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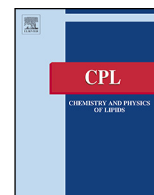

# Inhibitors of sphingosine-1-phosphate metabolism (sphingosine kinases and sphingosine-1-phosphate lyase)

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ABSTRACT

Sphingolipids (SLs) are essential structural and signaling molecules of eukaryotic cells. Among them, sphingosine 1 phosphate (S1P) is a recognized promoter of cell survival, also involved, inter alia, in inflammation and tumorigenesis processes. The knowledge and modulation of the enzymes implicated in the biosynthesis and degradation of S1P are capital to control the intracellular levels of this lipid and, ultimately, to determine the cell fate. Starting with a general overview of the main metabolic pathways involved in SL metabolism, this review is mainly focused on the description of the most relevant findings concerning the development of modulators of S1P, namely inhibitors of the enzymes regulating S1P synthesis (sphingosine kinases) and degradation (sphingosine 1 phosphate phosphatase and lyase). In addition, a brief overview of the most significant agonists and antagonists at the S1P receptors is also addressed.

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## 1. Introduction

Sphingolipids (SL) are key components of eukaryotic cells that contribute to the structural properties of the membrane and also to the regulation and cell homeostasis. The biosynthesis of SL comprises a highly organized system that takes place in different intracellular compartments (Fig. 1). Thus, the so-called biosynthesis *de novo* takes place in the endoplasmic reticulum (ER) and starts with the condensation of L-serine with palmitoyl-CoA to give 3-ketodihydrosphingosine (3-kdhSo) (Fig. 2) in a reaction catalyzed by serine palmitoyl transferase (SPT). By the action of a reductase, the ketone group of 3-kdhSo is reduced to a hydroxyl group to afford dihydrosphingosine (dhSo), which is *N*-acylated to dihydroceramides (dhCer) by specific ceramide synthases (CerS) of different chain length specificities (Mullen et al., 2012). The oxidation of dhCer to ceramide (Cer) by dhCer desaturase (Des1) constitutes the last step of the biosynthesis pathway (Fabrias et al., 2012). Despite the generic term "ceramide" comprises a family of several molecular species differing in the unsaturation of the sphingoid base as well as in the nature of the *N*-acyl chain (Hannun and Obeid, 2011), in this review we will refer to Cer to indicate the C18 monounsaturated species shown in Fig. 2, unless otherwise stated. Due to the metabolic inter-relations between Cer and other SL metabolites (see below), Cer has also been considered as the metabolic hub of SL biosynthesis (Hannun and Obeid, 2008). Part of the Cer generated in the ER is next transported to the trans Golgi apparatus by means of the specific transporter protein CerT (Kumagai et al., 2005) for its further transformation into sphingomyelin (SM), the major SL constituent of the cell membranes. Alternatively, after vesicular transport of Cer to the *cis*-Golgi, biosynthesis of glucosyl ceramide (GC) by means of glucosyl ceramide synthase (GCS) takes place, prior to its subsequent transport to *trans*-Golgi by FAPP2 to give complex glycosphingolipids (GSL). As with SM, GSL are transported by vesicular pathways to the cell membrane where they exert several

*Abbreviations:* 3-kdhSo, 3-ketodihydrosphingosine; aSMase, acid sphingomyelinase; aCDase, acid ceramidase; C1P, ceramide-1- phosphate; Cer, ceramide; CerK, ceramide kinase; CerS, ceramide synthases; CerT, ceramide transporter protein; cPLA2a, cytosolic phospholipase A2; Des1, dhCer desaturase; dhCer, dihydroceramide; dhSo, dihydrosphingosine (sphinganine); ER, endoplasmic reticulum; FAPP2, four-phosphate adaptor protein; GC, glucosyl ceramide; GCS, glucosyl ceramide synthase; GSL, complex glycosphingolipids; HDL, high-density lipoprotein; LPP, lipid phosphate phosphatases; nCDase, neutral ceramidase; nSMase, neutral sphingomyelinase; PEA, phosphoethanolamine; S1P, sphingosine-1-phosphate; S1PPase, sphingosine-1- phosphate phosphatase; SK1, sphingosine kinase 1; SK2, sphingosine kinase 2; SL, sphingolipids; So, sphingosine; SM, sphingomyelin; SPL, sphingosine-1- phosphate lyase; SPT, serine palmitoyl transferase.

