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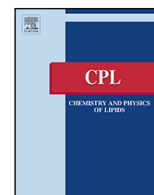

# Ceramide synthases in biomedical research

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ABSTRACT

Sphingolipid metabolism consists of multiple metabolic pathways that converge upon ceramide, one of the key molecules among sphingolipids (SLs). In mammals, ceramide synthesis occurs via *N*-acylation of sphingoid backbones, dihydrosphingosine (dhSo) or sphingosine (So). The reaction is catalyzed by ceramide synthases (CerS), a family of enzymes with six different isoforms, with each one showing specificity towards a restricted group of acyl-CoAs, thus producing ceramides (Cer) and dihydroceramides (dhCer) with different fatty acid chain lengths. A large body of evidence documents the role of both So and dhSo as bioactive molecules, as well as the involvement of dhCer and Cer in physiological and pathological processes. In particular, the fatty acid composition of Cer has different effects in cell biology and in the onset and progression of different diseases. Therefore, modulation of CerS activity represents an attractive target in biomedical research and in finding new treatment modalities. In this review, we discuss functional, structural and biochemical features of CerS and examine CerS inhibitors that are currently available.

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## 1. CerS in sphingolipid metabolism

Ceramide synthases (CerS) are a group of six enzymes that catalyse the formation of dhCer or Cer through *N*-acylation of the sphingoid bases, dihydrosphingosine (dhSo) or sphingosine (So) (Levy and Futerman, 2010; Mullen et al., 2012). DhSo is produced through a two step reaction in the *de novo* synthetic pathway of SLs. First the condensation of *L*-serine with palmitoyl-CoA to give 3-ketodihydrosphingosine (3-kdhSo) in a reaction catalyzed by serine palmitoyl transferase (SPT), then, the ketone group of 3-kdhSo is reduced to a hydroxyl group to afford dhSo, by the action of a reductase. After *N*-acylation of dhSo, the resulting dhCer is metabolized by dihydroceramide desaturase (Des1) to Cer (Hannun and Obeid, 2008). So originates from more complex SL catabolism in the recycling pathway (Mullen et al., 2012). Cer represents a central molecule in SL metabolism: it can be further metabolized to sphingomyelin (SM) (Holthuis and Luberto, 2010) or glucosylceramide (GlcCer) (Gault et al., 2010). In addition, Cer can be degraded by ceramidases (CDase) (Mao and Obeid, 2008) or phosphorylated, giving ceramide-1-phosphate (C1P). So and dhSo are also substrates of sphingosine kinase (SK), which produces sphingosine-1-phosphate (S1P) and dihydrosphigosine-1-phosphate (dhSo1P) (Wattenberg et al., 2006). The reverse reaction is catalyzed by sphingolsine-1-phosphate phosphatase (S1PP). Finally, S1P can be irreversible degraded by S1P lyase (S1PL) with the formation of hexadecenal and phosphoetanolamine (Gault et al., 2010) (Fig. 1).

## 2. Identification and characterization of mammalian CerS

Each of the CerS is the product of a unique gene located on different chromosomes (Pewzner-Jung et al., 2006). The first gene responsible for Cer synthesis was identified as *LAG1* in *Saccharomyces cerevisiae* (Egilmez et al., 1989), which was described as a longevity assurance gene (LASS) because its deletion promoted longer chronological lifespan in yeast (D'mello et al., 1994). Several years later, *LAG1* and its homologue *LAC1*, were found to be necessary for the synthesis of very-long chain Cer (C26) in yeast (Guillas et al., 2001). In 1991, a mammalian gene, upstream of growth and differentiation factor-1 (UOG-1), was discovered (Lee, 1991) and it was able to functionally complement the LAG1 and LAC1 double deletion in yeast (Jiang et al., 1998). However, it was not until 2002 that UOG-1 overexpression in mammalian cells was demonstrated to result in increased Cer synthesis, leading to the confirmation that this gene codes a mammalian CerS

*Abbreviations:* Cer, ceramides; Cer, Sceramide synthases; 1-deoxydhSo, 1-deoxydihydrosphingosine; dhCer, dihydroceramide; dhSo, dihydrosphingosine; dhSo1P, dihydrosphigosine-1-phosphate; ER, endoplasmic reticulum; FB1, Fumonisin B1; SLs, sphingolipids; So, sphingosine; S1P, sphingosine-1-phosphate.

