



Sphingosine 1-Phosphate and Atherosclerosis

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Sphingosine 1-phosphate (S1P) is a potent lipid mediator that works on five kinds of S1P receptors located on the cell membrane. In the circulation, S1P is distributed to HDL, followed by albumin. Since S1P and HDL share several bioactivities, S1P is believed to be responsible for the pleiotropic effects of HDL. Plasma S1P levels are reportedly lower in subjects with coronary artery disease, suggesting that S1P might be deeply involved in the pathogenesis of atherosclerosis. In basic experiments, however, S1P appears to possess both pro-atherosclerotic and anti-atherosclerotic properties; for example, S1P possesses anti-apoptosis, anti-inflammation, and vaso-relaxation properties and maintains the barrier function of endothelial cells, while S1P also promotes the egress and activation of lymphocytes and exhibits pro-thrombotic properties. Recently, the mechanism for the biased distribution of S1P on HDL has been elucidated; apolipoprotein M (apoM) carries S1P on HDL. ApoM is also a modulator of S1P, and the metabolism of apoM-containing lipoproteins largely affects the plasma S1P level. Moreover, apoM modulates the biological properties of S1P. S1P bound to albumin exerts both beneficial and harmful effects in the pathogenesis of atherosclerosis, while S1P bound to apoM strengthens anti-atherosclerotic properties and might weaken the pro-atherosclerotic properties of S1P. Although the detailed mechanisms remain to be elucidated, apoM and S1P might be novel targets for the alleviation of atherosclerotic diseases in the future.

Key words: Sphingosine 1-phosphate, HDL, Apolipoprotein M, Atherosclerosis

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Introduction

Sphingosine 1-phosphate (S1P) is a potent lipid mediator composed of one long hydrophobic chain and one phosphoric acid group. S1P exerts potent physiological effects through five S1P receptors (S1P1-5) located on cell membranes, while some reports have also demonstrated potential roles of S1P inside cells. The physiological activities of S1P are various: S1P promotes cell proliferation, prevents apoptosis¹, preserves the endothelial barrier², attracts lymphocytes³, and so on. Therefore, S1P is thought to be involved in various diseases including atherosclerosis, cancer⁴, diabetes⁵, congenital disorders⁶, kidney diseases⁷, and immunological diseases⁸. Among them, the asso-

ciation between S1P and atherosclerosis has been investigated for a long time.

A unique characteristic distribution of S1P in the circulation is that about two-thirds of S1P in plasma is carried on HDL, followed by albumin⁹. Importantly, Christoffersen *et al.* revealed that apolipoprotein M (apoM), a minor apolipoprotein on HDL¹⁰, is a carrier of S1P on HDL¹¹. Since HDL possesses several pleiotropic properties, such as anti-inflammation, anti-oxidation, anti-thrombosis, and vasorelaxation¹², and S1P shares many of these effects, S1P is believed to contribute to many of the cardioprotective properties of HDL¹³. In addition to the properties of apoM as a carrier of S1P, we demonstrated that apoM is not a mere carrier of S1P, but also a modulator of plasma and cellular S1P levels and that the homeostasis of apoM-containing lipoproteins can largely affect the plasma S1P levels. In addition, as described in this review, recent studies have elucidated that S1P bound to apoM/HDL possesses different properties from those of S1P bound to albumin, which may at least partly explain the dual nature of S1P in the fields of

