This review focuses on the role of sphingosine-1-phosphate (S1P) signaling in the heart, with particular emphasis on how it could be modulated therapeutically in the context of myocardial infarction (MI). After a brief general description of sphingolipid metabolism and signaling, this review will examine the relationship between S1P and the beneficial effects of high-density lipoprotein (HDL), and finally focus on the known actions of S1P on different mechanisms relevant to MI pathophysiology (cardiomyocyte protection, fibrosis, remodeling, arrhythmia, control of vascular tone and potential repair mechanisms). The potential of particular enzyme isoforms or receptor subtypes for the development of therapeutic agents for MI will also be explored. (Circ J 2014; 78: 795–802)

Key Words: Acute myocardial infarction; Coronary artery disease; Fibrosis; Hypertrophy; Lipids

Metabolism of S1P

The sphingosine backbone of the sphingolipids (the principal component of the plasma membrane in mammalian cells) is coupled to a fatty acid by an amide bond and forms ceramide, the central molecule in sphingolipid metabolism. Ceramide is deacylated by ceramidase to form sphingosine, which can be phosphorylated by either sphingosine kinase (SPK) 1 or SPK 2 to yield S1P. Elevated levels of ceramide or sphingosine, which occur in response to oxidative stress or tumor necrosis factor-α (TNFα), are often associated with increased apoptosis; in contrast, S1P protects cells from apoptosis and is associated with cell growth and proliferation. Cellular levels of S1P must therefore be tightly regulated. This is achieved not only by the activity of SPKs, but also at the level of S1P catabolism either by dephosphorylation by S1P phosphohydrolases or nonspecific lysosphospholipid phosphohydrolases, or, in a non-reversible manner, by a pyridoxal phosphate-dependent S1P lyase. The half-life of plasma S1P is short, suggesting the presence of highly active S1P-degrading pathways within the body. Because platelets lack S1P lyase, and erythrocytes lack both S1P lyase and phosphohydrolases, these cell types contain large amounts of S1P and were therefore initially thought to be the main source of the lipid in blood. But recent studies have shown that erythrocytes are the main blood cells storing and releasing S1P in plasma. Plasma S1P might also be accounted for by S1P synthesized and released by cells in the vessel wall, because extracellular S1P can be dephosphorylated into sphingosine, which is rapidly taken up by endothelial cells where it can be re-phosphorylated by SPK. It should also be mentioned that S1P can be synthesized locally in most organs. Of relevance to this review, expression of both SPK isoforms has been detected in the heart, particularly in fibroblasts, but also in cardiomyocytes. These enzymes seem to be an important source of endogenous S1P in the heart, and their appearance in mice as early as E8.5 suggests a key role in cardiac development. S1P generation in the heart is upregulated in response to a transient ischemia, suggesting a beneficial contribution of the SPK-S1P axis to ischemic pre- and post-conditioning (see Figure and later).
Receptors of S1P

