commentary

Potential role of sphingosine 1-phosphate in the pathogenesis of rheumatoid arthritis[1]

Wendy B. Bollag, *Editorial Board*[2]

Charlie Norwood VA Medical Center, and Institute of Molecular Medicine and Genetics, Medical College of Georgia

Rheumatoid arthritis is a chronic, destructive, autoimmune joint disease that affects one to two million Americans (or approximately 1% of the population of the United States). This disease can strike at any age and affects roughly three times as many women as men (http://ww2.arthritis.org/conditions/DiseaseCenter/RA/ra_who.asp). Symptoms include joint stiffness, swelling, and pain, as well as systemic effects associated with inflammation; and indeed, anti-inflammatory drugs are a mainstay of treatment (http://my.clevelandclinic.org/disorders/rheumatoid_arthritis/hic_what_drugs_are_used_to_treat_rheumatoid_arthritis.aspx). However, newer biologics that target the cytokine tumor necrosis factor-α (TNFα) have demonstrated efficacy, suggesting the importance of this agent in rheumatoid arthritis. Nevertheless, partial responses and nonresponses suggest that TNFα is not the sole mediator, and additional cytokines and chemokines are being sought as targets for the development of treatments for rheumatoid arthritis (as reviewed in Ref. 1).

Rheumatoid arthritis is characterized by inflammation of the lining of the joints, the synovium, followed by destruction of the cartilage and bone within the joint and invasion into these tissues of the rheumatoid pannus. The pannus is a hyperplastic, inflammatory tissue consisting largely of T, B, and dendritic cells and macrophages, constituting an immune compartment, and synovial fibroblasts, or fibroblast-like synoviocytes, comprising an erosive compartment (as reviewed in Ref. 2). These fibroblast-like synoviocytes also produce a number of growth factors, such as platelet-derived growth factor, fibroblast growth factor, vascular endothelial growth factor, and epidermal growth factor, and proinflammatory agents including interleukins (IL) -1-β, -6, -8, -11, -15, and -16, TNFα, transforming growth factor-β, prostaglandin E2, and receptor activator of nuclear factor-κB ligand (RANKL) (as reviewed in Ref. 2). RANKL may be critically involved in the erosion of bone in rheumatoid arthritis, because this agent induces differentiation of macrophages into bone-destroying osteoclasts (as reviewed in Refs. 2, 3), whereas the cytokines are probably key to inflammation and the growth factors important for the observed pannus hyperplasia. The mechanisms mediating this hyperplasia are unknown but may involve both increased proliferation and/or improved survival (i.e., decreased apoptosis) of fibroblast-like synoviocytes (as reviewed in Ref. 3).

In the article by Zhao et al. (4) reported in this issue, Bourgoin and colleagues identify another possible mediator of synoviocyte migration (invasion), survival, and cytokine production, i.e., sphingosine 1-phosphate (S1P). These investigators show that fibroblast-like synoviocytes express three of the five known S1P receptors, S1P1, S1P2, and S1P3, and that S1P or S1P agonists induce cell migration and secretion of IL-6 and -8 and reduce apoptosis. The S1P receptors mediating these processes were determined using receptor-selective agonists and antagonists, and the results are summarized in **Table 1**. Interestingly, these authors did not detect an effect of S1P on synoviocyte proliferation, although a previous study demonstrated a small effect of S1P on proliferation in synoviocytes of rheumatoid arthritis patients (5). As discussed by Zhao et al. (4), in this prior investigation, S1P's effects on proliferation were examined in the presence of 10% serum; thus, the difference may lie in the fact that whereas S1P by itself may not be sufficient to trigger proliferation, it may act synergistically with a component or components of serum to elicit synoviocyte growth. Nevertheless, the ability of S1P to promote fibroblast-like synoviocyte survival, whether or not this agent can also increase cell proliferation, could contribute to pannus hyperplasia (3).

This article by Zhao et al. (4) also examines the mechanisms underlying S1P's effects on synoviocytes. Using inhibitors of the various pathways, the authors find that S1P increases migration through activation of extracellular signal-regulated kinase-1 and -2 (ERK-1/2), as well as p38 and Rho kinase, a downstream effector of the small GTPase Rho. These three pathways also mediate S1P's regulation of cytokine production, although the involvement of ERK-1/2 in this cellular response is minor.

Manuscript received 31 July 2008.
DOI 10.1194/jlr.E800016-JLR200

[1] See referenced article, *J. Lipid Res.* 2008, 49: 2323–2337.

[2] To whom correspondence should be addressed.
e-mail: wbollag@mcg.edu

TABLE 1. Receptors mediating the effects of S1P on fibroblast-like synoviocyte cellular responses

	Migration	Survival	Inflammatory Mediator Secretion[a]
S1P1	+	+	−
S1P2	−	−	+
S1P3[b]	+	−	+

[a] Production of IL-6 and -8.
[b] Expression increased by TNFα pretreatment.