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Received: June 19, 2017

Accepted for publication: June 26, 2017

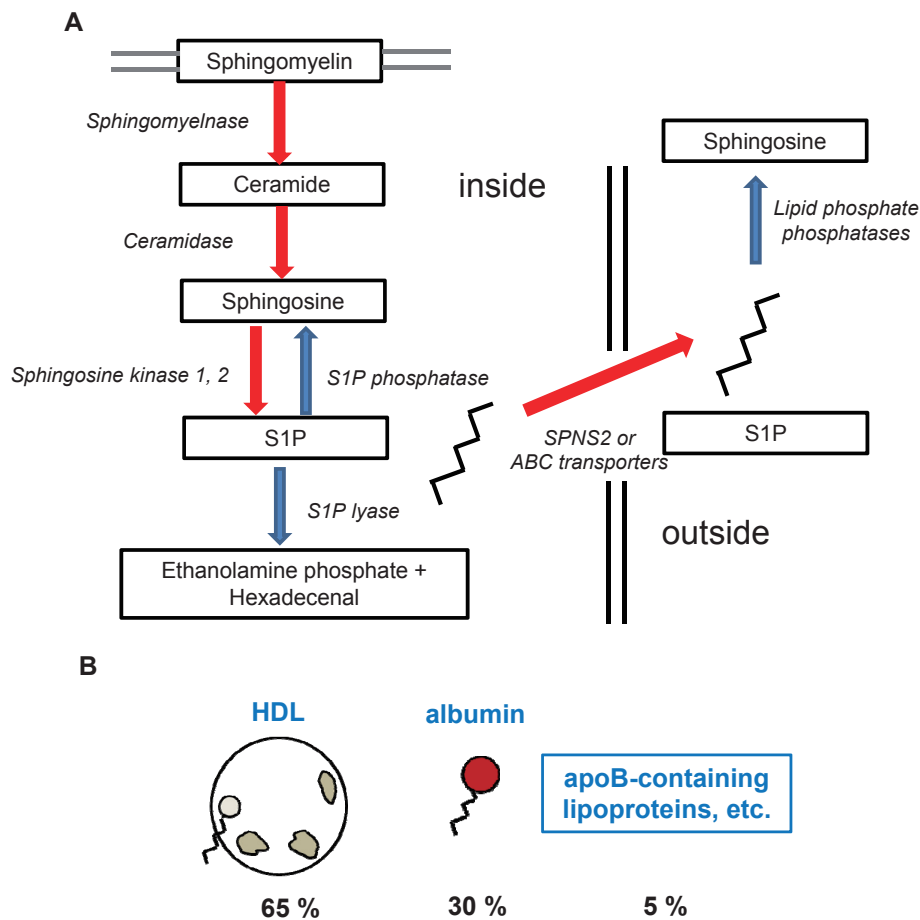


Fig. 1. Homeostasis of sphingosine 1-phosphate

The schema show the biosynthesis of sphingosine 1-phosphate (S1P) and its distribution in the circulation. (A) Biosynthesis, efflux, and degradation of S1P. (B) Distribution of S1P in plasma.

atherosclerosis.

Keeping these backgrounds in mind, the present review will provide an overview of recent findings on the association between S1P and atherosclerosis, focusing mainly on apoM.

Biosynthesis and Homeostasis of S1P

S1P is derived from ceramide inside cells, which is formed *de novo* or from the breakdown of membrane-resident sphingomyelin. Ceramide is converted to sphingosine by ceramidase, and then sphingosine is phosphorylated into S1P by sphingosine kinase (SphK) 1 or 2, which are the enzymes responsible for producing S1P¹⁴. In cells, S1P can be reversibly or irreversibly degraded to sphingosine or hexadecenal and phosphoethanolamine by S1P-specific phosphatase or S1P lyase (**Fig. 1A**). The main sources of S1P in the circulation are erythrocytes¹⁵, platelets¹⁶, and the endothelium¹⁷, while many kinds of cells express

SphKs and produce S1P *de novo*. Although how S1P is exported from cells remains to be fully elucidated, several transporters have been demonstrated to be involved in this process. S1P secretion from platelets has been speculated to occur via a vesicle-mediated manner¹⁸ or via some unknown S1P transporters¹⁹, and ATP binding cassette subfamilies²⁰ and Band3²¹ might be involved in the excretion of S1P from erythrocytes, while spinster homolog 2 has been shown to function as an S1P transporter in endothelium cells²². After S1P is secreted from cells, S1P can work as an agonist for S1P receptors located on cell membrane and can be rapidly degraded by lipid phosphate phosphatases²³. In circulation, about two-thirds of S1P is distributed to HDL, followed by albumin and other lipoproteins⁹ (**Fig. 1B**). It remains to be elucidated, however, how exported S1P is bound to these carriers, although a phospholipid transfer protein is reportedly required to maintain the S1P content on HDL²⁴.

