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Review

Sphingosine 1-phosphate is a key metabolite linking sphingolipids to glycerophospholipids ☆

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ABSTRACT

The sphingolipid metabolite sphingosine 1-phosphate (S1P) is a well-known lipid mediator. As a lipid mediator, S1P must be present in extracellular space and bind to its cell surface receptors ($S1P_{1-5}$). However, most S1P, synthesized intracellularly, is metabolized without being released into extracellular space, in other words, without functioning as a lipid mediator in the vast majority of cells except those supplying plasma and lymph S1P such as blood cells and endothelial cells. Instead, intracellular S1P plays an important role as an intermediate of the sole sphingolipid-to-glycerophospholipid metabolic pathway. The degradation of S1P by S1P lyase is the first irreversible reaction (committed step) of this pathway. This metabolic pathway is conserved in eukaryotes from yeast to human, indicating its much older origin than the function of S1P as a lipid mediator, which is found to be present only in vertebrates and chordates. The sphingolipid-to-glycerophospholipid metabolism takes place ubiquitously in mammalian tissues, and its defect causes an aberration of several tissue functions as well as abnormal lipid metabolism. Although this metabolic pathway has been known for over four decades, only recently the precise reactions and enzymes involved in this pathway have been revealed. This review will focus on the recent advances in our understanding of the sphingolipid metabolic pathway via S1P and its physiological and pathological roles. This article is part of a Special Issue entitled New Frontiers in Sphingolipid Biology.

1. Introduction

Sphingolipids are one of the major lipid components of eukaryotic biomembranes, especially the plasma membrane, and are involved in a variety of physiological functions, including cell adhesion, signaling, immunity, skin barrier formation, neural functions, and glucose metabolism [1–5]. Sphingolipids are comprised of a polar head group and a hydrophobic backbone called ceramide. The polar head group of mammalian sphingolipids is either phosphocholine (sphingomyelin (SM)) or a sugar chain (glycosphingolipids) [1]. The diversity of the sugar chain structure generates hundreds of complex glycosphingolipids [6].

Ceramide is composed of a long-chain base (LCB) with an amide-linked fatty acid. Sphingosine (SPH) is the major LCB in mammals and is produced solely by the ceramidase (CDase)-mediated hydrolysis of ceramide, not through the de novo sphingolipid biosynthetic pathway (Fig. 1A and B). The generated SPH is either recycled into the sphingolipid synthesis or converted to S1P by SPH kinase-catalyzed phosphorylation (Fig. 1B).

The sphingolipid metabolite S1P acts as a lipid mediator that regulates various cellular responses, such as cell proliferation, cell migration, actin cytoskeleton reorganization, and adherens junction assembly, by binding to one of five G-protein coupled receptors ($S1P_1$–$S1P_5$) [7]. In addition, S1P may also function in intracellular signaling, independently of its cell surface receptors, such as regulation of histone acetylation and NF-κB signaling through binding to histone deacetylase (HDAC) and tumor necrosis factor receptor-associated factor 2 (TRAF2), respectively [8–10]. S1P is especially important in the vascular and immune systems, since it plays a critical role in both vascular stabilization during fetal blood vessel formation [11] and the egress of T lymphocytes from thymus and secondary lymphoid tissues [12]. The role of S1P in the immune system has been appreciated clinically. Fingolimod (FTY720), a therapeutic agent for multiple sclerosis, is a S1P receptor agonist prodrug, which becomes an active S1P mimic in vivo following phosphorylation by SPH kinase [13,14]. The role of S1P as a lipid mediator and the mechanism of fingolimod have been reviewed elsewhere [7,12,15] and will not be further discussed herein.

2. Synthesis and degradation of S1P

LCB is characterized by the presence of one amino group at C2 and two hydroxyl groups at C1 and C3. SPH contains a *trans* double bond between C4 and C5 and its saturated analog is sphinganine, which is also

Abbreviations: CDase, ceramidase; DHS, dihydrosphingosine; DHS1P, dihydrosphingosine 1-phosphate; ER, endoplasmic reticulum; FALDH, fatty aldehyde dehydrogenase; HDAC, histone deacetylase; LCB, long-chain base; LCBP, long-chain base 1-phosphate; PE, phosphatidylethanolamine; PHS, phytosphingosine; PHS1P, phytosphingosine 1-phosphate; SLS, Sjögren–Larsson syndrome; SM, sphingomyelin; SMase, sphingomyelinase; S1P, sphingosine 1-phosphate; SPH, sphingosine; TRAF2, tumor necrosis factor receptor-associated factor 2