S1P has a low nanomolar affinity for all 5 S1P receptors, through their activation, it influences various cellular and physiological processes, depending on the relative expression of receptor subtypes as well as their capacity to interact with multiple Ga subunits, such as Ga12, Ga13, and Ga13. S1P receptors are unique because they are only coupled to Ga12, and S1P1 receptor activation is the predominant mechanism for S1P-mediated inhibition of adenylyl cyclase. In binding assays, the S1P2 and S1P3 receptors can promote the exchange of GDP for [35S]GTPγS on Gaq, and not Ga12, Ga13, but not Ga12. S1P2 and S1P3 receptors are expressed in many of the same tissues. In many cases, these receptors seem to function redundantly, and, upon deletion of both receptors, there is increased penetrance of the in vivo phenotypes seen when only one of them is deleted. This includes loss of cardioprotection against in vivo ischemia-reperfusion (IR). S1P2 and S1P3 receptors are coupled chiefly to Gaq, and S1P1 receptors are expressed in cardiovascular tissue, whereas expression of the S1P1 and S1P3 receptors is largely confined to cells of the immune and nervous systems. In addition to its well-characterized effect on membrane receptors, recent studies have also shown the existence of specific intracellular targets of S1P, such as TNF receptor-associated factor 2 (TRAF2), which is known to mimic IPC, activates SPK1 via interaction of its receptor with TNF receptor-associated factor 2 (TRAF2). Both TNFα- and PKC-induced phosphorylation of SPK1 are ERK1/2-dependent. SPK1 phosphorylation leads to its translocation to the cell membrane, where it produces S1P, which is exported out of the cell and acts on S1P receptors in an autocrine manner ("inside-out signaling"). Although the nature of the transporters involved in this process has not been studied in the adult heart, ATP-binding cassette (ABC) transporters and/or mammalian orthologs of Spinster-like protein 2 (Spns2) have been implicated in other systems. All 3 S1P receptor subtypes (S1P1, S1P2, and S1P3) have been shown to play a role in IPC of cardiomyocytes, but they activate several protective signaling cascades to various degrees. Akt (also known as PKB) plays a central role in these cascades. It is activated by phosphorylation-4,5-bisphosphate 3-kinase (PI3K), and counts endothelial nitric oxide synthase (eNOS), glycogen synthase kinase 3β (GSK3β), fork-head box protein O1 (FOXO1) and the p70S6 kinase as downstream effectors. In addition to the RISK pathway (Akt/ERK), S1P receptors can stimulate p21-activated protein kinases (Pak1) and the SAFE pathway (JAK/STAT-3), another major protective intracellular signaling cascade. These SPK1 and S1P-receptor-mediated pathways are all thought to converge on the mitochondria, where they prevent the induction of apoptosis by various mechanisms including the mitochondrial permeability transition pore (mPTP) and BH3-domain proteins (eg, Bad, Bcl-XL and ROS). Interestingly, although these pathways are activated in mice lacking SPK2 (shown by the phosphorylation of ERK1/2, Akt, STAT3 and GSK3β in these mice), IPC fails to afford protection in the absence of SPK2. This finding suggests that SPK2 may modulate the mPTP through an interaction between mitochondrial S1P and prohibitin 2 (PHB2) to control the assembly and function of the cytochrome oxidase IV complex (COX4) complex and components of the mPTP. Please note that these pathways are simplified, and some steps/interactions are omitted for the sake of clarity.
to MI is discussed in detail later in this review. S1P elicits numerous responses in the heart, such as protection, changes in contractility, altered calcium handling, cell migration, angiogenesis, and proliferation of endothelial and smooth muscle cells. S1P increases intracellular calcium concentrations in both neonatal and adult rat cardiomyocytes; the latter effect is mediated predominantly by S1P1 receptors. Furthermore, S1P3 receptor activation can antagonize β-adrenergic receptor-mediated increases in L-type calcium currents. S1P has also been shown to reduce heart rate, predominantly through S1P2 receptors, and cause negative inotropy ex vivo and in vivo.

Although S1P1 receptors predominate in cardiac myocytes, S1P2 receptors are the most prevalent subtype in cardiac fibroblasts. Activation of S1P receptors on fibroblasts can mediate migration and proliferation, responses that are necessary for fibrosis and critical to cardiac remodeling. For instance, adult cardiac fibroblast migration in response to growth factors is reduced by S1P1 receptor deletion. Persistent and exaggerated stimulation of S1P1 receptors in the myocardium, which can occur following ischemia, leads to cardiac fibrosis in vivo via multiple mechanisms, which include transactivation of TGFβ signaling pathway and activation of RhoA and Rac1 small GTPases, with downstream signaling involving reactive oxygen species (ROS) generation (reviewed by Takuwa et al).

**Blood S1P and Association With Lipoproteins**

S1P is present at sub to low micromolar concentrations in the blood, more than enough to fully activate its receptors. However, most circulating S1P is not free, but is bound to plasma proteins, which seem to “buffer” S1P: thus, 50–70% of total S1P in the plasma is transported by high-density lipoproteins (HDL) in particular. HDL3 particles, approximately 30% by albumin and <10% by low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL). HDL-associated S1P might fulfill a unique function in activating Akt and eNOS via S1P1 receptors, and it has been suggested that S1P binding to either albumin or HDL might account for different signaling outcomes depending on its plasma protein association.