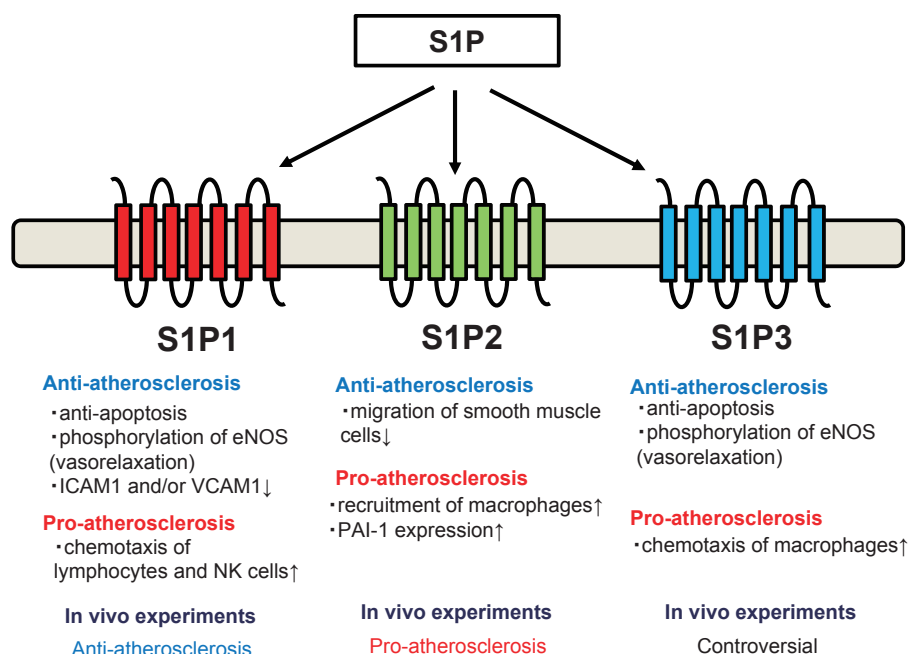


Fig. 2. Dual nature of sphingosine 1-phosphate in the pathogenesis of atherosclerosis
The biological properties exerted by S1P through each S1P receptor are shown.

Dual Nature of S1P in the Pathogenesis of Atherosclerosis

The roles of S1P in the fields of atherosclerosis have been demonstrated in many elegant reports; in general, S1P possesses protective roles in atherosclerosis, but it can also exert harmful effects during the pathogenesis of atherosclerosis (**Fig. 2**).

Regarding the protective properties of S1P, HDL-associated S1P promotes the survival and prevents the apoptosis of endothelial cells mainly through S1P1 and S1P3²⁵⁻²⁷, as is the case in macrophages²⁸. HDL-associated S1P also induces the phosphorylation of eNOS through S1P1 and S1P3, thereby promoting the relaxation of vessels^{29, 30} and accounting, at least in part, for the statin-induced activation of eNOS^{31, 32}. S1P also preserves the endothelial barrier function through the spreading of endothelial cells³³, the stabilization of endothelial cell-cell junctions³⁴, and the NO-mediated suppression of endothelial cell contractility³⁵ via the S1P1/PI3K pathway. S1P suppresses the attachment of blood cells, which is an initial step in the formation of atherosclerotic lesions, by inhibiting the expression of VCAM1 and/or ICAM1 on endothelial cells^{30, 36}. While only limited reports are presently available, S1P might also attenuate inflammatory responses in monocytes³⁷ and prevent atherosclerosis by inhibiting the migration of smooth muscle cells through S1P2³⁸. As well as its protective effects

on vessels, S1P can also protect the heart from damage, such as ischemia. S1P protects cardiomyocytes from apoptosis mainly through S1P1 and S1P3^{39, 40}.

