Vascular protection by high-density lipoprotein-associated sphingosine-1-phosphate

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Abstract
Epidemiological studies and animal experiments have consistently demonstrated cardiovascular protection by high-density lipoprotein (HDL). Findings from a growing number of studies further indicate that sphingosine-1-phosphate (S1P) mediates many of the beneficial effects of HDL on the cardiovascular system, including vasodilatation, angiogenesis, maintenance of endothelial barrier function, and protection against atherosclerosis and ischemia/reperfusion injury. In this review, we summarize the most recent literature investigating the effects of HDL-S1P on cardiovascular health and highlight potential opportunities for clinical translation of these findings.

Keywords: ApoM; HDL-associated S1P; Vascular function

1 Introduction
Epidemiological investigations and animal experiments have consistently demonstrated cardiovascular protection by high-density lipoprotein (HDL). The most common explanation for these findings is that the basic role of HDL plays in the reverse cholesterol transport process (RCT), by which excess cholesterol is transported from peripheral cells to the liver for elimination via biliary excretion or reutilization in the enterohepatic cycle. HDL particles are composed of apolipoprotein A-I (apo A-I), a phosphatidylcholine shell, more than 80 quantitatively minor proteins, hundreds of diverse lipid species, and micro-ribonucleic acids (microRNAs). Among these, apo A-I molecules have been established as structurally and functionally important components of HDL particles playing a critical role in RCT. Moreover, pleiotropic anti-inflammatory, anti-oxidative, anti-apoptotic, and vasodilatory effects of apo A-I have been confirmed and are proposed to independently contribute to HDL modulation of cardiovascular risk.

Separate from apolipoprotein effects, recent evidence suggests that the lysosphingolipid sphingosine-1-phosphate (S1P) may also contribute to many of the biological actions of HDL. S1P is a bioactive sphingolipid mainly contained within HDL. The S1P content of HDL has been proposed to modulate multiple pleiotropic functions of HDL. HDL employs S1P receptors via certain signaling pathways to exert HDL-ascribed biological effects. It has been confirmed that S1P and its receptors, five specific G protein-coupled receptors, can regulate multiple biological responses in kinds of system, including in the cardiovascular system. Studies indicate that S1P acts as a mediator for many of the cardiovascular effects of HDL, including vasodilatation, angiogenesis, maintenance of the endothelial barrier, and protection against atherosclerosis and ischemia/reperfusion injury. In this paper, we review current scientific knowledge regarding vascular protection by HDL-associated S1P (HDL-S1P), explore the mechanisms of these effects, and highlight opportunities for the clinical translation of these insights.

2 S1P biology
As a sphingolipid, S1P was previously believed only to be a structural component of biological membranes. Over the last 40 years, however, S1P has gradually become recognized as a key player in the regulation of multiple cellular functions, including cell growth, differentiation, proliferation, apoptosis, and inflammation. The origins of S1P in the blood have only recently begun to be identified. While hematopoietic cells (mainly erythrocytes and platelets) have been found to be the major sources of S1P in plasma, vascular endothelial cells have also been found to synthesize...
and release S1P.\textsuperscript{[13]} Within cells, S1P is synthesized by sphingosine kinase 1 and 2 (SphK 1 and 2), then it is exported to the extracellular space.\textsuperscript{[14]} Degradation of S1P is accomplished either by S1P lyase, which cleaves S1P into phosphoethanolamine and fatty aldehyde, or by S1P phosphatases 1 and 2 (SPP 1 and 2), which belong to the type 2 lipid phosphate phosphohydrolase family.\textsuperscript{[15]}

S1P moves freely between intracellular membranes inside the cell. However, for translocation to the outer leaflets of the cytoplasmic membrane, S1P requires specific transport mechanisms.\textsuperscript{[16]} The exact mechanisms of S1P export remain unknown. Evidence that S1P release from platelets and erythrocytes is inhibited by glibenclamide, an inhibitor of the adenosine triphosphate (ATP)-binding cassette (ABC) transporter, suggests that ABC transporters may be involved in the export of S1P.\textsuperscript{[17]} While the specific mechanism and controls of S1P extracellular transport remain to be further studied, the discovery of G protein-coupled receptors (GPCR) for S1P has enhanced our understanding of its extracellular actions. The existence of these receptors supports a function of S1P as an extracellular lipid mediator.

