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Review

Molecular and physiological functions of sphingosine 1-phosphate transporters ☆

Tsuyoshi Nishi [a,b,*], Naoki Kobayashi [a,1], Yu Hisano [a,c], Atsuo Kawahara [c], Akihito Yamaguchi [a,b]

[a] Department of Cell Membrane Biology, Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567-0047, Japan
[b] Faculty of Pharmaceutical Science, Osaka University, Suita, Osaka 565-0871, Japan
[c] Laboratory for Cardiovascular Molecular Dynamics, RIKEN Quantitative Biology Center (QBiC), Suita, Osaka 565-0874, Japan

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ABSTRACT

Sphingosine 1-phosphate (S1P) is a lipid mediator that plays important roles in diverse cellular functions such as cell proliferation, differentiation and migration. S1P is synthesized inside the cells and subsequently released to the extracellular space, where it binds to specific receptors that are located on the plasma membranes of target cells. Accumulating recent evidence suggests that S1P transporters including SPNS2 mediate S1P release from the cells and are involved in the physiological functions of S1P. In this review, we discuss recent advances in our understanding of the mechanism and physiological functions of S1P transporters. This article is part of a Special Issue entitled New Frontiers in Sphingolipid Biology.

1. Introduction

Sphingosine 1-phosphate (S1P) is a lipid mediator that is synthesized in cells and then released into the plasma, lymph and secretory fluids [1–3]. Extracellular S1P induces various cellular responses in the target cells through its specific receptors, and it has been implicated in immunity, allergy and cancer [4–6].

S1P was originally reported as an intracellular second messenger with physiological importance in the regulation of cell growth in response to extracellular stimuli [7,8]. Two homologous sphingosine kinases, SPHK1 and SPHK2 synthesize S1P by phosphorylating sphingosine. SPHK1 and SPHK2 have different intracellular localizations and functions (Fig. 1) although both of the kinases are widely expressed [9,10]. SPHK1 is activated by various stimuli and synthesizes S1P at the plasma membrane, while SPHK2 localizes to and synthesizes S1P in the mitochondria, ER and nucleus. Recently, it has been reported that nuclear SPHK2 is a component of repressor complexes that include histone deacetylases HDAC1 and HDAC2 [11]. In response to external stimuli, phosphorylated SPHK2, translocates into the nucleus and produces S1P, which specifically binds to HDAC1 and HDAC2 and inhibits their deacetylase activities [11]. These results clearly show that S1P plays an important role as a second messenger in intracellular signaling pathways.

The balance of S1P synthesis and degradation maintains intracellular and extracellular S1P concentrations (Fig. 1). S1P is dephosphorylated to regenerate sphingosine through S1P phosphatases (SPPs) and/or extracellular lipid phosphate phosphatases (LPPs). S1P lyase (SPL) irreversibly degrades S1P to the ethanolamine phosphate and hexadecenal. The S1P concentration is maintained at low levels in most tissues due to high S1P-degrading activity [12,13]. In contrast, the S1P in the plasma is maintained at higher concentrations (up to 1 μM), and it associates with HDL and albumin in the plasma [14–16], presumably contributing to its stability. Exogenously added C_{17}-S1P is rapidly degraded in the plasma (with a half-life of approximately 15 min), indicating that an active degradation pathway is present in plasma [17]. Therefore, the high S1P level in plasma must be maintained by a continuous S1P supply from S1P-producing cells [17–20].

Extracellular S1P binds to specific receptors on the target cells to exert its various physiological functions (Fig. 1) [2,21]. With the discovery of S1P receptors (S1PR1-5), the physiological importance of S1P as an extracellular signaling molecule in various cellular pathways was greatly and rapidly expanded.