Regarding the harmful properties of S1P, S1P is reported to induce inflammation and thrombosis. The most famous role of S1P in inflammation is its ability to act as a chemoattractant for lymphocytes, and this role is the target of a novel immunosuppressant, fingolimod⁴¹; the S1P gradient facilitates the egress of lymphocytes from lymphoid organs into the circulation and the recruitment of lymphocytes to sites of inflammation^{42, 43}. S1P is also believed to facilitate inflammation by activating other immune cells; S1P induces intracellular calcium signaling as a second messenger⁴⁴, activates NF- κ B⁴⁴, promotes chemotaxis, and stimulates the production of TNF- α in macrophages and/or monocytes^{45, 46}, and S1P is required for NK cells to egress from lymphoid tissue and bone marrow through S1P1 and S1P5^{47, 48}. A recent study also elucidated that the blockade of S1P2 signaling augments B1 lymphocytes⁴⁹, which are deemed to be atheroprotective cells. Another possible harmful aspect of S1P is that S1P or its receptors has been reported to be associated with coagulation factors. S1P has been shown to augment the thrombin-induced expression of tissue factor in endothelial cells⁵⁰, and S1P has also been proposed to induce the expression of PAI-1 in adipocytes^{51, 52}, hepatocytes⁵³, and glioblastoma cells⁵⁴, suggesting that S1P has a

pro-thrombotic property. SphK1 is also reported to be involved in the Factor-Xa-induced migration of smooth muscle cells⁵⁵. A recent study also demonstrated the possible involvement of S1P in platelet activation; when SphK2, which is an enzyme that produces S1P in platelets, is deleted in mice, the mice showed resistance to arterial thrombosis⁵⁶. In addition, although S1P preserves the barrier functions of endothelial cells, it can contrarily inhibit barrier functions via the S1P2/Rho/ROCK pathway⁵⁷.

Actually, several reports have investigated the physiological roles of S1P and S1P receptors in the pathogenesis of atherosclerosis using animal experiments. For example, S1P3 knockout mice exhibited resistance to the protective properties of HDL or S1P in a model of coronary infarction⁵⁸, while one report showed the promotion of monocyte/macrophage recruitment and neointima formation caused by carotid artery ligation in S1P3 knockout mice⁴⁵. S1P2 knockout mice developed atherosclerotic lesions to a lesser degree when they had a background of apoE deficiency with reduced macrophage recruitment⁵⁹. Regarding S1P1, although S1P1 knockout mice are embryonic lethal⁶⁰, pharmacological experiments using an S1P1 agonist showed that the S1P1 agonist protected LDL receptor knockout mice from atherosclerosis⁶¹. Together, these reports suggest that S1P1 and S1P3 mainly exert anti-atherosclerotic properties, while S1P2 exerts pro-atherosclerotic properties. Further studies are needed to investigate the involvement of S1P receptors in the pathogenesis of atherosclerosis. Regarding the effects of S1P levels, a sphingosine kinase inhibitor has been demonstrated to suppress atherosclerosis lesions in LDL receptor knockout mice fed a high cholesterol diet, but not in mice fed normal chow⁶². Contrary to the possible anti-atherosclerotic properties of lowering S1P using a SphK inhibitor, the overexpression of apoM in LDLr knockout mice and apoE knockout mice protected the mice against atherosclerosis, although the association with S1P was not mentioned⁶³. These results suggest that S1P bound to apoM might possess distinct properties from S1P bound to albumin in the pathogenesis of atherosclerosis.

