritis. Additional investigation is required to gain a comprehensive understanding of the role of S1P in the development of arthritis and to examine its potential as a treatment target for this diseases.

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