Sphingosine-1-Phosphate, a Platelet-Derived Lysosphospholipid Mediator, Negatively Regulates Cellular Rac Activity and Cell Migration in Vascular Smooth Muscle Cells

Yasuji Ryu, Noriko Takuwa, Naotoshi Sugimoto, Sotaro Sakurada, Soichiro Usui, Hiroyuki Okamoto, Osamu Matsui, Yoh Takuwa

Abstract—Previous studies demonstrated that sphingosine-1-phosphate (S1P) induced migration of human umbilical vein endothelial cells (HUVECs) whereas it inhibited that of vascular smooth muscle cells (SMCs). This study explored the molecular mechanisms underlying the contrasting S1P actions on vascular cell motility. In rat and human aortic SMCs, the chemottractant platelet-derived growth factor B-chain (PDGF) induced rapid 5- to 6-fold increases in the cellular amount of GTP-bound, active form of Rac. S1P did not affect PDGF-stimulated tyrosine phosphorylation of PDGF-β receptor, but strongly inhibited PDGF-induced Rac activation, with a dose-response relationship similar to that for inhibition of PDGF-elicited chemotaxis. Dihydrosphingosine-1-phosphate, which is a weaker agonist for the S1P receptors, but not an inactive ligand sphingosine, also inhibited PDGF-stimulated chemotaxis and Rac activation although to lesser extents compared with S1P, suggesting that negative regulation by S1P of both chemotaxis and Rac was a receptor-mediated process. In contrast, S1P by itself stimulated Rac activity in HUVECs. Among the five S1P receptor isoforms, SMCs prominently expressed Edg-5 mRNA, whereas HUVECs expressed abundant Edg-1 mRNA but lacked detectable expression of Edg-5 mRNA. Adenovirus-mediated expression of a dominant-negative form of either Rac or Cdc42, but not RhoA, markedly attenuated chemotaxis of SMCs and HUVECs toward PDGF and S1P, respectively. Overexpression of Edg-1 in SMCs and Edg-5 in HUVECs reduced S1P-induced inhibition and stimulation, respectively, of Rac activity and migration. These results together indicate that Edg isoform-specific, negative or positive regulation of cellular Rac activity is critically involved in S1P-mediated bimodal regulation of cell motility in SMCs and HUVECs. (Circ Res. 2002;90:325-332.)

Key Words: sphingosine-1-phosphate ▪ chemotaxis ▪ Rac ▪ platelet-derived growth factor ▪ vascular smooth muscle

Migration of medial vascular smooth muscle cells (SMCs) into the intima is a crucial step that gives rise to the formation of atheroma and postangioplasty restenosis. Understanding the molecular basis for the regulation of SMC migration could help develop a novel way of preventing the formation of such vascular lesions. It is well established that peptide growth factors for SMCs, including platelet-derived growth factor B-chain (PDGF) and epidermal growth factor, exhibit vigorous chemotactic activity for SMCs in vitro and have been implicated in migration of SMCs into the intima in vivo. On the other hand, our knowledge about migration-inhibitory factors for SMCs is scanty.

Sphingosine-1-phosphate (S1P) is a recently established lipid mediator that exerts pleiotropic effects on diverse cell types. These include stimulation of mitogenesis, prevention of apoptosis, cell differentiation, smooth muscle contraction, and regulation of cell migration. S1P acts through at least five isoforms of the Edg family G protein-coupled receptors, ie, Edg-1, -3, -5, -6, and -8. In addition, some of the biological activities of S1P were reported to be through its intracellular actions. A number of studies demonstrated that vascular SMCs and endothelial cells are targets for S1P; it is mitogenic for either cell type, constricts blood vessels, and also stimulates production of nitric oxide from endothelial cells. S1P is present in plasma at a considerably high concentration in a form bound to plasma proteins including albumin and lipoproteins. It is demonstrated to be released from platelets and mast cells on their activation. These findings would support the notion that S1P acts as a local hormone or autacoid under certain physiological and pathological conditions. With regard to this point, it is of note that S1P is found in oxidized LDL, and a high concentration of oxidized LDL could mimic mitogenic and other actions of S1P on both SMCs and endothelial cells, implicating a role for S1P in the atherogenic activity of oxidized LDL. On the other hand, S1P could also exert antiathero-
genetic and antirestenotic activities, at least under certain circumstances, because S1P potently inhibits migration of vascular SMCs and stimulates nitric oxide production in endothelial cells. The molecular mechanisms underlying S1P-inhibited inhibition of SMC migration remain yet to be elucidated.