Several lines of evidence indicate that the S1P content of HDL might underlie the epidemiological observation that high plasma HDL levels prevent the development of atherosclerosis, and many of the beneficial effects of HDL can be blocked following interference with S1P signaling. These effects include vasorelaxation, angiogenesis, endothelial cell survival and migration, inhibition of TNFα-induced endothelial adhesion molecule expression and inflammatory cell adherence to the vascular wall. The fact that HDL induces COX-2 expression and release of the antithrombotic and vasorelaxing prostacyclin in endothelial cells by activating SPK2 via activation of S1P1 or S1P2 receptors, points to the existence of auto- or paracrine mechanisms.

In addition to indirect cardioprotective effects of HDL, secondary to its anti-atherogenic activity, experimental MI studies point to direct cardioprotection mediated by HDL, possibly involving S1P as its mediator: HDL protects mouse cardiomyocytes after hypoxia-reoxygenation through lipoprotein-associated S1P acting on S1P1 and S1P2 receptors. In a mouse MI/reperfusion model, HDL was shown to inhibit inflammatory neutrophil recruitment and cardiomyocyte apoptosis in wild-type, but not in S1P1-deficient mice. S1P1 receptors might also have a beneficial role, as HDL protects cardiomyocytes against apoptosis induced by doxorubicin via this subtype. HDL also activate Stat3 mainly through S1P2 receptors [Stat3 promotes cardiomyocyte survival and hypertrophy, as well as cardiac angiogenesis, and might play an important role in cardiac remodeling; this transcription factor plays a key role in a pro-survival signaling pathway, named survivor activating factor enhancement, or SAFE, pathway, activated in particular by ischemic pre- and post-conditioning]. Both S1P2 and S1P3 receptors protect against in vivo MI/reperfusion injury via Akt activation.

It should be noted that HDL have effects that are partially or not at all mediated by S1P. For example, only 50% of the vasodilatation mediated by HDL is abolished in arteries of S1P1-knockout mice, while that of free S1P is completely abrogated. Furthermore, HDL administration increases cardiac perfusion, whereas S1P decreases it. This has led to the proposal that, although the effects of HDL-bound S1P are uniformly positive, free S1P can exert proinflammatory, vasoconstrictive, and other potentially adverse cardiovascular effects.

Because of the high circulating levels of S1P in normal subjects, it is important to assess the concentrations of plasma S1P in MI, or in conditions predisposing to MI (eg, obesity, atherosclerosis, diabetes), to predict the potential efficacy of agents targeting S1P receptors in the management of cardiovascular diseases. Patients with acute MI have lower plasma S1P levels than healthy subjects, an observation recently confirmed in a mouse model. This decrease contrasts with the increased plasma S1P levels seen within 1 min of transient ischemia mediated by short periods of coronary vessel occlusion in humans. In addition, a significant correlation is observed between angiographically determined coronary artery disease and S1P levels, which rise with the degree of stenosis. Considering the findings summarized in the previous paragraph, it is important to consider not only the concentration of free S1P, but its association with lipoproteins. Clinical studies investigating S1P levels in atherosclerotic diseases have reported that, although S1P in non-HDL fractions and serum S1P are increased, HDL-linked S1P is decreased in atherosclerosis. Another study suggested that the reduced endothelial nitric oxide synthase activation by HDL isolated from MI patients with high inflammatory response could be explained by the significantly reduced S1P levels in HDL from these patients. In contrast, S1P levels in HDL were significantly increased in type 2 diabetic subjects (who are at a higher risk of experiencing MI) compared with controls, and diabetic HDL led to enhanced COX-2 induction and prostacyclin release by endothelial cells; this study, taken together with increased S1P levels observed in animal models of type 1 diabetes, suggests that HDL and S1P might exert compensatory protective effects in diabetes.

**Effects on the Failing Heart**

SPK and S1P1 receptor mRNAs are decreased in the non-infarcted tissue after MI; this decrease is associated with a gradual loss of S1P1 receptor protein and a decline of SPK activity in chronic post-MI remodeling. These observations led to the hypothesis that S1P signaling is impaired during remodeling of the non-infarcted ventricle and that enhancing S1P signaling would ameliorate ventricular dysfunction. Indeed, oral administration of the S1P1-selective agonist SEW2871 during the first 2 weeks after MI reduced apoptosis in the remote, uninfarcted myocardium and resulted in improved myocardial function. These data, supported by several other reports, indicate a possible therapeutic role for the pharmacological S1P1 receptor agonism in the post-MI heart.