3 HDL-S1P

3.1 HDL is a major carrier of S1P

S1P levels are extremely low in most tissues. However, S1P levels are very high in blood and lymph. Almost all S1Ps are found together with lipoproteins or albumin in the blood. Approximately 70% of circulating plasma S1P is carried by HDL, 30% by albumin, and < 10% by low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL).\textsuperscript{[18]} HDL particles are more than LDL particles in plasma, therefore, HDL particles are the primary source of S1P for cells.\textsuperscript{[19]} Depending on the lipoprotein carrier, major differences exist in the biochemical packaging and bioactivity of S1P. Growing evidence indicates that S1P is predominantly associated with small, dense HDL3 particles. In one study, average molar S1P concentration in HDL3 particles was found to be twice that of HDL2 particles (40–50 mmol S1P/mol HDL3, compared with 15–20 mmol S1P/mol HDL2).\textsuperscript{[20]} Furthermore, the amount of HDL-S1P has been found to influence the quality and quantity of HDL-dependent functions. HDL not only exerts its effects depending on the level of S1P content, but also HDL may itself influence S1P signaling by modulating S1P bioactivity and receptor presentation.

The physiological sources of S1P in HDL are currently unknown. HDL can take up S1P directly from erythrocytes through physical contact with the plasma membrane.\textsuperscript{[21]} In the lymphatic system and vascular endothelial cells, spinster homolog 2 (Spns2) has been identified as major player in S1P release and secretion.\textsuperscript{[22,23]} Although endothelial cell-specific Spns2-deficient mice have diminished S1P content in their HDL fraction, this does not establish that Spns2 transports S1P specifically to HDL, since this observation may simply reflect over 50% reduction in overall plasma S1P.\textsuperscript{[23]} Recently, other studies showed that hepatocytes secrete S1P in complex with apolipoprotein M (apoM).\textsuperscript{[24]} Hepatocyte-specific apoM transgenic mice had S1P-rich HDL particles and increased synthesis and release of S1P.\textsuperscript{[25]}

3.2 ApoM is a chaperone of HDL-S1P

As an amphipathic molecule, S1P must bind to a carrier in order to be present in biological fluids such as blood and lymph. The main plasma apolipoprotein which S1P physically binds to is apoM.\textsuperscript{[26]} ApoM was discovered in 1999. ApoM is a 25-kDa plasma apolipoprotein belonging to the lipocalin superfamily and containing a small hydrophobic binding pocket. Both the liver and kidneys produce apoM, but plasma apoM levels are believed to be maintained predominantly by liver expression.\textsuperscript{[27]} Multiple factors may influence expression of apoM at the post-transcriptional and transcriptional levels both in vivo and ex vivo, but the specific mechanisms underlying these processes remain unknown. S1P maybe bind to hydrophobic binding pocket within the apoM protein. This feature facilitates the formation of pre β-HDL and thus promotes many of the atheroprotective effects exerted by HDL.\textsuperscript{[28]}

ApoM plays a crucial role in the formation of nascent HDL and cholesterol efflux to HDL via binding of lipid compounds with its fatty acid side chains. More than 95% of plasma apoM is bound to HDL.\textsuperscript{[29]} In human plasma, the S1P content of HDL is confined to apoM-containing particles.\textsuperscript{[20]} ApoM has anti-atherogenic functions due to its promotion of pre-HDL formation, stimulation of cholesterol efflux from macrophage foam cells and potentiation of the antioxidant activity of HDL.\textsuperscript{[30]} In addition to acting as an HDL-binding protein, apoM can impact HDL metabolism.\textsuperscript{[31]} Because S1P signaling maintains endothelial integrity and immune system homeostasis, HDL-apoM may also exert additive atheroprotective effects by transporting S1P through the plasma compartment to deliver it to endothelial and immune cell receptors.\textsuperscript{[32]} Christoffersen, et al.\textsuperscript{[33]} has reported that apoM-bound S1P can activate S1P1 receptors on endothelial cells and that deficiency of apoM abolishes the presence of S1P in HDL. Their researches showed that the lack of apoM resulted in impaired endothelial barrier function in the lungs of mice. In humans, low plasma apoM is found in sepsis, which is characterized by impaired endothelial function.