We have recently demonstrated in a heterologous expression system that the ubiquitously expressed three isoforms of the S1P receptors, Edg-1, -3, and -5, show differential intracellular signaling mechanisms and contrasting activities on cell migration: Edg-1 and -3 mediate S1P-directed cell migration, whereas Edg-5 mediates the S1P inhibition of cell migration toward a chemoattractant such as insulin-like growth factor I. Rac, Cdc42, and Rho, are essential regulators of actin cytoskeletons and thus cell migration. We demonstrated that the S1P receptors displayed isoform-specific, differential activities on regulation of the Rac family GTPases: Edg-1 mediated stimulation of Rac, Edg-3 mediated stimulation of both Rac and RhoA, whereas Edg-5 mediated inhibition of Rac and also stimulation of RhoA. These and other observations taken together strongly suggested that the Edg-5-mediated inhibition of the Rac activity is, at least in part, responsible for S1P-induced inhibition of cell migration.

In the present study, we explored the effects of S1P and related sphingolipids on migration and the activities of the Rac family G proteins in SMCs and endothelial cells. S1P and a less potent Edg agonist, dihydrospingosine-1-phosphate (DH-S1P), but not sphingosine, which does not serve as an agonist for the S1P receptors, suppressed Rac-dependent migration toward PDGF with different potencies. S1P and DH-S1P, but not sphingosine, also inhibited PDGF-induced Rac activation. By contrast, in human umbilical vein endothelial cells (HUVECs) S1P stimulated Rac by itself and elicited chemotaxis in a Rac-dependent manner.

Materials and Methods
An expanded Materials and Methods section can be found in the online data supplement available at http://www.circresaha.org.

Results
S1P Inhibits PDGF-Directed Migration of Rat Vascular SMCs Without Affecting PDGF-β Receptor Activation
As reported previously, PDGF strongly induced migration of rat SMCs (Figure 1A). The chemotactic effect was detectable at a concentration as low as 0.41 nmol/L of PDGF, with the peak response observed at 1.23 nmol/L and a typical decline of the migration response at the supramaximal concentrations of PDGF. When S1P was added to PDGF, migration toward PDGF was markedly attenuated. The inhibition of chemotaxis was S1P dose-dependent, with a complete inhibition observed at 10 μmol/L of S1P (Figure 1B). S1P alone did not stimulate or inhibit SMC migration. In addition to S1P, DH-S1P, which is a less potent agonist for the Edg family S1P receptors, also inhibited PDGF-induced migration with a nearly 10-fold less potency than S1P (Table 1). Sphingosine, which does not act as an agonist for the S1P receptors but is rapidly incorporated into cells to serve as the distal site of S1P action, was essentially ineffective at the maximal dose used. S1P did not inhibit PDGF-induced stimulation of tyrosine phosphorylation of PDGF-β receptor (Figure 1C). These results indicate that S1P acts through either of the Edg receptors to inhibit PDGF-evoked migration of SMCs, and that the site of S1P action is distal to PDGF receptor activation.

S1P Inhibits PDGF-Induced Activation of the Small GTPase Rac
We next examined the effects of PDGF and S1P on the activities of the Rac family GTPases in rat vascular SMCs. PDGF induced a rapid and sustained increase in the cellular amount of a GTP-bound, active form of Rac (GTP-Rac), with a peak 6-fold increase at 2 minutes (Figure 2A). S1P by itself did not alter the cellular level of GTP-Rac; however, S1P added to PDGF markedly reduced PDGF-induced increases in GTP-Rac. The

### Table 1. Effects of Various Sphingolipids on Chemotaxis of SMCs Toward PDGF

<table>
<thead>
<tr>
<th>Concentration, μmol/L</th>
<th>Migration (Percent Control) in the Presence of S1P</th>
<th>Migration (Percent Control) in the Presence of DH-S1P</th>
<th>Migration (Percent Control) in the Presence of Sph</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>78 ± 4*</td>
<td>82 ± 1*</td>
<td>ND</td>
</tr>
<tr>
<td>1</td>
<td>48 ± 7**</td>
<td>71 ± 3**</td>
<td>94 ± 1</td>
</tr>
</tbody>
</table>

*Migration of rat aortic SMCs was determined in the presence of PDGF (0.41 nmol/L) and various concentrations of indicated sphingolipids in the lower chambers. The values are expressed as a percentage of the control value (optical density value at 595 nm) in the presence of PDGF alone.

