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Invited critical review

ABCA1, ABCG1, and SR-BI: Transit of HDL-associated sphingosine-1-phosphate

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ABSTRACT

Sphingosine-1-phosphate (S1P) is a zwitterionic lysophospholipid generated by the sphingosine kinase-catalyzed phosphorylation of sphingosine. A number of the biological effects of S1P are mediated by its binding to five specific G protein-coupled receptors located on the cell surface or intracellular targets. However, the synthesis and secretion of S1P require release out of cells for binding with receptors by certain transporters and carriers. High-density lipoprotein (HDL) is an important carrier of S1P in the blood, but the mechanism by which it does so is unclear. This review discusses the mechanism how S1P is transported, and focuses particularly on how the formation of HDL-associated S1P (HDL-S1P) is mediated by certain transporters and carriers. A hypothesis that the ATP-binding cassette transporter A1 (ABCA1), ABCG1, and scavenger receptor class B memberI (SR-BI) play pivotal roles in HDL-S1P formation is also described.

Contents

1. Introduction

Lipids are generally known to fulfill three functions: energy storage, structural functions, and acting as messengers [1]. Sphingolipids, possessing the latter two functions, are a class of lipids that are derived from the aliphatic amino-alcohol sphingosine. Sphingolipid metabolites including ceramide, sphingosine, ceramide-1-phosphate (C1P), and S1P are not only components of eukaryotic cell membranes, but also important bioactive signaling molecules. They regulate a diverse array of biological responses, such as cell movement, differentiation, survival, inflammation, angiogenesis, calcium homeostasis, and immunity. In particular, S1P as a kind of sphingolipid metabolites, has emerged as a pivotal signaling mediator participating in the regulation of multiple cellular processes and diseases. S1P can function either through a family of five G protein-coupled membrane receptors (S1PR1–5) [2,3] or via intracellular targets, such as histone deacetylase (HDAC) [4], TNF receptor-associated factor 2 (TRAF2) [5] and prohibitin 2 [6], and thereby triggers a wide variety of signaling cascades [7]. In most tissues, S1P levels are extremely low; however, in blood and lymph the S1P levels are in the micromolar or hundreds of nanomolar range, respectively [8,9]. Several cells release S1P to the extracellular region, forming a gradient which is retrorse and

Abbreviations: S1P, sphingosine-1-phosphate; HDL-S1P, HDL-associated S1P; ABCA1, ATP-binding cassette transporter A1; SR-BI, scavenger receptor class B memberI; C1P, ceramide-1-phosphate; HDAC, histone deacetylases; TRAF2, TNF receptor-associated factor 2; SPHK, sphingosine kinase; apoM, apolipoprotein M; PL, phospholipid; apoA-I, apolipoprotein A-I; RA, retinoic acid; HCBS, high-capacity binding site; PC, phosphatidylcholine; PS, phosphatidylserine; SM, sphingomyelin.

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maintained by energy (ATP). Although S1P is an amphiprotic lysophospholipid made up of single-chain lipids and with sufficient aqueous solubility to move between membranes [10–12], almost all S1Ps are of the conjunction type with lipoproteins or albumin in the blood [13]. In particular, most of the S1Ps are bound to HDLs in the plasma. This indicates that S1P acts as a messenger, depending on some enzymes and transporters, ATP, and HDL. Epidemiologic studies have shown that high concentrations of HDL have a protective value against cardiovascular diseases such as ischemic stroke and myocardial infarction, although there are some exceptions. The S1P composition in HDL probably defines HDL functions similar to estrogen in HDL, which is the typical in women. Therefore, this review explores the mechanism by which HDL-S1P formation is mediated by certain transporters and carriers.

2. S1P synthesis and degradation

There are two pathways involved in the synthesis of S1P: *de novo* synthesis and hydrolysis of the membrane sphingomyelin (SM) [11]. Ceramide plays a pivotal role in S1P formation, but a key enzyme sphingosine kinase (SPHK) can phosphorylate its substrate sphingosine to generate S1P [14]. There are two forms of Sphk — Sphk1 and Sphk2. Sphk1 is found in the cytosol of eukaryotic cells, and it migrates to the plasma membrane on activation. Sphk2 is mainly localized to the nucleus.

Sphk1, after activation by phosphorylation of Ser225, Thr54 and Asn89, enhances the membrane affinity and selectively binds phosphatidylserine (PS) and targeting of membrane [15]. Interestingly, a secretion type-Sphk1 in endothelial cells [16], airway smooth muscle cells [17], and monocytic cells [18] may contribute to the establishment of the vascular S1P gradient [19]. In sharp contrast, Sphk2 is not secreted. To accumulate S1P, which might interact on membrane receptors (S1PR1–5) or intracellular targets, Sphk1 is usually regulated by many factors. The high activity of Sphk is a mechanism to overcome the transitory half-life of S1P. The reason for this is that S1P can be degraded by S1P phosphohydrolases [20,21] or S1P lyase [22]. However, S1P can resist both of these enzymes through binding carriers in the blood.