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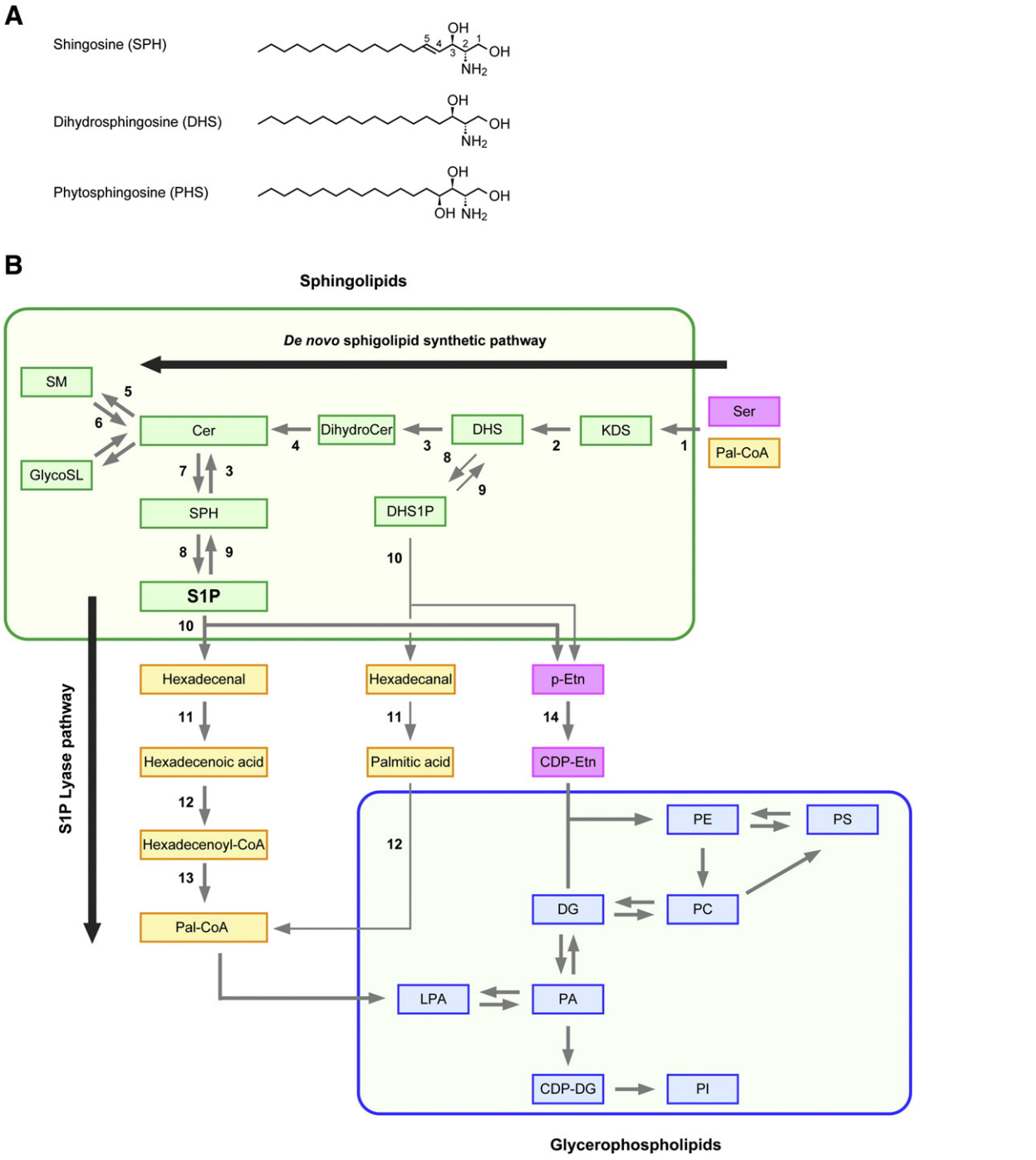

Fig. 1. The metabolic pathways involved in the conversion of sphingolipids to glycerophospholipids. (A) The structures of sphingosine (SPH), dihydrosphingosine (DHS), and phytosphingosine (PHS) are illustrated. (B) The sphingosine 1-phosphate (S1P) lyase pathway (the S1P metabolic pathway) links the sphingolipid metabolism to the glycerophospholipid metabolism. The enzymes catalyzing each reaction are as follows: 1, serine palmitoyltransferase; 2, 3-ketodihidrosphingosine reductase; 3, ceramide synthase; 4, dihydroceramide desaturase; 5, SM synthase; 6, SMase; 7, CDase; 8, SPH kinase; 9, S1P phosphatase; 10, S1P lyase; 11, FALDH; 12, acyl-CoA synthetase; 13, 2,3-*trans* enoyl-CoA reductase; and 14, CTP: phosphoethanolamine cytidyltransferase. Cer, ceramide; CDP-Etn, CDP-ethanolamine; DG, diacylglycerol; DHS, dihydrosphingosine; DHS1P, dihydrosphingosine 1-phosphate; DihydroCer, dihydroceramide; GlycoSL, glycosphingolipid; KDS, 3-ketodihydrosphingosine; LPA, lysophosphatidic acid; PA, phosphatidic acid; Pal-CoA, palmitoyl-CoA; PC, phosphatidylcholine; PE, phosphatidylethanolamine; p-Etn, phosphoethanolamine; PI, phosphatidylinositol; PS, phosphatidylserine; SM, sphingomyelin; S1P, sphingosine 1-phosphate; and SPH, sphingosine.

called dihydrosphingosine (DHS) (Fig. 1A). DHS (but not SPH) is synthesized in the de novo sphingolipid synthetic pathway from serine and acyl-CoA [16] (Fig. 1B) and exists in all tissues, albeit at a lesser level than SPH. Phytosphingosine (PHS) is the 4-hydroxy analog of DHS, i.e., 4-hydroxysphinganine (Fig. 1A). PHS is present in limited mammalian tissues, such as skin, small intestine, and kidney [2,17–19]. PHS and DHS are the two major LCBs in the yeast *Saccharomyces cerevisiae* [20], which, however, does not produce SPH.

LCB is phosphorylated by SPH/LCB kinase to yield LCB 1-phosphate (LCBP), including S1P, dihydrosphingosine 1-phosphate (DHS1P), and phytosphingosine 1-phosphate (PHS1P). Mammals contain two SPH kinases (SPHK1 and SPHK2) [21,22]. SPHK1 exhibits higher substrate specificity than SPHK2 and prefers SPH and DHS to PHS and fingolimod [21–23]. SPHK1 is localized mainly in the cytosol and partly in the plasma membrane [24,25], whereas SPHK2 is in the cytosol and the plasma and internal membranes [26] as well as in the nucleus [27]. Although