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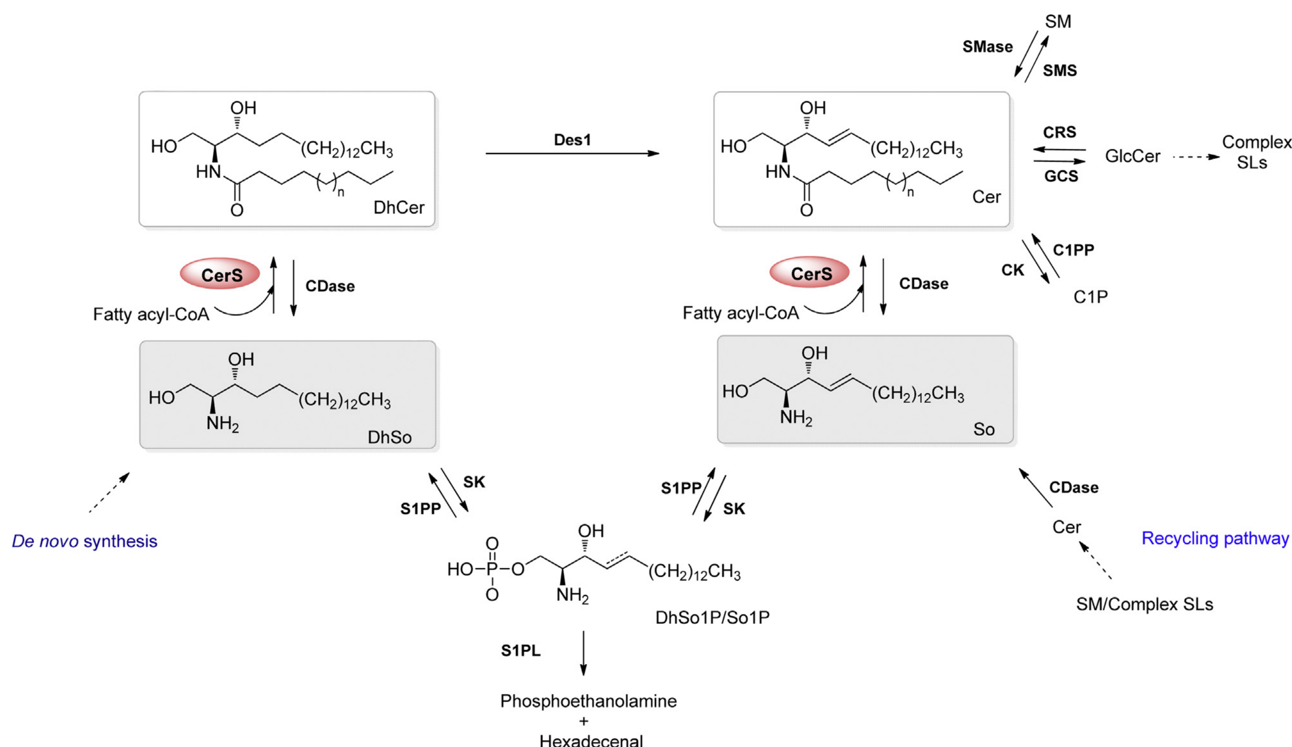


**Fig. 1.** CerS in SL metabolism. DhCer, dihydroceramide; Cer, ceramide, DhSo, dihydrosphingosine; So, sphingosine; DhSo1P, dihydrosphingosine-1.phosphate; So1P, sphingosine-1-phosphate; GlcCer, glucosylceramide; SM, sphingomyelin; C1P, ceramide-1-phosphate. CerS, ceramide synthase; CDase, ceramidase; Des1, dihydroceramide desaturase; SMase, sphingomyelinase; SMS, sphingomyelin synthase; CRS, cerebrosidase; GCS, glucosylceramide synthase;.CK ceramide kinase; C1PP, ceramide-1-phosptate phosphatase; SK, sphingosine kinase; S1PP, sphingosine-1-phopshate phosphatase.