Several hematopoietic cell types have been reported to supply plasma S1P [22]. Erythrocytes, platelets and mast cells have the ability to produce and release S1P into the plasma, and erythrocytes play a central role in maintaining the plasma S1P levels [19]. The S1P concentration gradient between high S1P level of the plasma and low S1P levels of secondary lymphoid tissues is reported to be an essential for lymphocyte egress into the blood stream [12,19]. In addition to the hematopoietic

Abbreviations: ATP, adenosine triphosphate

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* Corresponding author at: Department of Cell Membrane Biology, Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka, Japan. Tel.: +81 6 6879 8547; fax: +81 6 6879 8549.
E-mail address: tnishi@sanken.osaka-u.ac.jp (T. Nishi).
[1] Present address: Faculty of Pharmaceutical Science, Teikyo Heisei University, Nakano, Nakano-ku, Tokyo 164-8530, Japan.

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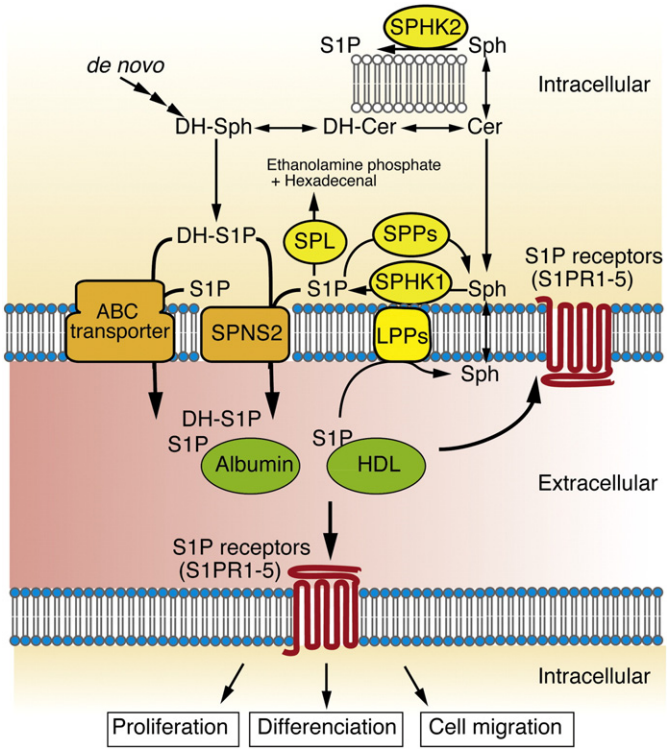

Fig. 1. Intra- and intercellular S1P signaling. Sphingosine 1-phosphate (S1P) is synthesized through the phosphorylation of sphingosine by the sphingosine kinases SPHK1 and SPHK2. S1P is dephosphorylated to regenerate sphingosine by S1P phosphatases (SPPs) and/or extracellular lipid phosphate phosphatases (LPPs). S1P lyase (SPL) irreversibly degrades S1P to the ethanolamine phosphate and hexadecenal. S1P is exported from the cells *via* ABC transporters and SPNS2. S1P is bound to carrier proteins such as albumin and HDL in the extracellular space. Exported S1P is recognized by S1P receptors and induces various cellular responses.

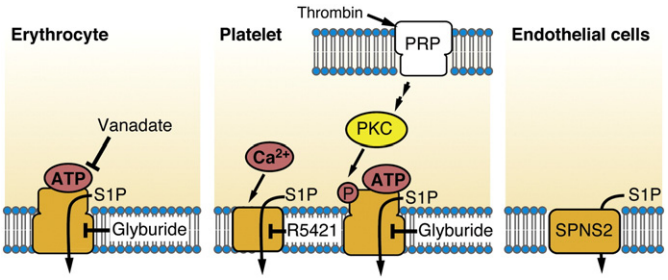

Fig. 2. S1P export from erythrocytes, platelets and vascular endothelial cells. Schematic illustrations of S1P export from cells. In erythrocytes, S1P is exported by an ATP-dependent and vanadate- and glyburide-sensitive transporter. S1P export from platelets requires an extracellular stimulus such as thrombin. S1P is exported through two independent transporters, a Ca^{2+}-dependent transporter and an ATP-dependent glyburide-sensitive transporter. In vascular endothelial cells, S1P is exported by SPNS2, which is a passive transporter.

cells, astrocytes and vascular endothelial cells have been proposed to be S1P-producing cells. Several different types of cells secrete S1P; however, the precise molecular mechanism of S1P release remains obscure. In this review, recent findings related to the mechanism of S1P export from the cells and S1P transporters will be discussed.