ApoM Modulates the Homeostasis of Plasma S1P Levels

As described above, the distribution of S1P in plasma is unique compared with those of other lysophospholipids; about two-thirds of S1P in plasma is carried on HDL. For a long time, the reason for this distribution of S1P remained unknown. In 2011, however, Christoffersen *et al.* reported that apoM

serves as a carrier of S1P on HDL¹¹. In addition to the role of apoM as a vehicle of S1P, we have demonstrated that apoM increased S1P levels in the whole body; when we overexpressed apoM in HepG2 cells or murine livers, we observed that not only did the S1P levels in the supernatant or plasma increase, but the S1P contents in the cells or liver also increased. The mechanism for the apoM-mediated modulation of S1P metabolism has now been fully elucidated, and we reported the possibility that apoM might retard the degradation of S1P levels⁶⁴. Although still uncertain, apoM possesses a lipophilic pocket, which might bind S1P¹¹; therefore, enzymes that degrade S1P, such as lipid phosphate phosphatase, cannot physically access S1P. Considering the same modulation of plasma S1P levels reported in several papers^{65, 66}, the net amount of S1P in the total body might be affected by apoM. Of note, however, human plasma S1P levels were not or were only weakly correlated with serum apoM levels⁶⁷ (data not shown in our previous article⁶⁸). The reasons might be that S1P is also distributed to albumin as well as HDL and/or that apoM can bind to lipids other than S1P, such as retinol⁶⁹.

Since apoM rides on lipoproteins, especially HDL¹⁰, the apoM and S1P levels are affected by lipoprotein homeostasis (**Fig. 3**). Interestingly, when we investigated the correlation between S1P levels and lipoproteins, we observed the significant correlation between S1P levels and LDL cholesterol levels⁷⁰. Therefore, we investigated the modulation of plasma S1P levels by the LDL receptor, which largely affects the LDL cholesterol levels. When we overexpressed the LDL receptor in the livers of wild-type mice, we observed a marked decrease in the plasma apoM and S1P levels, especially the S1P levels on HDL. When we overexpressed the LDL receptor in the livers of apoE-deficient mice, however, no modulations of the plasma apoM and S1P levels were seen⁷¹. Considering that both apoE and apoB act as ligands for the LDL receptor, we concluded that the LDL receptor cleared S1P on apoM-containing lipoproteins, using apoE as a ligand. Actually, in a human study, statin was reported to decrease the serum apoM levels, which agrees with this conclusion^{72, 73}. In addition to the LDL receptor, we also investigated the modulation of plasma apoM and S1P levels using cholesteryl ester transfer protein (CETP), since CETP largely affects the HDL-cholesterol levels and has attracted attention as a possible target for overcoming hypo-HDL cholesterolemia⁷⁴. When we overexpressed CETP in murine livers, we observed no modulation of the plasma apoM or S1P levels. Regarding the distribution of apoM and S1P, however, we found that the apoM and S1P contents shifted from HDL to apoB-containing