Several other lines of research suggest that S1P treatment after the acute MI phase could be beneficial and improve the function of the infarcted ventricle. Although the left ventricu-
lar ejection fraction (LVEF) was decreased and end-diastolic diameter was increased was increased 8 weeks after experimental MI in control rats, adenosine-mediated overexpression of S1P receptors ameliorated LV contractility and increased the EF; adverse LV remodeling (as measured by ventricular dilatation) progressed further in control rats, and this was prevented by S1P gene delivery. S1P also acts on hematopoietic progenitor cells as a chemotactic factor, most likely via S1P1 receptors expressed by both primitive and committed CD34+ hematopoietic progenitor cells, attracting peripheral blood CD34+ cells in vitro. Sustained activation of S1P receptors with the non-subtype selective agonist fingolimod (FTY720) during the homing process results in increased engraftment in vivo. This observation might underlie the very recent clinical finding that plasma obtained at hospital admission and 6 h after acute MI strongly chemoattracted human BM-derived CD34+Lin– and CXCR4+/Lin– cells and that this effect was blunted after depletion of S1P from plasma or even further inhibited by specific S1P receptor antagonists such as W146 and VPC23019. Taking into account the known contribution of primary hematopoietic stem cells to tissue repair in MI, it is tempting to speculate that S1P might stimulate regeneration of the infarcted tissue by attracting hematopoietic stem cells to the scarred area and thereby improve cardiac function.

Besides attracting progenitor and stem cells to the infarct zone, the preservation of mitochondrial function might be another mechanism by which S1P might be critical for cardiac cell survival. Although mitochondria are key determinants of myocardial injury during IR, their interaction with critical cytoprotective signaling systems is not fully understood. It has been shown that S1P produced by SPK1 protects the heart from IR-induced damage. A new role for mitochondrial S1P produced by the other SPK isoformal, SPK2, was recently described. In in this study, S1P was shown to regulate complex IV assembly and respiration via interaction with mitochondrial prohibitin-2. Mice lacking SPK2 and their wild-type littermates underwent MI/reperfusion. Despite the activation of cytoprotective signaling pathways in both groups, preconditioning reduced the infarct size in wild-type, but not SPK2−/− mice. SPK2−/− mitochondria exhibited decreased oxidative phosphorylation and increased susceptibility to permeability transition (PTP), while preconditioning prevented ischemic damage to electron transport or the increased susceptibility to PTP in the wild-type, but not the SPK2−/− mice. In order to further delineate the mechanism involved in the preconditioning-resistant phenotype, PTP resistance was studied following knock-down of SPK2, prohibitin-2, and cytochrome oxidase IV in cardiomyoblasts; preconditioning-associated protection was abolished by each knockdown concomitant with decreased PTP resistance. This study, taken together with observations by another group, suggests that mitochondrial S1P generated by mitochondrial SPK2 in cardioprotection acts downstream from S1P generated by SPK1. This model reconciles the results from preconditioning studies in the heart, implicating SPK1 as well as SPK2; it posits that preconditioning would first activate SPK1, leading to increased cytosolic S1P concentration, S1P release and auto- or paracrine activation of membrane S1P receptors (“inside-out” signaling). Receptor activation would then activate cytoprotective signaling cascades that would converge on mitochondria as the effector of protection (Figure). The mitochondrial pool of S1P regulates oxidative phosphorylation (via “SPK”-generated S1P, prohibitin-2, and cytochrome oxidase) and ROS production, leading to an inhibition of PTP opening and cell survival.

The studies mentioned above suggest that activating SPKs might be a useful approach in the clinical setting. It is, however, easier for medicinal chemists to design enzyme inhibitors. With this in mind, it is worth mentioning that mice heterozygous for deletion of the S1P-degrading enzyme S1P lyase gene and wild-type mice receiving an SPL inhibitor (which show elevated S1P levels in both plasma and cardiac tissues) have reduced sensitivity to IR injury, raising a possibility of cardioprotection with an S1P lyase inhibitor, or possibly phosphohydrolase inhibitors, for the management of MI.