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Christoffersen, et al.\(^{[26]}\) reported that only the human HDL containing apoM carried S1P and the HDL fraction from apoM-deficient mice hadn’t contained S1P. However, other studies revealed there was no correlation between apoM and S1P in human plasma or HDL has been found.\(^{[25,34]}\) Sutter, et al.\(^{[35]}\) have reported that S1P efflux is enhanced in the presence of HDL from apoM transgenic mice compared with HDL from wild-type (wt) mice, but it is not diminished in the presence of HDL from apoM knockout (apoM\(^{-/-}\)) mice. In addition, the lipophilic pocket of apoM that accommodates S1P also serves as a binding domain for other compatible biological substances such as retinol and oxidized phospholipids.\(^{[24]}\) Therefore, these findings suggest that there may be other molecular partners for S1P within HDL besides apoM and that their presence and/or association with S1P may depend on an equilibrium with apoM-associated S1P.\(^{[24]}\) In conclusion, HDL appears to facilitate S1P efflux from erythrocytes by apoM-dependent and apoM-independent mechanisms.

4 HDL-S1P and vascular function

HDL triggers an array of signaling events in endothelial cells and vascular smooth muscle cells (VSMCs). Many of these signaling events can be attributed to HDL-S1P through specific GPCRs. In particularly, the activation of extracellular signal-regulated kinase (ERK), Adenosine 5’-monophosphate activated kinase (AMPK), and Protein Kinase B (PKB) is crucial for S1P-dependent signaling.\(^{[36]}\) These signaling pathways modulate endothelial cell and VSMC proliferation, survival, and migration; vascular barrier function; tube formation; and vascular tone.\(^{[37]}\)

4.1 S1PR signaling pathways and vascular expression

S1P effects are mediated through five GPCR termed S1PR1-5. They are widely expressed but exhibit differential expression patterns depending on cell type. S1PR1-3 are ubiquitously expressed; S1PR4 is mainly found in lymphoid tissues and lung; and S1PR5 is restricted to brain and skin tissues. The mechanisms of the binding and activation at the molecular level are not yet well understood.\(^{[38]}\) S1P receptors exhibit different coupling mechanisms to G-protein subunits. The complexity of S1P coupling to G proteins permits the precise regulation of multiple downstream signaling pathways, eliciting an intricate pattern of cellular responses depending on the relative expression levels of each S1P receptor.\(^{[39]}\) Interestingly, despite the apparent redundancy in intracellular signaling pathways linked to S1P receptors, Sensken, et al.\(^{[39]}\) have shown that certain S1P receptor agonists are able to selectively activate special signaling pathways coupled to these receptors.

In the vasculature, the distribution patterns for S1P receptors have not been clearly established, although S1PR1, S1PR2, and S1PR3 are the preponderant receptors expressed in endothelial cells and VSMCs. Many effects of S1P on the vasculature are mediated by endothelial cell expression of S1PR1. For example, as a result of defective coverage of the large vessels by pericytes and VSMCs, S1PR1\(^{-/-}\) embryos die in utero at E12.5–E14.5.\(^{[40]}\) The cell-specific S1PR1 knockout mice has clarified the roles of endothelial cell and VSMC S1PR1 in the regulation of post-natal vascular development, maturation, and function.\(^{[41]}\) Induced overexpression of endothelial cell S1PR1 suppresses vascular sprouting.\(^{[42]}\) Changes in the vascular architecture of S1PR1\(^{-/-}\) endothelial cells result in increased vascular permeability due to altered cadherin localization at endothelial cell-cell junctions.\(^{[43]}\) Recently, Galvani, et al.\(^{[44]}\) found that the endothelial S1PR1 signal was enhanced in regions of the arterial vasculature experiencing inflammation. These results confirm that S1PR1 is the main receptor regulating effects of S1P on vascular development and microvascular barrier function.