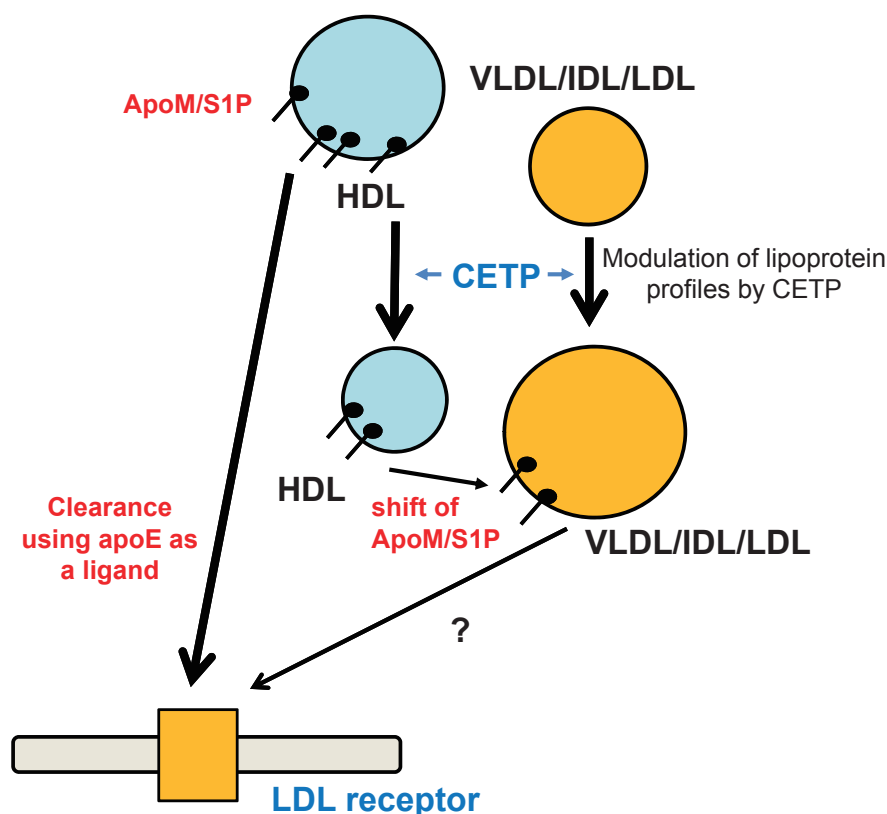


Fig. 3. Modulation of plasma sphingosine 1-phosphate levels by homeostasis of apolipoprotein M-containing lipoproteins

Apolipoprotein M (ApoM)-containing lipoproteins are cleared through the LDL receptor using apolipoprotein E (apoE) as a ligand, and modulation of the lipid profile by cholesteryl ester transfer protein (CETP) (i.e., a decrease in HDL cholesterol and an increase in VLDL/IDL/LDL cholesterol) shifts sphingosine 1-phosphate (S1P) bound to apoM-containing HDL to VLDL/IDL/LDL.

lipoproteins. Interestingly, we also observed that S1P bound to apoB-containing lipoproteins possessed rather stronger properties in the phosphorylation of eNOS in HUVECs and the secretion of insulin from MIN6 cells. Therefore, CETP might augment the physiological properties of S1P in the plasma by shifting the distribution of S1P and apoM from HDL to apoB-containing lipoproteins, on which S1P might exert more potent bioactivities⁷⁵.

In agreement with this idea, we and others have demonstrated that the modulation of apoM by some reagents or conditions affects the plasma S1P levels both inside and outside of cells. Regarding reagents, we have recently revealed that resveratrol modulates S1P levels by affecting apoM levels⁷⁶. Resveratrol increases the cellular expression of apoM in HepG2 cells and therefore increases cellular S1P levels; regarding medium levels of apoM and S1P, although resveratrol increased the medium apoM and S1P levels when administered at a concentration up to 2 μ M, it

decreased the medium apoM and S1P levels when administered at a concentration of 20 μ M by augmenting the LDL receptor-mediated clearance of apoM and S1P, as described above⁷¹. In human subjects, however, considering that a moderate intake of resveratrol did not increase the resveratrol concentrations *in vivo* to a concentration of 20 μ M and that a decrease in the apoM and S1P levels was not observed in the medium of human primary hepatocyte cultures, resveratrol, which has been proposed as a supplement to prevent atherosclerosis⁷⁷, might exert its anti-atherosclerotic properties, at least in part, by increasing the plasma apoM and S1P levels. Another reagent deeply involved in the regulation of apoM and S1P is insulin. Insulin treatment decreased the expression of apoM levels in murine plasma, livers, and kidneys, as well as in HepG2 cells⁷⁸. The physiological regulation of apoM and S1P levels by insulin, however, remains to be elucidated. While an elevation in plasma and hepatic apoM and S1P levels was observed in strepto-

zotocin-induced diabetic mice⁷⁸), another group reported that the apoM levels were down-regulated by insulin in an alloxan-diabetic mouse model⁷⁹), which is a model of insulin deficiency similar to streptozotocin-induced diabetic mice. Although the involvement of apoM has not been determined, S1P levels are reportedly modulated by several other reagents, such as propofol⁸⁰, intralipid⁸¹, and rosiglitazone⁸²). Further studies are necessary to elucidate the involvement of the regulation of apoM by these reagents, considering the emerging importance of apoM in the functions of S1P as described below.