In a Langendorff preparation, S1P can stimulate 2 major protective intracellular pathways against myocardial IR injury: the RISK pathway (Akt/Erk), including its downstream target FOXO-1 and, the SAFE pathway (TNF/STAT-3). S1P has also been shown to be an important endogenous cardioprotectant released not only during ischemic preconditioning, but also during postconditioning. When present during pre- or postconditioning, the mixed S1P1/S1P3 receptor antagonist VPC23019 blocked protection afforded by either 2 cycles of preconditioning or 4 postindex ischemia cycles. This antagonist also blocked preconditioning of isolated rat cardiac myocytes subjected to hypoxia-reoxygenation injury. The study also showed increased release of S1P from myocytes in response to preconditioning, suggesting that S1P released in response to preconditioning protects the heart by binding to membrane S1P receptors.

This is congruent with findings that fingolimod improved recovery of function after myocardial IR in vitro and ex vivo; this effect appears to be mediated by S1P receptors, based on the similar effect of the agonist SEW2871. Fingolimod has been also studied in pharmacological postconditioning to test whether it reduces infarct size when administered directly before reperfusion in vivo. In contrast to the Langendorff approach, neither the pre- nor the postconditioning had an effect of the infarct size 24 h post infarction, although fingolimod treatment attenuated granulocyte infiltration and TNFα protein expression in reperfused myocardium. But increased mortality because of induction of fatal ventricular tachyarrhythmias was observed when fingolimod was administered once before reperfusion, whereas animals were protected against reperfusion arrhythmias when it was only given 24 h prior to ischemia. Mechanistically, pretreatment selectively downregulated S1P receptors within the myocardium and this prevented detrimental stimulation of the receptor post MI. Such detrimental effects were replicated with SEW2871. Isolated perfused rat hearts exposed to S1P or SEW2871 were subjected to 30 min of global no-flow ischemia and 120 min of reperfusion. S1P significantly reduced infarct size and creatine kinase release, whereas the effect of SEW2871 on infarct size was modest. SEW2871 significantly prolonged the duration of ventricular tachycardia and ventricular fibrillation, leading to irreversible reperfusion tachyarrhythmias in 60% of the hearts. Taken together, the stimulation of arrhythmia by S1P analogues might have significant clinical implications as the use of S1P before myocardial ischemia might be cardioprotective as well as the treatment after the acute phase of infarct, whereas treatment immediately after MI (until 24 h) seems to be contraindicated.

Following MI, cardiac fibroblasts proliferate and form a scar tissue that substitutes for lost cardiomyocytes to achieve cardiac repair. Although this process can initially be beneficial, deposition of myofibroblast-derived extracellular matrix eventually confers stiffness to myocardium, which leads to impaired cardiac relaxation and contraction (ie, heart failure). This pathological remodeling is a major target of therapeutic intervention. S1P has been shown to increase α-smooth muscle actin (a myofibroblast marker) and collagen expression in a S1P1 receptor-dependent manner; TGFβ, which plays a crucial role in inducing pathological cardiac remodeling, increased S1P expression.
Sphingosine-1-Phosphate and MI

Reduced infarct area compared with wild-type mice. Concomitant deletion of S1P3 receptors in these mice alleviated cardiac fibrosis and was associated with reduced Smad3 phosphorylation, suggesting that activation of TGFβ signaling is involved in S1P3-dependent development of cardiac fibrosis. A role S1P3 receptors is further supported by the fact that fingolimod can induce the differentiation of fibroblasts into myofibroblasts and that this effect is absent following treatment with S1P3-specific antisense oligonucleotide or in fibroblasts from S1P3 knock-

Table. Effect of Sphingosine-1-Phosphate (S1P) Signaling and Specific S1P Receptor Subtype on Cardiac Cell Types and Functions Relevant to the Management of Myocardial Infarction

