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

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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. 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. These fibroblast-like synoviocytes express three of the five known S1P receptors, S1P1, S1P2, and S1P3, and that S1P or S1P agonists induce cell proliferation, although a previous study demonstrated a small effect of S1P on proliferation in synoviocytes of rheumatoid arthritis patients. As discussed by Zhao et al., 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. As discussed by Zhao et al., 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. In this prior investigation, S1P effects on synoviocytes 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.

This article by Zhao et al. 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.
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.

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

<table>
<thead>
<tr>
<th>Migration</th>
<th>Survival</th>
<th>Inflammatory Mediator Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1P1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>S1P2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S1P3†</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

†Production of IL-6 and -8.

†Expression increased by TNFα pretreatment.

### REFERENCES