Of extreme interest is the fact that Zhao et al. (4) found that pretreatment of fibroblast-like synoviocytes with TNFα results in synergistic effects on inflammatory cytokine/chemokine (including IL-8) production upon subsequent exposure to S1P. This action appears to result from an ability of TNFα to upregulate the expression of the S1P3 receptor. Indeed, a previous report indicated that the synovium of rheumatoid arthritis patients expresses the S1P3 receptor (5). [These investigators also determined that, similar to its ability to enhance TNFα-induced cytokine/chemokine production (4), S1P enhances the production of prostaglandin E2 in response to TNFα or IL-1 in rheumatoid arthritis synoviocytes (5)]. The potential relevance of this interaction is obvious, in that the elevated TNFα levels observed in synovial fluid of patients with joints affected by rheumatoid arthritis (6) could make fibroblast-like synoviocytes more responsive to increases in S1P in this disease. In turn, as shown in this article (4), enhanced responsiveness to S1P through the S1P3 receptor could increase synoviocyte survival and migration, and production of cytokines and chemokines, all processes that probably contribute to the pathology of rheumatoid arthritis. In addition, TNFα could potentially increase production of S1P: in some cells, TNFα is known to activate sphingosine kinase, the enzyme that synthesizes S1P (7), and to increase the levels of ceramide, a precursor of S1P, which can be formed from ceramide through the combined action of the enzymes ceramidase and sphingosine kinase (as reviewed in Refs. 8, 9). Thus, TNFα and S1P could possibly synergize in multiple ways to contribute to rheumatoid arthritis etiology and progression, and the article by Zhao et al. (4) published in this issue of the *Journal of Lipid Research* suggests mechanisms by which S1P may mediate pathological consequences of rheumatoid arthritis. These consequences include the invasion (migration) of fibroblast-like synoviocytes into bone and cartilage, the survival of these cells (hyperplasia), and the inflammation (due to release of inflammatory cytokines) observed in rheumatoid arthritis.

In summary, S1P functions through multiple receptors, of which three are expressed in fibroblast-like synoviocytes, a cell type that appears to malfunction in rheumatoid arthritis. Bourgoin and colleagues demonstrated the role of these receptors in synoviocyte migration, survival, and inflammatory cytokine production, processes that are involved in the pathophysiology of rheumatoid arthritis. Furthermore, these authors showed that pretreatment of fibroblast-like synoviocytes with TNFα increases expression of the S1P3 receptor and enhances inflammatory cytokine/chemokine production in response to this agent, an effect that probably serves to exacerbate the disease process. Thus, the results reported here suggest the possibility of using S1P receptor antagonists and/or inhibitors of sphingosine kinase, either alone or in combination with drugs that target the TNFα pathway, for the treatment of rheumatoid arthritis.

REFERENCES

1. Asquith, D. L., and I. B. McInnes. 2007. Emerging cytokine targets in rheumatoid arthritis. *Curr. Opin. Rheumatol.* **19:** 246–251.
2. Abeles, A. M., and M. H. Pillinger. 2006. The role of the synovial fibroblast in rheumatoid arthritis: cartilage destruction and the regulation of matrix metalloproteinases. *Bull. NYU Hosp. Jt. Dis.* **64:** 20–24.
3. Knedla, A., E. Neumann, and U. Müller-Ladner. 2007. Developments in the synovial biology field 2006. *Arthritis Res. Ther.* **9:** 209–216.
4. Zhao, C., M. J. Fernandes, M. Turgeon, S. Tancrede, J. Di Battista, P. E. Poubelle, and S. G. Bourgoin. 2008. Specific and overlapping sphingosine-1-phosphate receptor functions in human synoviocytes: impact of TNF-alpha. *J. Lipid Res.* **49:** 2323–2337.
5. Kitano, M., T. Hla, M. Sekiguchi, Y. Kawahito, R. Yoshimura, K. Miyazawa, T. Iwasaki, and H. Sano. 2006. Sphingosine 1-phosphate/sphingosine 1-phosphate receptor 1 signaling in rheumatoid synovium. *Arthritis Rheum.* **54:** 742–753.
6. Petrovic-Rackov, L., and N. Pejnovic. 2006. Clinical significance of IL-18, IL-15, IL-12 and TNF-alpha measurement in rheumatoid arthritis. *Clin. Rheumatol.* **25:** 448–452.
7. Xia, P., L. Wang, J. R. Gamble, and M. A. Vadas. 1999. Activation of sphingosine kinase by tumor necrosis factor-alpha inhibits apoptosis in human endothelial cells. *J. Biol. Chem.* **274:** 34499–34505.
8. Pettus, B. J., C. E. Chalfant, and Y. A. Hannun. 2002. Ceramide in apoptosis: an overview and current perspectives. *Biochim. Biophys. Acta.* **1585:** 114–125.
9. Bollag, W. B. 2003. Paradoxical effects of sphingosine-1-phosphate. *J. Invest. Dermatol.* **120:** xiii–xiv.