<table>
<thead>
<tr>
<th>Cell type/system/Receptor</th>
<th>Effect</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyocytes S1P1</td>
<td>Ca2+ release</td>
<td>20</td>
</tr>
<tr>
<td>S1P1</td>
<td>ERK activation</td>
<td>72</td>
</tr>
<tr>
<td>ND</td>
<td>Reduction of spontaneous pacing rate</td>
<td>73</td>
</tr>
<tr>
<td>S1P1</td>
<td>Hypertrophy (neonatal)</td>
<td>63</td>
</tr>
<tr>
<td>S1P1</td>
<td>Negative inotropy</td>
<td>74</td>
</tr>
<tr>
<td>S1P1</td>
<td>Inhibition of the inotropic response to isoproterenol</td>
<td>75</td>
</tr>
<tr>
<td>S1P1</td>
<td>Survival</td>
<td>76, 77</td>
</tr>
<tr>
<td>ND</td>
<td>Connexin-43 phosphorylation; decreased Gap junction permeability</td>
<td>78</td>
</tr>
<tr>
<td>S1P2, S1P3</td>
<td>Survival</td>
<td>56</td>
</tr>
<tr>
<td>S1P1, S1P3</td>
<td>Pro-survival effects of HDL</td>
<td>30</td>
</tr>
<tr>
<td>S1P2</td>
<td>Pro-survival effects of HDL</td>
<td>32</td>
</tr>
<tr>
<td>S1P3α</td>
<td>Activation inward-rectifying potassium channel</td>
<td>79–83</td>
</tr>
<tr>
<td>Progenitors and stem cells ND</td>
<td>Differentiation into cardiomyocytes</td>
<td>84</td>
</tr>
<tr>
<td>S1P3</td>
<td>Angiogenesis and neovascularization by endothelial progenitor and bone marrow-derived mononuclear cells</td>
<td>85</td>
</tr>
<tr>
<td>Fibroblasts S1P2</td>
<td>Increased collagen production</td>
<td>60</td>
</tr>
<tr>
<td>ND</td>
<td>Increased proliferation</td>
<td>86</td>
</tr>
<tr>
<td>S1P3</td>
<td>Differentiation of fibroblasts into myofibroblasts</td>
<td>62</td>
</tr>
<tr>
<td>Coronary artery S1P2</td>
<td>Constriction</td>
<td>67</td>
</tr>
<tr>
<td>S1P3</td>
<td>Constriction</td>
<td>66</td>
</tr>
<tr>
<td>S1P1</td>
<td>Relaxation</td>
<td>68</td>
</tr>
<tr>
<td>Aortic valves S1P2</td>
<td>Contraction; nodule formation</td>
<td>65</td>
</tr>
<tr>
<td>Isolated heart S1P1</td>
<td>Tachyarrhythmias after IR injury</td>
<td>59</td>
</tr>
<tr>
<td>ND</td>
<td>Increased sinoatrial rate; decreased coronary flow</td>
<td>87</td>
</tr>
<tr>
<td>S1P1</td>
<td>Decreased IR injury-associated arrhythmias</td>
<td>88</td>
</tr>
<tr>
<td>S1P3</td>
<td>Prolonged duration of IR-induced ventricular tachycardia and fibrillation</td>
<td>59</td>
</tr>
<tr>
<td>ND</td>
<td>Cardioprotection</td>
<td>46–48</td>
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<tr>
<td>In vivo S1P3</td>
<td>Bradycardia</td>
<td>83, 89, 90</td>
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<td>S1P3</td>
<td>Decreased cardiac perfusion</td>
<td>34</td>
</tr>
<tr>
<td>S1P1</td>
<td>Decreased infarct size; improved myocardial function</td>
<td>38, 45</td>
</tr>
<tr>
<td>S1P2, S1P3</td>
<td>Decreased infarct size</td>
<td>15</td>
</tr>
<tr>
<td>S1P3</td>
<td>Decreased infarct size</td>
<td>31</td>
</tr>
<tr>
<td>S1P3</td>
<td>Fibrosis</td>
<td>61</td>
</tr>
</tbody>
</table>

aThe S1P receptor subtype mediating this response in unclear; the response was blocked by suramin in one study, but it is worth mentioning that this agent is highly unspecific.
IR, ischemia-reperfusion; ND, not determined.