**DH-S1P indicates dihydroS1P. Sph, sphingosine; and ND, not determined.

* and **Statistically significant compared with the value in the presence of PDGF alone at P values of <0.05 and <0.01, respectively.
SIP inhibition of PDGF-induced Rac activation was dependent on the duration of SIP pretreatment; the maximal extent of inhibition was achieved within 5 minutes after SIP addition and was sustained for at least 20 minutes. The inhibition of PDGF-induced Rac activation by SIP was dose-dependent (Figure 2B). In addition to SIP, DH-SIP dose dependently inhibited PDGF-induced Rac activation with less potency compared with SIP (Table 2). Sphingosine was without any effect on a cellular level of GTP-Rac. These results are consistent with the results of the effects of the sphingolipids on cell migration shown in Table 1.

PDGF and SIP, either alone or in combination, did not alter the cellular amount of GTP-Cdc42 during the observation period (Figure 3A). SIP, but not PDGF, induced time-dependent increases in the amount of GTP-RhoA with a peak 8-fold rise at 2 minutes (Figure 3B). PDGF did not considerably affect the SIP stimulation of GTP loading on RhoA. DH-SIP, but not sphingosine, also dose dependently stimulated RhoA although less potently than SIP (Table 2).

**TABLE 2. Effects of Various Sphingolipids on Activation of Rac and RhoA in SMCs**

<table>
<thead>
<tr>
<th>Stimuli</th>
<th>Mean Level (Fold Over Background)±SE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rac</td>
</tr>
<tr>
<td>None</td>
<td>1.0±0.1</td>
</tr>
<tr>
<td>PDGF alone</td>
<td>4.2±0.1</td>
</tr>
<tr>
<td>+SIP (0.1 μmol/L)</td>
<td>1.9±0.5**</td>
</tr>
<tr>
<td>+SIP (1 μmol/L)</td>
<td>1.6±0.4**</td>
</tr>
<tr>
<td>+DH-SIP (0.1 μmol/L)</td>
<td>3.6±0.2*</td>
</tr>
<tr>
<td>+DH-SIP (1 μmol/L)</td>
<td>2.3±0.4**</td>
</tr>
<tr>
<td>+Sph (1 μmol/L)</td>
<td>4.3±0.7</td>
</tr>
<tr>
<td>RhoA</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0±0.2</td>
</tr>
<tr>
<td>PDGF</td>
<td>1.7±0.1</td>
</tr>
<tr>
<td>S1P (0.1 μmol/L)</td>
<td>5.2±0.2**</td>
</tr>
<tr>
<td>S1P (1 μmol/L)</td>
<td>8.2±0.8**</td>
</tr>
<tr>
<td>DH-SIP (0.1 μmol/L)</td>
<td>2.8±0.8*</td>
</tr>
<tr>
<td>DH-SIP (1 μmol/L)</td>
<td>5.4±0.7**</td>
</tr>
<tr>
<td>Sph (1 μmol/L)</td>
<td>1.3±0.2</td>
</tr>
</tbody>
</table>

For GTP-Rac assay, rat aortic SMCs were pretreated with sphingolipids at indicated concentration for 5 minutes and then stimulated with PDGF (0.41 nmol/L) for 2 minutes. For GTP-Rho assay, the cells were stimulated with PDGF (0.41 nmol/L) or sphingolipids at induced concentrations for 2 minutes.

* and **Statistically significant compared with the value in the presence of PDGF alone for GTP-Rac assay and in the absence of a stimulus for GTP-Rho assay, at P values of <0.05 and <0.01, respectively.