2. S1P transporters in platelets and erythrocytes

Among the hematopoietic cells, platelets are highly enriched in intracellular S1P because of their high levels of sphingosine kinase activity and lack of S1P lyase activity [23]. S1P is released from rat platelets in response to various stimuli, such as thrombin, collagen and ADP [23]. In response to these stimuli, most of signaling molecules are secreted by exocytosis through one of three different secretory vesicles; α-granules, dense granules or lysosomes [24]. However, we demonstrated that S1P is localized to the inner leaflet of the plasma membrane, not inside the secretory vesicles, and is released in transporter-mediated manner [25].

S1P release from rat platelets may occur through two independent pathways, the ATP-dependent and Ca^{2+}-dependent pathways [26]. The ATP-dependent pathway is stimulated by either thrombin or the protein kinase C (PKC) activator TPA and is inhibited by both staurosporine (a PKC inhibitor) and glyburide (an ABCA1 inhibitor) but not by the multidrug resistance-associated protein (MRP) inhibitor MK571 or the multidrug resistance protein (MDR) modulator cyclosporine A [25]. The Ca^{2+}-dependent pathway is induced by Ca^{2+} influx through the ionophore A23187 and inhibited by phospholipid scramblase (PLSCR) inhibitor R5421 but is not affected by either staurosporine or glyburide (Fig. 2) [26].

Erythrocytes are the most abundant type of blood cell and are a major source of plasma S1P [20,27,19]. S1P is released from rat erythrocytes into the medium in a time-dependent manner following the addition of sphingosine to the cells [25]. Unlike platelets, erythrocytes constitutively release S1P and do not require any stimuli, such as thrombin, TPA or Ca^{2+} + A23187, to induce S1P release from the cells. We developed an S1P transport activity assay system using rat erythrocyte inside-out membrane vesicles (IOVs) [25]. S1P transport into erythrocyte IOVs is significantly enhanced by ATP, dATP or adenosine 5′-(β,γ-imido)triphosphate (AMP-PNP, a non-hydrolyzable ATP analog) and requires carrier proteins such as albumin [25]. This S1P transport was inhibited by vanadate and glyburide. These results suggest that ATP-hydrolysis is not essential for S1P transport in rat erythrocytes and that a novel ATP-dependent glyburide-sensitive transporter(s), most likely an ABCA type transporter, is involved in S1P release from rat erythrocytes and platelets (Fig. 2).

3. Functional roles of ABC transporters in the extracellular export of S1P

The ATP-binding cassette (ABC) transporters family includes 48 members encoded by different genes in human. Among the members of this family, several ABC transporters have the ability to transport various lipids and other hydrophobic and amphiphilic compounds to the outside of the cells. These ABC transporters use ATP hydrolysis to drive the effective export of their substrates from cells. We observed that both the erythrocyte and platelet S1P transporters require ATP and are inhibited by the ABCA1 inhibitor glyburide. Furthermore, recent studies using several cell lines suggested that ABC transporters are involved in the release of S1P from the cells (Table 1) [29,36,25,29–31].

ABCA1 is an ABCA-type transporter which shares a common structure with other ABC transporters; two ABC domains and two transmembrane domains containing six membrane-spanning α-helices; it also exhibits characteristics typical of the ABC A-subfamily, namely a large extracellular loop region between the first and second transmembrane helices. ABCA1 exports cholesterol and phospholipids on the cell surface where they are removed by apolipoproteins to form the nascent high-density lipoprotein (HDL) [32].

S1P is accumulated in HDL and albumin in the plasma. Among the various types of apolipoproteins, apolipoprotein M (apoM) has been reported to associate with S1P to form a HDL in the blood [16]. S1P is also abundantly detected in the brain, however, the mechanism through which extracellular S1P is supplied in the brain is not known. Sato et al. demonstrated that the treatment of rat astrocytes with retinoic acid (RA) and dibutyryl cAMP induces apolipoprotein E (apoE) synthesis and the formation of HDL-like lipoprotein [28]. The treatment of astrocytes with RA/dibutyryl cAMP in the presence of sphingosine induces