As well as reagents, several pathological conditions have been reported to affect plasma S1P levels by regulating apoM. For example, apoM and/or S1P levels were reduced in subjects with severe infectious diseases^{83, 84}) and septic animal models⁸⁵). In sepsis, the plasma apoM and S1P levels are reduced. Considering the vasoprotective properties of S1P, this decrement in apoM during sepsis might somehow explain the organ injuries and disturbed vascular barrier function⁸⁶). As expected from the modulation of apoM by insulin, diabetes, which is one of the major risk factors for atherosclerosis, might be associated with plasma apoM/S1P levels; S1P bound to HDL has been demonstrated to be higher in subjects with type 2 diabetes⁸⁷), and although the concentration of apoM and S1P was not modulated, apoM and S1P were shifted toward light HDL particles in type 1 diabetes⁸⁸). In addition, several reports have demonstrated an association between SNPs of *APOM* and diabetes^{89, 90}).

Modulation of S1P Functions by apoM

In addition to the modulation of S1P metabolism by apoM, apoM might possibly influence the biological functions of S1P. S1P bound to apoM exerts more potent activities on S1P1 in endothelial cells; S1P bound to apoM containing HDL activates the ERK and Akt signals through S1P1 to a greater degree than S1P bound to albumin¹¹), and S1P bound to apoM containing HDL activated Gi signaling to a greater degree than S1P bound to albumin and attenuated the TNF α -induced activation of NF- κ B and the expression of ICAM-1⁹¹). Along with endothelial cells, S1P bound to apoM augmented insulin secretion from MIN6 cells, a cell line of pancreatic β -cells, through S1P1 and/or S1P3⁹²). The reason why apoM augments the biological properties of S1P remains to be elucidated, but several possibilities exist. One possibility is that apoM maintains the S1P concentration in the medium by inhibiting S1P from degrading as a result of lipid phosphate phosphatases⁹²). Another possibility is that S1P bound to apoM-containing HDL

might access S1P1 located on the cell membrane through HDL receptors, such as SR-BI, more easily³⁰).

Interestingly, some reports demonstrated that apoM did not only increment S1P activities, but that it might attenuate some aspects of S1P bioactivities. Unlike S1P bound to albumin, which promotes the egress of lymphocytes, S1P bound to apoM does not promote lymphocyte trafficking and instead inhibits lymphopoiesis through S1P1⁹³). Therefore, the inflammatory properties of S1P, regarding the activation of lymphocytes as described above^{42, 43, 94}), might be limited only to S1P bound to albumin, and not to S1P bound to apoM. Regarding the pro-thrombotic properties of S1P, the carrier might also influence the physiological roles of S1P. As described above, S1P is thought to induce PAI-1, which causes thrombotic conditions⁵¹⁻⁵⁴). However, the abilities of S1P to increase the expression of PAI-1 have not been compared between S1P bound to albumin and S1P bound to apoM. Recently, we measured the plasma S1P levels and the apoM levels and compared them with the active PAI-1 concentrations. A significant correlation was observed only between PAI-1 and S1P, and not between PAI-1 and apoM. Therefore, we compared the ability of S1P bound to albumin and that of S1P bound to apoM to induce PAI-1 expression in 3T3L1 adipocytes and found that only S1P bound to albumin, and not S1P bound to apoM, increased the PAI-1 expression. Moreover, when we performed similar experiments using HUVECs, we observed that S1P bound to apoM decreased the expression of PAI-1⁶⁸). Since the induction of PAI-1 by S1P can be ascribed to S1P2 signaling⁶⁸), we speculated that S1P bound to apoM might not or only weakly work as an agonist for S1P2.

Considering these reports on the modulation of S1P functions by apoM, apoM appears to strengthen the agonist properties of S1P for S1P1 and/or S1P3, while it weakens the agonist properties for S1P2 (**Fig. 4**). Moreover, although the involvement of apoM was not investigated, S1P bound to HDL has been reported to possess mainly beneficial effects, as described above, supporting this idea. Further studies are necessary to prove this hypothesis.

