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Review

The role of sphingomyelin and sphingomyelin synthases in cell death, proliferation and migration—from cell and animal models to human disorders ☆

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ABSTRACT

Sphingomyelin constitutes membrane microdomains such as lipid raft, caveolae, and clathrin-coated pits and implicates in the regulation of trans-membrane signaling. On the other hand, sphingomyelin emerges as an important molecule to generate bioactive sphingolipids through ceramide. Sphingomyelin synthase is an enzyme that generates sphingomyelin and diacylglycerol from phosphatidylcholine and ceramide. Although ceramide has a well-known role as a lipid mediator to regulate cell death and survival, the only known biological role of sphingomyelin regulated by sphingomyelin synthases was limited to being a source of bioactive lipids. Here, we describe the basic characters of sphingomyelin synthases and discuss additional roles for sphingomyelin and sphingomyelin synthase in biological functions including cell migration, apoptosis, autophagy, and cell survival/proliferation as well as in human disorders such as cancer and cardiovascular disorders. It is expected that a better understanding of the role of sphingomyelin regulated by sphingomyelin synthase will shed light on new mechanisms in cell biology, physiology and pathology. In the future, novel therapeutic procedures for currently incurable diseases could be developed through modifying the function of not only sphingolipids, such as sphingomyelin and ceramide, but also of their regulatory enzymes. This article is part of a Special Issue entitled New Frontiers in Sphingolipid Biology.

1. Introduction

Sphingolipids are the essential components of cellular membranes and are involved in diverse cell functions. Sphingolipid metabolism (Fig. 1) is constituted of stepwise reactions and controlled by numerous enzymes. The sphingolipid, ceramide, which occupies the central position of the sphingolipid network, is well-known as a lipid mediator that induces cell death, differentiation, senescence, autophagy, and migration [1,2]. Ceramide is generated through *de novo* synthesis, salvage pathway, and sphingomyelin (SM) cycle *via* sphingomyelinase (SMase). Inversely, ceramide can act as the substrate of other sphingolipids (Fig. 1). SM and glucosylceramide (GlcCer) are produced from ceramide by SM synthases (SMSs) and glucosylceramide synthase (GCS), respectively. Sphingosine (Sph) is generated from ceramide *via* ceramidase (CDase) and then is metabolized into sphingosine-1-phosphate (S1P) by sphingosine kinase (SphK). Ceramide is also converted to ceramide-1-phosphate (C1P) by ceramide kinase. Thus, ceramide seems to be the central lipid of sphingolipid metabolism and a reservoir for production of other bioactive lipids such as S1P and C1P.

The *de novo* synthesis of ceramide begins with the condensation of serine and palmitoyl CoA *via* serine palmitoyltransferase (SPT) to form 3-ketodihydrosphingosine [3,4]. Then, this is catalyzed to dihydrosphingosine (sphinganine) by 3-ketosphinganine reductase. Sphinganine is acylated to turn into dihydroceramide by ceramide synthases (CerSs). Finally, ceramide is formed from dihydroceramide by dihydroceramide desaturase in the endoplasmic reticulum (ER). This *de novo* pathway is activated by chemotherapeutic agents [5], heat stress [6], oxidized LDL [7], and cannabinoids [8]. Recently, Orm family proteins, which are implicated in asthma [9], have been reported to control sphingolipid homeostasis through the regulation of SPT in the *de novo* ceramide synthesis. Breslow et al. showed that Orm1 and Orm2 form the complex with SPT, resulting in inhibition of ceramide generation [10]. When sphingolipid biosynthesis is impaired, Orm proteins are inactivated by phosphorylation, which decreases the inhibition of SPT and enhances generation of sphingolipid precursors. This phosphorylation of Orm proteins is catalyzed by protein kinase Ypk1 under regulation of the TORC2 pathway [11]. Suppression of the *de novo* ceramide synthesis by myriocin, which is an inhibitor of SPT,

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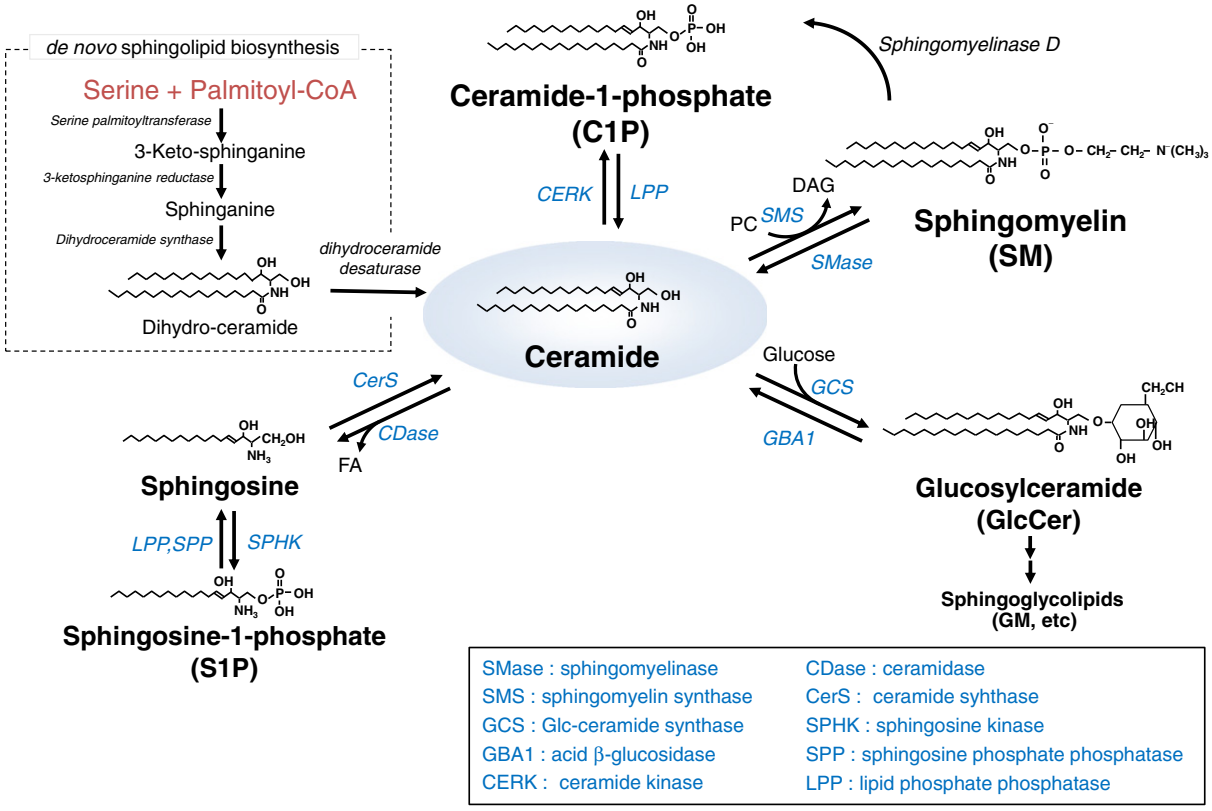