(Venkataraman et al., 2002). Moreover, the Cer produced by UOG-1 only contained a C18 fatty acid, demonstrating that this enzyme, now known as CerS1, specifically uses stearic acid for Cer synthesis. Subsequent bioinformatic analyses (Jiang et al., 1998; Venkataraman and Futerman, 2002; Winter and Ponting, 2002) revealed additional mammalian Lag homologues, originally characterized as translocating chain-associating membrane protein homologs (TRH). Overexpression of THR1 and THR4 (now known as CerS4 and CerS5, respectively) found that these genes confers increased CerS activity and sphingolipid synthesis in mammalian cells (Riebeling et al., 2003). Particularly, Cer synthesized by TRH1 was shown to contain stearic (C18) and arachidic (C20) acids, whereas Cer synthesized by TRH4-overexpressing cells were preferentially enriched in palmitic acid (C16). Two more mammalian homologues, Lass3 (CerS3) and Lass6 (CerS6), were subsequently identified and cloned (Mizutani et al., 2006; Weinmann et al., 2005). CerS2 was cloned as Lass2 in 2001 (Pan et al., 2001) however, it was in 2008 that Laviad and co-workers reported that long chain acyl- CoAs (C20–C26) are preferred by CerS2 for Cer synthesis (Laviad et al., 2008).

## 3. Subcellular localization and tissue distribution

CerS are located in the endoplasmic reticulum (ER) (Hirschberg et al., 1993), although a subset of CerS have been partially purified from a mitochondria-enriched fraction (Shimeno et al., 1998). CerS are integral membrane proteins (Kageyama-Yahara and Riezman, 2006), with their active site probably facing the cytosol (Hirschberg et al., 1993). Although the transmembrane topology of the mammalian CerS has not been resolved experimentally, comparison of several prediction programs to assess topology suggested that the CerS have six membrane-spanning domains. However, significant disagreement between the various prediction programs was noted for the fourth putative transmembrane domain, in which the Lag1p motif is located, with some programs suggesting one membrane-spanning domain in this region and others two (Tidhar et al., 2012). However an odd-number of trans-membrane domains is supported by recent experimental data (Laviad et al., 2012). A number of studies on the tissue distribution of mammalian CerS have shown that each tissue has a different profile of CerS expression and that this profile changes during development. CerS1 is mainly expressed in brain and at low levels in skeletal muscle and testis (Laviad et al., 2008). It was also shown that it is up-regulated postanatally, which may reflect the synthesis of neuronal plasma membranes (Becker et al., 2008). CerS2 is much more widely expressed than CerS1, and two different studies showed that CerS2 is abundant in many tissues, mainly kidney and liver (Cai et al., 2003; Laviad et al., 2008). CerS3 is found mainly in skin and testis (Mizutani et al., 2006), and is highly expressed in keratinocytes, with its expression increasing during differentiation (Mizutani et al., 2008). Less information is available about CerS4, which appears to be found at high levels in skin, leukocytes, heart and liver, although its mRNA expression levels in this tissue is lower than those of other CerS, such as CerS2 (Laviad et al., 2008). CerS5 is the main CerS detected in lung epithelia (Xu et al., 2005). In brain, CerS5 mRNA is detected in most cells within the gray and white matter (Becker et al., 2008). CerS6 shows high homology to CerS5, however much less is known about this isoform. CerS6 is found in intestine and kidney (Laviad et al., 2008). Decreased expression of CerS6, together with decreased expression of CerS2, occurs during mouse brain development, especially in myelin-producing cells (Becker et al., 2008). However, CerS mRNA expression does not always correlate with the sphingolipid acyl chain composition in a particular tissue, suggesting a variety of post-translation mechanisms, and other possible mechanisms, that may regulate CerS activity, which would determine levels of Cer containing specific acyl chains (Laviad et al., 2008).

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