Sphingosine 1-phosphate (S1P) is a naturally occurring bioactive lysophospholipid that regulates immune responses and inflammatory processes in a variety of different organ systems, including the cardiovascular system. Within the cardiovascular system, S1P mediates cardioprotection following ischemia/reperfusion injury, cardiac remodeling, vascular tone, angiogenesis, and fibroblast migration, proliferation, and differentiation, as well. In the current issue of Circulation, Meissner and colleagues present novel findings in a murine heart failure model (left anterior descending artery ligation) which suggest that S1P activity is modulated by a cAMP-responsive chloride channel termed the cystic fibrosis transmembrane regulator (CFTR). CFTR, a member of the ATP-binding cassette family of genes, was identified as the gene responsible for the loss of chloride secretion in patients with cystic fibrosis. Based on a previous report by the same group, which showed that the intracellular enzyme S1P phosphohydrolase that degrades extracellular S1P, was also an endogenous regulator of S1P-mediated vasoconstriction, the authors hypothesized that S1P must be imported by vascular smooth muscle cells. In their current report, Meissner et al show that CFTR mRNA was present in conduit and resistance arteries throughout the vascular tree in mice. They further noted that CFTR was required for S1P uptake by vascular smooth muscle cells, and that vascular smooth muscle cells from wild-type (CFTR+/−) possessed a higher rate of proliferation than vascular smooth muscle cells from CFTR null (CFTR−/−) mice, consistent with the known antiproliferative effects of S1P on vascular smooth muscle cells. At the whole organ level, S1P-mediated vasoconstriction of small resistance arteries (eg, the posterior cerebral artery) was more potent in CFTR−/− than in CFTR+/+ mice, whereas the vasoconstrictor response to phenylephrine and the vasodilator response to acetylcholine did not differ between CFTR−/− and CFTR+/+ mice. Finally the authors showed that CFTR mRNA levels were decreased in resistance vessels of wild-type mice that had undergone acute left anterior descending artery ligation, suggesting that decreased uptake of S1P of CFTR resulted in sustained S1P signaling and enhanced vascular tone. The authors further made the interesting observation that CFTR mRNA levels were down-regulated by tumor necrosis factor, a proinflammatory cytokine that is increased in heart failure, and that treatment with etanercept, a tumor necrosis factor antagonist, rescued many aspects of the heart failure phenotype, including normalization of vascular tone, and downregulation of CFTR, as well. Given that the CFTR downregulation was reversible and that increased peripheral vasoconstriction contributes to disease progression in heart failure, Meissner et al suggest that CFTR may represent a novel target for cardiovascular conditions such as heart failure wherein inflammation is present. Before addressing this interesting question, it is instructive to first review S1P signaling within the cardiovascular system.

**S1P Signaling in Cardiovascular Disease**

Sphingosine 1-phosphate, which was once regarded as a simple intermediate of sphingolipid metabolism, is now recognized as a critical regulator of a broad variety of pathophysiological processes, including atherosclerosis, diabetes mellitus, osteoporosis, multiple sclerosis, Alzheimer’s disease, and cancer. S1P is formed within cells by phosphorylation of sphingosine, which is a backbone component of all sphingolipids, by the action of 2 isoenzymes of sphingosine kinase, SphK1 and SphK2, which differ in their catalytic properties, subcellular location, and tissue distribution. S1P not only functions as an external ligand for G protein-coupled receptors after it is secreted by cells (inside-out signaling), but it can also act as an intracellular second messenger, as discussed below. Most of the known actions of S1P are mediated by binding of secreted S1P to a family of 5 G protein-coupled receptors, termed S1P1-5. Thus far, S1P1-3 receptors have been detected in the heart. In the heart, S1P1-mediated signaling inhibits cAMP formation and antagonizes adrenergic-mediated contractility through the Gs pathway. The S1P/S1P receptor axis has also been shown to be important in terms of controlling vascular permeability through activation of S1P1 (which decreases vascular permeability), and vascular tone through S1P3 activation, as well. S1P also has been shown to have important intracellular targets, including histone deacetylases, protein kinase Cδ, tumor necrosis factor receptor–associated factor 2, and prohibitin 2, a highly conserved protein that regulates mitochondrial assembly and function. Viewed together, these observations suggest that S1P signaling exerts a broad array of different extracellular and intracellular effects, which has

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(Circulation. 2012;125:2692-2694.)