**Adenovirus-Mediated Expression of N\(^{17}\)-Rac and N\(^{17}\)-Cdc42, but not N\(^{19}\)-RhoA, Inhibits PDGF-Directed Chemotaxis**

The Rho family GTPases, Rac, Cdc42, and Rho, are implicated in the regulation of migration in a number of cell types. However, their involvement in migration of vascular SMCs has not so far been fully analyzed. By using the adenovirus-mediated gene transfer technique, which enables nearly 100% of SMCs to be transduced, we expressed a dominant-negative form of Rac, Cdc42, and RhoA (N\(^{17}\)-Rac, N\(^{17}\)-Cdc42, and N\(^{19}\)-RhoA, respectively) or LacZ as a control. Expression of the dominant-negative Rho family GTPases in infected cells was confirmed by Western blotting using respective specific antibodies (Figure 4B). In LacZ-expressing SMCs, directed migration toward PDGF was observed as in noninfected SMCs (compare Figures 1A and 4A). Expression of either N\(^{17}\)-Rac or N\(^{17}\)-Cdc42 substantially inhibited migration toward PDGF by >60%. In contrast, expression of N\(^{19}\)-RhoA rather slightly enhanced PDGF-induced migration. The results indicate that Rac and Cdc42 play essential roles in PDGF-elicted migration.

**SIP Inhibits PDGF-Induced, Rac-Dependent Membrane Ruffling**

We next examined how SIP affected PDGF-induced reorganization of the actin cytoskeleton. Shown in Figure 4C are SMCs stained with tetramethyl rhodamine B isothiocyanate...
(TRITC)-labeled phalloidin to visualize F-actin. In an unstimulated state, SMCs showed stress fibers (a). The addition of PDGF vigorously induced membrane ruffling and reduced stress fibers (b). These PDGF-induced changes were abolished by adenovirus-mediated expression of N17−Rac (f) and N17−Cdc42 (g), but not N19−RhoA (h), indicating that Rac and also probably Cdc42 are required for these PDGF-elicited responses. S1P alone slightly enhanced the formation of stress fibers (c). Importantly, S1P abolished PDGF-induced membrane ruffling (d). This latter observation is consistent with the fact that S1P inhibited PDGF-induced Rac activation and cell migration.

S1P Inhibits PDGF-Induced Migration and Rac Activity in Human SMCs, Whereas It Stimulates Rac Activity and Migration in HUVECs

We examined whether S1P exerted similar inhibitory activities on vascular SMCs from other species. As shown in Figures 4D and 4E, S1P dose dependently inhibited PDGF-induced migration and Rac activation in human vascular SMCs, just like rat SMCs. In sharp contrast, S1P by itself served as a chemoattractant for HUVECs to induce chemotaxis (Figure 5A), as reported previously.12,23,24 In the latter cell type, S1P increased Rac and Cdc42. N17−Rac and N17−Cdc42, but not N19−RhoA, substantially attenuated S1P-directed chemotaxis of HUVECs (Figure 5D), indicating that SMCs and HUVECs use common machinery for cell migration. Expression of the dominant-negative Rho family GTPases was confirmed by Western blot analysis (Figure 5C). These results indicate that S1P-induced Rac stimulation contributes to S1P-directed chemotaxis in HUVECs.

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Northern blot analysis of total RNA from the vascular cells showed a reciprocal expression of Edg-1 and Edg-5 (Figure 5E). Thus, Edg-1 mRNA is abundantly expressed in HUVECs but is only slightly expressed in SMCs. By contrast, Edg-5 is the predominant isoform expressed in SMCs but is undetectable in HUVECs. Both cell types show comparable extent of moderate expression of Edg-3 mRNA.

Overexpression of Edg-1 and Edg-5 in SMCs and HUVECs, Respectively, Reduces S1P-Induced Inhibition and Stimulation, Respectively, of Migration and Rac Activation

The SMCs that stably overexpressed Edg-1 (Figure 6A) were established and assayed for migration and Rac activity. In the Edg-1–overexpressing SMCs, S1P inhibition of migration was attenuated: S1P only at concentrations equal to and higher than 1 μmol/L inhibited PDGF-induced chemotaxis (Figure 6B). On the other hand, the vector-transfected cells showed dose-dependent inhibition of migration in response to S1P, similar to nontransfected SMCs (Figure 1B). In the vector-transfected cells, S1P (0.1 μmol/L) inhibited PDGF-induced Rac stimulation, whereas in the Edg-1–overexpressing cells S1P did not inhibit PDGF-induced Rac stimulation and instead by itself stimulated Rac (Figure 6C).