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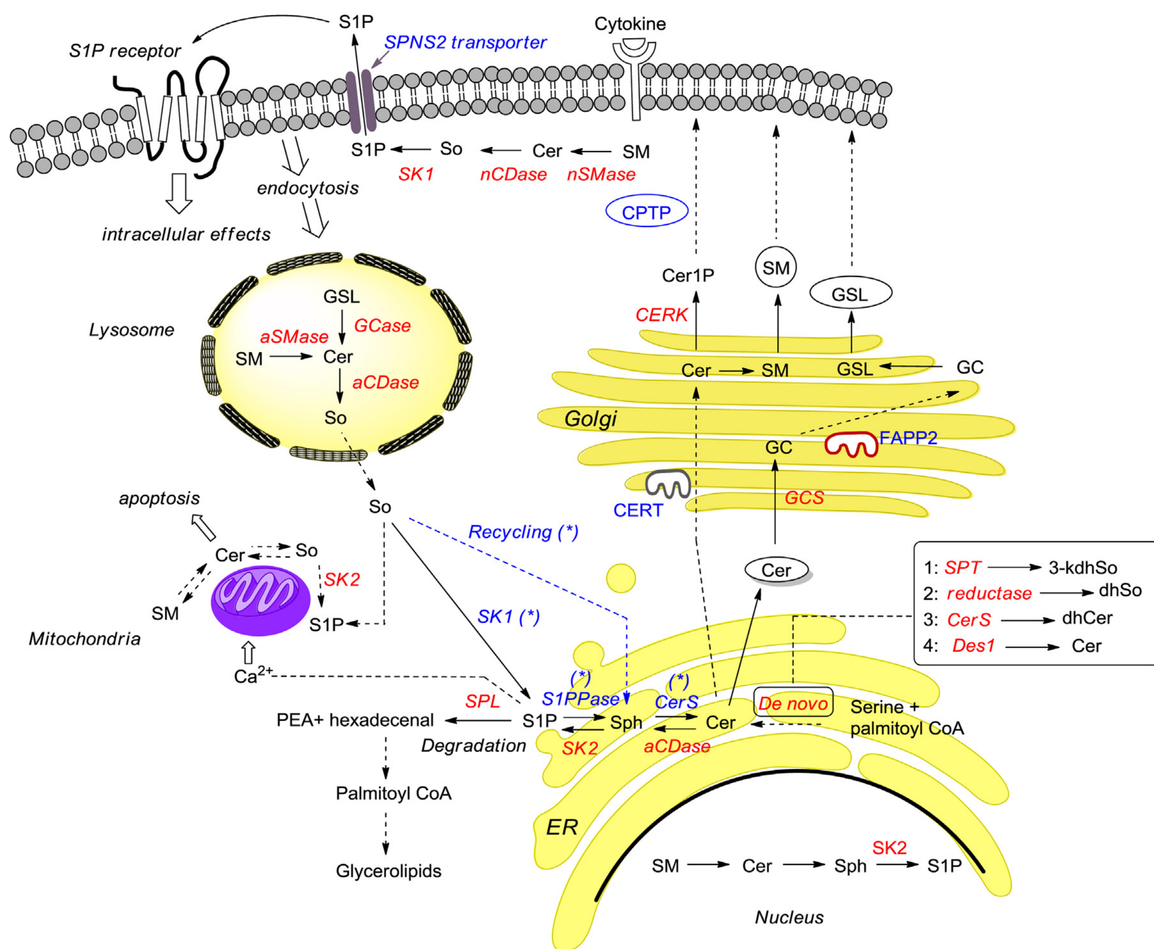


**Fig. 1.** Compartmentalization of SL biosynthesis. For the structures, see Fig. 2. Adapted from (Maceyka and Spiegel, 2014); (*): salvage pathway; For abbreviations, see above.

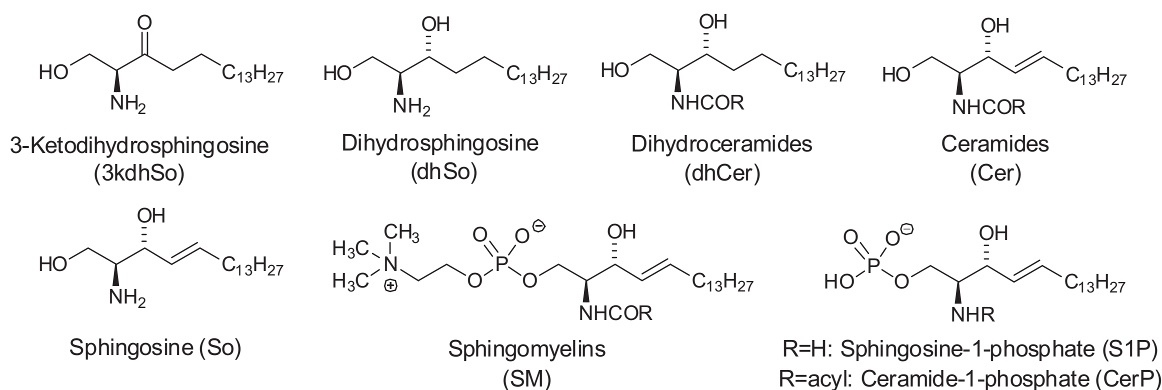


**Fig. 2.** Chemical structures of the most relevant SL (see also Fig. 1).

and capital functions concerning cell-cell communications and responses to external stimuli (Wennekes et al., 2009). By the action of specific cytokines or by other external stimuli, activation of neutral forms of sphingomyelinase (nSMase) and ceramidase (nCDase) can give rise to a buildup of sphingosine (So) at the membrane level. Phosphorylation of So by the action of the specific sphingosine kinase-1 (SK1) leads to sphingosine-1-phosphate (S1P), which is secreted to elicit a plentiful of extracellular actions by interaction with specific receptors (see below).

In addition to the biosynthesis *de novo*, which provides a flux of SL from the ER to the cell membrane, these membrane SL can also be internalized by endocytic pathways and degraded in the lysosome by acidic forms of acid sphingomyelinase (aSMase), glycosidases (GCase) and acid ceramidase (aCDase). The So thus generated can be recycled back to Cer (by the action of CerS) in what is known as the *salvage pathway* (Fig. 1).

In an alternative degradation process, S1P can be generated at the ER to be further transformed by sphongosine-1-phosphate lyase (SPL) into 2-hexadecenal and phosphoethanolamine (PEA),

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