and activity while TGFβ-stimulated α-smooth muscle actin production was inhibited by SPK1 or S1P1 siRNA, an SPK inhibitor, and an anti-S1P monoclonal antibody (showing the occurrence of an “inside-out” signaling), whereas no reduction was observed in response to knock-down of S1P1 or S1P3 receptors. Transgenic mice overexpressing SPK1 under a universal promoter develop spontaneous cardiomyocyte degeneration and fibrosis without hypertrophy. However, somewhat surprisingly, in IR injury experiments, these transgenic mice showed a reduced infarct area compared with wild-type mice. Concomitant deletion of S1P1 receptors in these mice alleviated cardiac fibrosis and was associated with reduced Smad3 phosphorylation, suggesting that activation of TGFβ signaling is involved in S1P1-dependent development of cardiac fibrosis. A role S1P3 receptors is further supported by the fact that fingolimod can induce the differentiation of fibroblasts into myofibroblasts and that this effect is absent following treatment with S1P3-specific antisense oligonucleotide or in fibroblasts from S1P3 knock-
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out mice.62 These findings suggest that the role of S1P in the failing heart is complex, with some positive effects counterbalancing detrimental consequences. Among the latter influences and in addition to the pro-fibrotic effects described before, S1P induces hypertrophy of neonatal rat cardiomyocytes in vitro via S1P1 receptors.63 It should be noted, however, that the Gαi- and RhoA-mediated hypertrophy induced by S1P occurs more slowly and is less robust than the more hypertrophic responses elicited through the activation of Gαq/PLC signaling by norepinephrine or phenylephrine.64 In fact, the recent demonstration that S1P1 receptors are downregulated in isoproterenol-induced cardiac hypertrophy in mice suggests that S1P1 receptor inactivation could play a role in the progression toward heart failure, because adenovirus-mediated S1P1 gene delivery in a rat MI model led to significant functional and structural cardiac recovery and cardiac function improvement. The authors of the study hypothesized that the favorable action of S1P1 overexpression was caused by either a direct cardioprotective effect or an increased angiogenic response that promoted an adaptive, angiogenesis-dependent LV hypertrophy instead of a transition to a maladaptive state.38

Among other potentially deleterious effects of S1P, it is worth mentioning that this lipid induces contraction of valvular interstitial cells from porcine aortic valves and leads to the formation of nodules via S1P1 receptors, effects that might eventually be associated with valve dysfunction.65 S1P is also known to constrict coronary arteries,66,67 although this constriction is weaker than that of other vessels, and vasorelaxing responses have also been reported.68 S1P signaling might also affect vasoconstrictor abnormalities and increased peripheral resistance exacerbating heart failure. In rodents, myogenic responses and vasomotor abnormalities and increased peripheral resistance exacerbating heart failure are diminished and/or lack specificity.69 In studies using knockout mice, compensatory changes might have accounted for the observed results. With these caveats in mind, it is nevertheless possible to propose that stimulating S1P signaling might be of therapeutic benefit in the context of MI and ensuing heart failure (Table). It is likely that, although some S1P-mediated effects might be deleterious, selectively targeting the right receptor subtype (eg, S1P1 receptors) during the correct window of time following MI, would increase the chances of successful treatment.

Conclusion

The studies discussed in this review describe complex effects of sphingolipid signaling on the heart, particularly after MI. It is important to note that many of these reports did not characterize the pharmacological profile of the S1P-mediated responses, or did so with imperfect tools. The fact that some of the studies yielded apparently conflicting results might therefore reflect not only the multifaceted nature of this lipid, but also the fact that many agonists and antagonists are poorly characterized and/or lack specificity.71 In studies using knockout mice, compensatory changes might have accounted for the observed results. With these caveats in mind, it is nevertheless possible to propose that stimulating S1P signaling might be of therapeutic benefit in the context of MI and ensuing heart failure (Table). It is likely that, although some S1P-mediated effects might be deleterious, selectively targeting the right receptor subtype (eg, S1P1 receptors) during the correct window of time following MI, would increase the chances of successful treatment.

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