4.2 ApoM-associated HDL-S1P vascular protection effects

Recent work has confirmed in vitro experiments that apoM, as a carrier of S1P in HDL, mediates the protective effects of HDL-S1P on endothelium.\(^{[45]}\) This discovery sheds a new light on the biology of the effects of apoM and HDL on the vessel wall. ApoM- and HDL-bound S1P has been proposed to be a primary contributor to the vasoprotective actions of HDL, which are mediated by S1P interacting with S1PR1 on the endothelium.\(^{[46]}\) Moreover, S1P also plays an important role on modulating effects of cell-to-cell contacts within the endothelium, regulating basal barrier function and inflammation-induced vascular leakage. S1P bound to apoM provides a tonic stimulus for S1PR1, which is important for the formation of the endothelial adherens junctions that are crucial for vascular barrier function.\(^{[47]}\) The drastic decrease in plasma apoM concentrations caused by the severe acute-phase response of sepsis is believed to result in decreased S1P concentrations which then may consequently diminish endothelial barrier function.\(^{[48]}\) Increased vascular leakage is a hallmark of sepsis, and it is likely that the decrease in S1P-associated apoM contributes to this finding.

4.3 HDL-S1P and endothelial cells

4.3.1 Effects on endothelial cell survival, proliferation, and migration

S1P may influence HDL-induced cell survival through
S1PRs pathways and cell migration through S1PR1 and S1PR3 in human umbilical vein endothelial cells. Another study suggests that endothelial lipase (EL) is crucial for HDL-stimulated S1P-dependent signaling in endothelial cells. The migration, angiogenic responses, and PKB activation are defective in endothelial cells without EL. S1PR1 had been identified to mediate EL-dependent effects of HDL on endothelial cell migration and PKB activation. Moreover, other studies have demonstrated that HDL-associated S1P promotes endothelial cell tube formation via the activation of Adenosine 5'-monophosphate activated kinase (MAPK) cascade, and that enrichment of HDL particles with exogenous S1P further stimulates the angiogenic response.

4.3.2 Regulation of vessel tone

Vascular tone is usually regulated by the sympathetic nervous system, myogenic autoregulation, shear stress, and a variety of circulating compounds, including endothelial-derived factors such as prostaglandins and nitric oxide (NO). The most essential cellular messenger for the regulation of arterial tone induced by HDL is NO. S1P involvement in vasoconstriction and vasodilatation occurs via two main signal transduction pathways:

Firstly, HDL-S1P induces endothelial NO synthase (eNOS) leading to vasodilatation. One mechanism of vascular protection by HDL is stimulation of endothelial NO release. HDL-S1P partially accounts for HDL-induced eNOS stimulation, NO generation, and ensuing vasodilatation. The absence of S1PR3 reduces HDL-mediated vasodilatation by 60%, and the S1PR3 receptor is critical for HDL-induced vasodilatation effects, which have been found to be absent in aorta specimens and endothelial cells from S1P3-deficient mice. Accordingly, Fingolimod (FTY720), a kind of structural S1P analogue, elicited an endothelium-dependent vasodilatory response in pre-contracted aortic rings from wild-type animals, but not from either S1PR3- or eNOS-deficient mice. S1PR1 has also been found to influence HDL-mediated NO release via intracellular Ca2+ mobilization and by phosphorylating lipostatin 3 kinase (PI3K)/PKB (Akt) pathway activation.

Secondly, HDL-S1P regulates vascular tone by inducing production of cyclooxygenase-2 (COX-2) and prostaglandin I-2 (PGI-2).