In the HUVECs that were cotransfected with the expression vectors for Edg-5 and enhanced green fluorescent protein (EGFP) (Figure 6D), S1P (1 μmol/L)-stimulated chemotaxis was markedly reduced compared with the cells transfected with the empty vector and EGFP vector (Figure 6E). In the HUVECs cotransfected with the expression vectors for Edg-5 and myc-tagged Rac, S1P-induced Rac stimulation was reduced compared with vector-transfected cells (Figure 6F).
Discussion

The present study demonstrated that the platelet-derived lysophospholipid mediator S1P exerted vascular cell type–specific, bimodal regulation on the activity of Rac, a molecular switch for regulating cell motility, and consequently motility via a receptor-mediated mechanism: in SMCs S1P inhibited the chemoattractant PDGF-induced Rac activation and Rac-dependent chemotaxis (Figures 1, 2, and 4), whereas in HUVECs S1P by itself robustly stimulated Rac activity and chemotactic migration (Figure 5).

The Rho family GTPases Rac, Cdc42, and Rho regulate actin cytoskeletal reorganization and contractile actomyosin activity, thereby controlling cell motility. On the other hand, S1P exerts an unique inhibitory activity on cell motility in SMCs11,13(Figure 1). It is unknown in SMCs how S1P regulates Rac activity to control cell motility. On the other hand, S1P is a powerful chemoattractant for endothelial cells12,23,24 (Figure 5), likely underlying its potent angiogenic activity. A recent study demonstrated in endothelial cells that S1P stimulated both Rac and Rho. Specific inactivation of endogenous Rho with C3 toxin was shown to reduce S1P-stimulated chemotaxis.23 However, the involvement of Rac has not been directly tested. In the present study, we tried to understand in depth the roles for the three Rho family GTPases in S1P-induced regulation of migration in the two vascular cell types. To address this question, we first quantified amounts of active, GTP-bound forms of the Rho family GTPases in PDGF- and S1P-stimulated cells. PDGF induced an increase in GTP-Rac, as expected (Figures 2 and 4). Notably, S1P markedly reduced amounts in GTP-Rac in PDGF-stimulated SMCs.

This inhibitory effect was dose-dependent with a dose-response relationship similar to that for S1P inhibition of chemotaxis (Figures 1B and 2B) and was also time-dependent. Consistent with Rac inhibition, S1P abolished PDGF-induced membrane ruffle formation, which is a Rac-dependent process (Figure 4C). In contrast to this, S1P stimulated Rac activity in HUVECs with a dose-response relationship similar to that for S1P-stimulated chemotaxis (Figures 5A and 5B). To further explore roles for Rac in PDGF- and S1P-stimulated chemotaxis, we expressed a dominant-negative form of Rac. Adenovirus–mediated expression of N17–Rac substantially attenuated both PDGF- and S1P-induced cell migration in SMCs and HUVECs, respectively (Figures 4A and 5D), indicating requirement of Rac for cell migration triggered by a receptor tyrosine kinase as well as a G protein–coupled receptor in SMCs and endothelial cells, respectively. Taken together, these results strongly suggest that S1P-induced inhibition of SMC migration is mediated, at least in part, through suppression of PDGF-induced Rac activation, whereas S1P-stimulated chemotaxis of HUVECs is mediated by S1P-induced increases in Rac activity.

Accumulating evidence demonstrates that Cdc42 and Rho have distinct roles for promoting cell motility from Rac. In fact, expression of N17–Cdc42 suppressed chemotaxis in both SMCs and HUVECs that were stimulated with PDGF and S1P, respectively, suggesting requirement of Cdc42 for migration of these cell types. However, it is also possible that the inhibitory effects of N17–Cdc42 expression on migration might have been brought about by inhibition of a cellular guanine-nucleotide exchange factor for Rac (Rac-GEF), because a number of Rac-GEFs were also shown to act as GEFs for Cdc42.28 Consistent with this notion, we found that expression of N17–Cdc42 as well as N17–Rac inhibited PDGF-induced membrane ruffling, a morphological change typically caused by activation of Rac, but not Cdc4221 (Figure 4C, f and g).