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Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.112.107797

2692
Is S1P Signaling a Therapeutic Target in Heart Failure?

Unfortunately, at the time of this writing, it is unclear whether one would want to augment or diminish S1P signaling in patients with heart failure. The results of the carefully done study by Meissner and colleagues suggest that sustained S1P signaling secondary to decreased CFTR-mediated uptake of S1P may be deleterious because of enhanced microvascular tone in small resistance arteries. Although it is certainly true that increased peripheral vascular resistance contributes to functional limitations in patients with heart failure, and progressive pump dysfunction in advanced heart failure, it is unclear whether the increase in vascular tone in small resistance arteries (mesenteric, cremasteric, and posterior cerebral artery) is also present in the systemic arteries that are responsible for the increased peripheral vascular resistance in heart failure. Indeed, whereas S1P constricts small arteries in the mesentery, cerebral, and renal arteries, S1P has no effect on the aorta, carotid, or femoral arteries, and S1P signaling has been associated with vasodilation in various studies in small and large arteries, which is likely related to the unique distribution of S1P receptors in different vascular beds. Moreover, we have no information on what happens to S1P receptors in the peripheral vasculature of patients with heart failure. It is also important to recognize that that S1P levels are not elevated in the peripheral circulation of patients with symptomatic heart failure, suggesting that the S1P/S1P receptor axis may not be dysregulated in heart failure. Finally, as noted above, the extant literature suggests that enhanced S1P signaling is generally beneficial in the setting of acute cardiac injury. Thus, at the time of this writing, there simply is insufficient information to suggest that strategies that either upregulate or downregulate S1P signaling will be effective in the setting of heart failure. Nonetheless, one of the qualities of important research is that it frequently stimulates more questions than can be answered in a single study. Given the proliferation of pharmacological agents that are capable of modulating S1P signaling at a variety of different levels, including S1P antagonists/agonists, and inhibitors of S1P synthesis/degradation, as well (Table), the provocative questions raised in the important study by Meissner and colleagues are likely to stimulate a number of laboratories to focus future research efforts on this burgeoning area of cardiovascular biology.

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Table. Small-Molecule Inhibitors of the S1P/S1P Receptor Signaling Axis

<table>
<thead>
<tr>
<th>Agonist/Antagonist</th>
<th>Target</th>
<th>Animal Studies</th>
<th>Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTY720 (Fingolimod)*</td>
<td>S1P1,2/3/4/5</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AAL-R</td>
<td>S1P1/2/3/4/5</td>
<td>ND</td>
<td>ND</td>
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<tr>
<td>KRP-203</td>
<td>S1P1</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>AUY954</td>
<td>S1P1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>RG3477</td>
<td>S1P1</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>SEM2871</td>
<td>S1P1</td>
<td>Yes</td>
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<td>CYM-5442</td>
<td>S1P1</td>
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<tr>
<td>W146</td>
<td>S1P1</td>
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<tr>
<td>Compound 5</td>
<td>S1P1</td>
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<td>JTE013</td>
<td>S1P2</td>
<td>Yes</td>
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<tr>
<td>TY-52156</td>
<td>S1P3</td>
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<tr>
<td>VPC23019</td>
<td>S1P1</td>
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<td>VPC44116</td>
<td>S1P1</td>
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<td>ND</td>
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<tr>
<td>SK-1-1</td>
<td>SphK1</td>
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<td>ND</td>
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<tr>
<td>Safingol</td>
<td>SphK1</td>
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<tr>
<td>SK</td>
<td>SphK1</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>ABC294640</td>
<td>SphK2</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>DMS</td>
<td>SphK1.2</td>
<td>Yes</td>
<td>ND</td>
</tr>
<tr>
<td>SK-II</td>
<td>SphK1</td>
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</tr>
<tr>
<td>Reservatrol</td>
<td>SphK1</td>
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<td>Yes</td>
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<tr>
<td>LX2931</td>
<td>S1P lyase</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*S1P indicates sphingosine 1-phosphate; ND, not done; SphK, sphingosine kinase. *Food and Drug Administration approved for the treatment of multiple sclerosis. Modified from Schuchardt et al. and Edmonds et al. with permission of the publishers. Copyright © 2011, Elsevier and John Wiley and Sons.
Sources of Funding
This research was supported by research funds from the National Institutes of Health (R01 HL58081, R01 HL61543, R01 HL-42250).

Disclosures
None.

References

Key Words: Editorials • genes • heart failure • vascular response • sphingosine-1-phosphate • therapeutic target
Sphingosine 1-Phosphate as a Therapeutic Target in Heart Failure: More Questions Than Answers
Douglas L. Mann

Circulation. 2012;125:2692-2694; originally published online April 25, 2012;
doi: 10.1161/CIRCULATIONAHA.112.107797
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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