S1P and apoM in Atherosclerosis in Human Samples

Despite the possible involvement of S1P in the pathogenesis of atherosclerosis, clinical evidence of the involvement of S1P in atherosclerosis has remained insufficient, possibly because plasma S1P levels should be measured in samples collected under specific conditions⁷⁰) and because it would be better to investigate

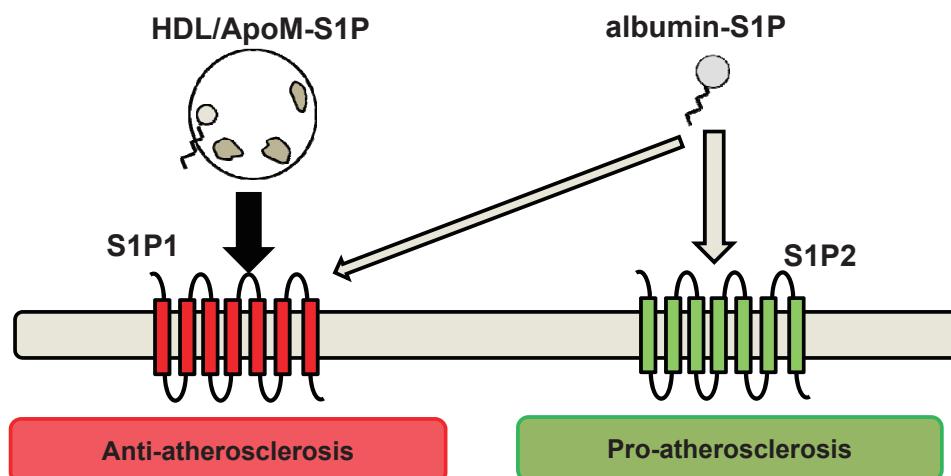


Fig. 4. Modulation of the functions of sphingosine 1-phosphate by apoM

Apolipoprotein M (ApoM) strengthens the agonist properties of sphingosine 1-phosphate (S1P) for S1P1 (anti-atherosclerotic S1P receptor), while it weakens the agonist properties for S1P2 (pro-atherosclerotic S1P receptor).

the association between S1P and atherosclerosis by separating S1P bound to HDL from S1P bound to albumin. At present, only four studies have shown an association between plasma S1P levels and atherosclerotic diseases⁹⁵⁻⁹⁸). Among them, Sattler *et al.* reported that S1P bound to HDL was less prevalent, while S1P uncoupled from HDL was more prevalent, in subjects with myocardial infarction and stable angina⁹⁶), supporting the idea that S1P bound to apoM possesses anti-atherosclerotic properties while S1P bound to albumin might be somehow involved in the harmful effects of S1P (**Fig. 4**). Other clinical studies have also demonstrated that the plasma S1P levels were lower in patients with myocardial infarction^{95, 97}) and that S1P bound to HDL might predict the severity of coronary heart disease⁹⁸).

Regarding apoM, although an association between the total apoM level and atherosclerosis has not been shown⁶⁸), *APOM* polymorphism has been reported to be associated with atherosclerosis^{99, 100}). Further studies are needed to elucidate the involvement of apoM in human atherosclerosis.

Conclusions

The results of basic studies suggest that S1P is involved in the pathogenesis of atherosclerosis. However, a dual nature, i.e., both anti-atherosclerotic and pro-atherosclerotic properties, has been reported. Recently, apoM has been shown to act as a carrier and a modulator of S1P. ApoM largely affects the homeostasis of S1P, and importantly, S1P bound to apoM

might possess only anti-atherosclerotic effects. Although further studies are needed, the emerging importance of apoM suggests that apoM might be useful for laboratory testing and/or medical therapy to realize the pleiotropic effects of HDL in clinical practice.

Acknowledgements

This work was supported by CREST from the JST/AMED, a Grant-in-Aid for Scientific Research on Innovative Areas 15H05906 (Y.Y.), JSPS KAKENHI Grant Numbers 1 16H06236 (M.K.), the Takeda Science Foundation, and the MSD Life Science Foundation, Public Interest Incorporated Foundation (M.K.).

Conflicts of Interest

None.

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