Fig. 1. Biosynthesis of sphingolipids. The biochemical pathways and chemical structural formulae of sphingolipids are shown, enzymes in italics. Pathway of C1P production from SM through sphingomyelinase D is found in bacteria and unknown in mammals. SM generation from C1P is uncertain. PC, phosphatidylcholine; DAG, diacylglycerol; FA, fatty acid; GM, ganglioside.

induces TORC2-dependent phosphorylation of Ypk, resulting in the activation of SPT through an inhibition of Orm by the phosphorylation, resulting in the activation of SPT [11].

In the salvage pathway, Sph, which is metabolized from ceramide or S1P, is acylated to produce ceramide by CerS [12]. CerS has six isoforms (CerS1-6), which show a different specificity for each carbon chain length of fatty acyl CoAs, thus producing distinct ceramides having different acyl-chain lengths. Long-chain (C14–C18), medium-long-chain (C18–C20), very-long-chain (C18–C24) and ultra-long-chain ceramide (up to C34) are produced by CerS5/6, CerS1/4, CerS2/3 and CerS3, respectively [13]. CerS also acts as dihydroceramide synthase. Thus, CerS is essential for ceramide generation in both *de novo* synthesis and salvage pathway [13]. Generation of ceramide through CerSs can be induced by various stimuli such as tumor necrosis factor-α (TNF-α) [14], ultraviolet (UV) light [15], phorbol ester [16,17], ionizing radiation [18,19], and anti-cancer drugs [5,20], resulting in apoptotic cell death.

In the proposed "SM cycle," ceramide is also generated *via* hydrolysis of SM by the activation of either acid or neutral SMases [21]. This pathway is stimulated in response to treatment with TNF-α [22], Fas ligand [23], or oxidative stress [24]. On the other hand, SM is generated from ceramide *via* SMS in SM cycles. The human and mouse genes responsible for SMS were identified in 2004 (Fig. 2) [25,26]. The works of S. Yamaoka, et al. and of K. Huitema, et al. focused on ceramide and its cellular functions, and the biological role of SM itself and its regulation in a diverse of cell functions have been investigated. However, these functions have remained unclear. In this review, we describe the recent advances made involving the biological and pathological implications of SM in the membrane and its regulation by SMS in cell proliferation, autophagy, apoptosis, migration and cancer treatment.

2. SM and SMS

SM is widely distributed in animal species, from mammals [27] and nematodes [28] to protozoa such as the human malaria parasite *Plasmodium falciparum* [29]. It is known that nematodes (*e.g.*, *Caenorhabditis elegans* [28]) or apicomplexa (*e.g. Apis mellifera* [30]) have SM and SMS homologues. On the other hand, SM is not found in fungi (*Saccharomyces cerevisiae* [31]) and viridiplantae (*Arabidopsis thaliana* [32]), which produce inositol phosphoceramide (ICP) instead of SM. Interestingly, *S. cerevisiae* and *A. thalantae* also have no SMS genes, suggesting that the distribution of SM in animal species is linked to the presence of SMS genes in the genome [33]. SM is generated from ceramide by the transfer of phosphocholine from phosphatidylcholine (PC) with the generation of diacylglycerol (DAG) through SMS (Fig. 1). It is possible that SM can be generated from lysosphingomyelin (lysoSM) by fatty acid acylation or by a direct transfer of phosphocholine to ceramide without PC [34]. However, although these pathways may exist, the responsible enzymes have not been established, and the genes are not cloned yet. Except for the role of SMS in the generation of SM, little else has been published [35]. There are three homologues, SMS1, SMS2, and SMS related proteins (SMSr) (Table 1). Among them, SMSr does not show any enzymatic activity regulating SM synthesis. SMS1 is located in the Golgi apparatus and SMS2 is in the plasma membrane and Golgi apparatus. SMS1 and SMS2 act in a similar way to generate SM *in vitro*, but in overexpressing cells, SMS1 shows higher SM content than SMS2 (Fig. 3) [36].

2.1. SM/ceramide cycle

SMS1 and SMS2 may regulate SM and DAG contents in the plasma membrane. In the experiment using siRNA method for SMS1 and