Expression of N19–RhoA, on the other hand, slightly but consistently stimulated PDGF-induced migration of SMCs and had no effect on S1P-stimulated migration of HUVECs. Previous observations concerning the effects of inhibiting Rho and its downstream effector Rho kinase on cell migration in various cell types are inconsistent: the inhibition of Rho activity using N19–RhoA and C3 toxin in macrophages,25 intestinal epithelial cells,29 and colonic carcinoma cells29,30 reduced cell migration. Quite differently from these observations, Rho inhibition in fibroblastic cell types did not reduce cell migration,26,27 and a Rho kinase inhibition in these cell types even stimulated cell migration under a certain condition.26 Thus, the migration responses of SMCs and HUVECs to expression of N19–RhoA, observed in the present study are similar to the latter observations. It is well known that Rho stimulates contractile actin–myosin filaments, resulting in the formation of stress fibers and focal adhesions, which likely inhibits cell locomotion.22,26 On the other hand, Rho-mediated stimulation of contractile actomyosin activity may also play a role in cell movement.22 In both SMCs and HUVECs, we found that stress fibers and focal adhesions were well developed under basal unstimulated conditions. Thus, these cell types likely have significant basal Rho activities. In the present experimental condition in which the expression of N19–RhoA reduced, but not totally abolished, stress fibers in SMCs (data not shown), some basal Rho activity that was enough for cell movement likely remained, resulting in stimulation of migration with a reduced cell adhesion to the substratum.26

Because S1P failed to inhibit PDGF-induced tyrosine phosphorylation of PDGF receptor in SMCs, the site of S1P action was likely distal to PDGF receptor activation itself. Previous studies demonstrated that cAMP- and cGMP-elevating receptor agonists and cell permeable analogues of cAMP and cGMP reduced chemotaxis in SMCs. It was shown previously that S1P increased intracellular cAMP concentration in SMCs.11 However, it is unlikely that the S1P inhibition of PDGF-induced Rac stimulation and chemotaxis was due to an increase in cellular cAMP, because we observed that forskolin at a concentration that induced a similar extent of cellular cAMP rise to that caused by S1P failed to inhibit Rac in SMCs (Y. Ryu and Y. Takuwa, unpublished observation, 2001). We recently found in Chinese hamster ovary cells expressing Edg-5 that S1P stimulated the activity of GTPase-activating protein for Rac, but did not inhibit the activity of a GEF for Rac,21 suggesting that stimulation of Rac-GAP activity accounted for observed Rac inhibition in S1P-stimulated cells. Whether or not this mechanism is operating in S1P-stimulated SMCs remains to be proven.
Both SMCs and HUVECs express more than a single type of S1P receptors (Figure 5E). We recently demonstrated in a heterologous expression system of cloned Edg receptors that among the three most widespread S1P receptors Edg-1, -3, and -5, Edg-1 and -3 acted as chemoattractant receptors with stimulation of Rac, whereas Edg-5 acted as a chemotaxis-inhibiting or chemorepellent receptor, with inhibition of Rac. Edg-1 and Edg-5 are dominant types of S1P receptors in endothelial cells and SMCs, respectively (Figure 5E). Thus, these observations together with previous findings suggest that Edg-5 mediates inhibition of Rac activity and migration in SMCs, whereas Edg-1 and also Edg-3 mediate Rac stimulation and chemotaxis in HUVECs. The observed less potency of the S1P-related agonist DH-S1P in inhibiting SMC migration compared with S1P (Tables 1 and 2) lends support to the notion that Edg-5 mediates S1P-induced inhibition of Rac and migration, because DH-S1P was previously shown to be at least a one order less potent agonist for Edg-5, but not for Edg-1 and Edg-3. Relative expression of the attractant receptors Edg-1 and Edg-3 and the repulsive receptor Edg-5 seems to determine the motility response to S1P. Consistent with this notion, we observed that the overexpression of Edg-1 in SMCs attenuated S1P inhibition of PDGF-directed chemotaxis and reciprocally that of Edg-5 in HUVECs reduced S1P stimulation of chemotaxis (Figure 6). Relative expression of the Edg S1P receptors seems to vary among different SMCs and thus to generate a difference in the cell motility response to S1P among the cell types. For example, it was recently reported that PDGF stimulation of human SMCs induced production and secretion of S1P, which then stimulated Edg-1 receptor on SMCs to induce chemotaxis.

In the vascular wall, S1P, which likely derives from abundantly stored in platelets, is a normal constituent of human plasma and activates SMCs. may exert a variety of actions on both SMCs and endothelial cells; S1P could stimulate proliferation of SMCs and endothelial cells, modulate vascular tone bimodally by directly constricting SMCs and stimulating endothelial production of nitric oxide, and and angiogenesis. The present study has added the unique inhibitory actions of S1P on Rac and migration in SMCs to a panel of the pleiotropic activities of S1P on vascular cells. This S1P action together with its stimulatory activity on endothelial nitric oxide production may represent antiatherogenic activity of S1P.

Acknowledgments

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References


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