3. Lipoprotein, particularly HDL, is an important carrier of S1P

Although a series of growth factors may stimulate increasing intracellular production of S1P by activating Sphk, its main receptors require binding to extracellular S1P. Previously, studies have reported that plasma contains ~400 nM to 1 μM S1P and that lymph contains ~80 nM S1P [23]; however, peritoneal exudate during peritonitis contained only 20 nM S1P. Different reports show that the concentration of S1P in the plasma is estimated to be between 0.1 and 0.6 mM; in contrast, tissue S1P levels are quite low. Therefore, a large concentration gradient of S1P is maintained between vascular (plasma) and extravascular compartments in mammals [24], and S1P synthesized intra-cellular need mighty transporters to realize this big concentration gradient. More than 65% of the S1P in blood is associated with the lipoproteins LDL, VLDL, and HDL, with the majority of lipoprotein-associated S1P (>54%) being bound to HDL [13]. Findings from a growing number of studies indicate that S1P is a mediator in many of the cardiovascular effects of HDL, including the ability to promote vasodilation, vasoconstriction, and angiogenesis, protect against ischemia/reperfusion injury, and inhibit/reverse atherosclerosis [25]. Further, the composition of (presence or quantity) of S1P in HDL defines HDL function, which is again dependent on the presence and quantity of HDL [26,27]. In turn, the interaction of S1P with lipoproteins reduces its bioactivity and active concentration, indicating that HDL may offer a compatible concentration for S1PR. The reason for this is that, K_d values of S1P receptors and the bioactive S1P fraction in plasma has been estimated in approximately 10 nM, which is significantly less than the concentration in blood [28]. On the other hand, the half-life of HDL-S1P is ~4-fold that of albumin-associated S1P [29]. Moreover, apolipoprotein M (apoM), which is crucial for the formation of nascent HDL and cholesterol efflux to HDL [30–32], can bind lipid compounds with its fatty acid side-chains. A recent study has confirmed in *in vitro* experiments that apoM, as a carrier of S1P in HDL, possesses a binding site of S1P [33,34]. Therefore, not only is HDL an important carrier of S1P but S1P defines and modulates many functions of HDL.

4. ABCA1, ABCG1, and SR-BI promote S1P outflow to HDL

Because of a retrorse concentration gradient of S1P between the intra- and extracellular compartments, energy-requiring transport methods become the most probable mechanisms. ATP-binding cassette transporters (ABC-transporters) are members of a protein superfamily that is one of the largest and most ancient families with representatives in all extant phyla from prokaryotes to humans [35]. These transporters use the energy of ATP hydrolysis to carry out certain biological processes, including translocation of various substrates, such as metabolic products, lipids, sterols, bile acids, xenobiotics, heavy-metal ions, inorganic acids, glutathione conjugates, sugars and peptides for antigen presentation, and drugs, across membranes [36].

Thus far, a rapidly increasing body of genetic data has implicated ABC transporters in the transbilayer movement of multiple lipids. With regard to HDL, major advances have occurred in defining the important roles of the ABCA1 and ABCG1 transporters as well as the SR-BI receptor in HDL metabolism and cholesterol transport. Therefore, these have also been identified to play pivotal roles in HDL-S1P formation. It has been reported [37,38] that S1P is exported from the erythrocytes by ATP-dependent manner. Further, ATP acts as a trigger to open the S1P transport pore of the transporter, because vanadate, which inhibits a large number of ATPases, decreases the S1P transport activity in a dose-dependent manner. A phosphate group at the γ-position of ATP, dATP, and AMP-PNP is also important for S1P transport activity. Notably, S1P release was decreases by an ABCA1 transporter inhibitor, glyburide, but not by a multidrug resistance-associated protein inhibitor, MK571, or a multidrug-resistance protein inhibitor, cyclosporine A [37].

4.1. ABCA1

ABCA1 not only plays a major role in HDL biogenesis and in the reverse cholesterol transport process but also has emerged as a potential target for therapies designed to inhibit the development of atherosclerotic vascular disease. The nascent HDL created by ABCA1-mediated efflux of cellular phospholipid (PL) and free (unesterified) cholesterol (FC) to apolipoprotein A-I (apoA-I) is a rate-limiting step in cholesterol efflux [39,40]. However, more than 54% of the S1P in blood is associated with the HDL [13] and ABCA1 is probably bound to HDL-S1P. The extracellular accumulation of S1P is coupled with the formation of HDL-like lipoproteins through ABCA1 in astrocytes [41]. Retinoic acid (RA)/cAMP, which have been shown to activate lipoprotein through ABCA1 [42], induce S1P accumulation in the HDL fraction and up-regulation of ABCA1 expression is necessary for RA/cAMP-induced extracellular accumulation of S1P in astrocytes. In contrast, treatment of the cells with both ABCA1 inhibitor and siRNA observably inhibited RA/cAMP-induced S1P efflux. Moreover, astrocytes from Abca1$^{-/-}$ mice showed a low S1P-release activity in response to RA/cAMP. Accumulation of extracellular S1P in HDL-like lipoproteins but apoE as the component of HDL is not sufficient to cause S1P release. However, the majority of extracellular S1P is trapped into abundantly existing albumin but is not bound to apoE or HDL. Therefore, although ABCA1 is necessary for HDL formation and HDL-S1P in the central nervous