COX-2 expression and PGI-2 production in endothelial cells are involved in the regulation of vascular tone and thrombogenicity. Studies have shown that HDL can induce the expression of COX-2 in endothelial cells in a dose-dependent manner, which can then facilitate PGI-2 release. However, the molecular mechanisms by which HDL promotes COX-2 expression in vascular endothelial cells are unclear. Tong, et al., have reported that different doses of S1P reconstituted on HDL induce COX-2 expression in endothelial cells via the phosphorylation of the extracellular signal-regulated kinases (ERK) signal pathway. Xiong SL, et al., have observed that silencing of sphingosine kinase 2 (SphK-2) blocks HDL-induced COX-2/PGI-2 activation. In addition, HDL-activated SphK-2 phosphorylation was found to be accompanied by increased S1P levels in the nucleus. These results suggest that S1P can contribute to HDL-induced COX-2 expression in endothelial cells.

4.3.3 Effects on endothelial barrier integrity

Studies suggest that HDL-S1P is essential for endothelial barrier homeostasis and that HDL-S1P may be protective against the loss of endothelial barrier function in some disease states. Bekpinar, et al., reported that low levels of S1P in patients with nephropathy may adversely affect endothelial barrier function. The main reason was that S1P severed urinary albumin loss due to nephropathy in these patients. A main function of S1P and S1PR1 is the maintenance of tight junctions between endothelial cells to sustain an intact endothelial barrier. Another study further strongly supports the role of S1P-S1PR1 interactions and PKB activation in maintaining endothelial barrier integrity. In addition, Wilkerson, et al., have demonstrated that HDL-S1P is more effective than albumin-bound S1P for stimulating long-term barrier effects, and this effect was found to be related to the inhibitory action of HDL-S1P on S1PR1 degradation. Moreover, in endothelial cells, only apoM-containing HDL was found to induce typical responses of S1P-S1PR1 axis activation, such as S1PR1 internalization, activation of MAP kinase and PKB. These findings with respect to HDL-S1P indicate that the HDL-S1P/S1PR1-Pi3K/Akt-eNOS pathway mediates sustained endothelial barrier activity.

4.4 HDL-S1P and vascular smooth muscle cells (VSMCs)

HDL-S1P promotes VSMC proliferation and migration. González-Díez, et al., previously analyzed the role of S1P and its receptors in COX-2 upregulation induced by HDL in human VSMCs. The results of their experiments demonstrated that siRNA targeting S1PR2 or S1PR3 significantly reduced the ability of HDL and S1P to upregulate...
COX-2. Some studies revealed that free S1P mimics can induce COX-2 expression and PGI-2 production.\(^6\) Moreover, S1P receptors, expressed by VSMCs (S1PR2 and S1PR3), participate in COX-2-mediated PGI-2 release induced by free S1P and HDL.\(^6\) HDL activates S1PR 2 and 3, resulting in an increase in VSMC PGI-2 synthesis via upregulated transcription of the inducible COX isoform.\(^6\)

In addition, HDL may markedly inhibit platelet-derived growth factor-induced migration of VSMCs through S1PR2.\(^7\) HDL-S1P has also been found to act as a mediator for these anti-inflammatory effects of HDL-S1P in VSMCs.

5 Future directions and conclusions

We are processing some mechanism research on vascular protection by HDL-S1P. The initial results showed that HDL-S1P may inhibit endothelial cell autophagy and activated autophagy-inhibitor PI3K/Akt signaling. Further, using reconstituted HDL (HDL-S1P) to improve vascular function would provide a novel therapeutic approach.

In summary, the cardioprotective effects of HDL have been firmly established over the last two decades. S1P is now known to play a significant role in these processes. In this review, we summarize the most recent advances in our understanding of how HDL-S1P confers vascular protection. Given the magnitude and specificity of these effects, we anticipate great potential for the development of new therapeutic agents based on further basic science and clinical investigations of these processes.

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Fan WANG provided the idea and Xi WANG wrote the first draft of the manuscript. We had read and approved the final manuscript.

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The authors declare that they have no competing interests.

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WANG X, et al. Vascular protection by HDL-S1P

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