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Review

Biological functions of sphingomyelins

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ABSTRACT

Sphingomyelin (SM) is a dominant sphingolipid in membranes of mammalian cells and this lipid class is specifically enriched in the plasma membrane, the endocytic recycling compartment, and the *trans* Golgi network. The distribution of SM and cholesterol among cellular compartments correlate. Sphingolipids have extensive hydrogen-bonding capabilities which together with their saturated nature facilitate the formation of sphingolipid and SM-enriched lateral domains in membranes. Cholesterol prefers to interact with SMs and this interaction has many important functional consequences. In this review, the synthesis, regulation, and intracellular distribution of SMs are discussed. The many direct roles played by membrane SM in various cellular functions and processes will also be discussed. These include involvement in the regulation of endocytosis and receptor-mediated ligand uptake, in ion channel and G-protein coupled receptor function, in protein sorting, and functioning as receptor molecules for various bacterial toxins, and for non-bacterial pore-forming toxins. SM is also an important constituent of the eye lens membrane, and is believed to participate in the regulation of various nuclear functions. SM is an independent risk factor in the development of cardiovascular disease, and new studies have shed light on possible mechanism behind its role in atherogenesis.

Contents

Abbreviations: CERT, ceramide transport protein; CPE, ceramide phosphoethanolamine; ER, endoplasmic reticulum; HDL, high density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; LDL, low density lipoprotein; OSBP, oxysterol binding protein; PC, phosphatidylcholine; PIP_2, phosphatidylinositol-4,5-bisphosphate; SAC, subapical compartment; SPT, serine palmitoyl transferase; SM, sphingomyelin; SMase, sphingomyelinase; SMS, sphingomyelin synthase; SMSr, sphingomyelin synthase related protein; StnII, sticholysine II; Tf, transferrin; TMD, transmembrane domain.

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1. Introduction

Sphingolipids constitute a fairly large class of lipids, whose common feature is the long-chain base (usually sphingosine or 1,3-dihydroxy-2-amino-4-octadecene [1]). The long-chain base can be modified by functional groups, to yield e.g., sphingosine-1-phosphate, and ceramide [2,3]. Ceramide can further be modified to yield ceramide-1-phosphate [4], sphingomyelin (SM) [5], and simple or complex glycosphingolipids [6,7], including the various gangliosides [8,9]. Additional structural variations (hydroxylation, methyl-branching, acyl chain length) allow for even more molecular species within the sphingolipids [10]. Since the sphingolipids are capable of forming multiple hydrogen bonds with other molecules [11–13], they have been found to be important molecules in various cell signaling events [14]. Being selectively enriched in one of the membrane leaflets, they also provide for a unique lateral asymmetric structure in the bilayers [15]. Sphingolipids also serve as receptor molecules for a plethora of extracellular ligands [16], as well as for establishing various types of glycosynapses between membrane layers [17,18]. Fascinatingly, human familial longevity appears to associate with the presence of certain more unusual SM species [19].

In this review, some of the more important *direct* biological roles of SMs are described and discussed. The biophysical aspects of SMs are not covered in detail here, since a recent review addresses those [10]. The various biological roles played by ceramides, and other sphingolipids are also not covered in detail in this review, since so many excellent reviews are available on those topics [3,20–26]. Disturbed SM degradation may lead to severe disease states – however, the inborn errors of SM metabolism are not covered in this review, and the reader is referred to relevant reviews [27–30].

2. Sphingomyelin synthesis and molecular species distribution in cells

2.1. Cellular synthesis of sphingomyelin, and its organelle distribution

The first committed step in sphingolipid biosynthesis involves the condensation of L-serine with palmitoyl-CoA by a *serine palmitoyl transferase* in the endoplasmic reticulum (ER) (see Fig. 1). The product of the reaction, 3-keto-sphinganine, is rapidly reduced to sphinganine (by *3-keto-sphinganine reductase*) and further acylated to yield dihydro-ceramide [31]. The acylation of dihydro-sphinganine is catalyzed by one of several possible *ceramide synthases*, each with different acyl chain preference [32]. A further desaturation of dihydro-ceramide will yield the corresponding ceramide with a *trans* double bond in the 4-position of the long-chain base. All these steps are believed to take place on the cytosolic side of the ER membrane [33]. Further modifications of ceramide can take place in different organelles. For SM synthesis, the reactions take place either on the luminal side of *trans* Golgi (by *sphingomyelin synthase 1*; SMS1), or in the extracellular leaflet of plasma membranes (by SMS2) [34–36]. There also appears to be SM synthase activity in the nucleus [37].

Ceramide for SM synthesis is delivered from the ER to the Golgi by a ceramide transfer protein (CERT) [38,39]. Phosphatidylcholine (PC) is used as the donor of the phosphocholine head group in this SMS-catalyzed reaction in which also diacylglycerol is produced. This diacylglycerol may result in protein kinase D recruitment to Golgi, catalyzing the formation of secretory vesicles [40]. SMS2 in the plasma membrane is apparently not dependent on CERT-mediated ceramide delivery, but may principally convert ceramide produced locally by a *sphingomyelinase* (SMase) back to SM [41]. The ER has been shown to have a sphingomyelin synthase related protein (SMSr) which converts ER-produced ceramide into ceramide phosphorylethanolamine (CPE) [42]. The CPE could potentially be converted into SM by head group exchange or by head group methylation. However, the rate of CPE production in the ER is very low compared to the rate of SM synthesis in the Golgi, and it is believed that SMSr activity is most important for regulation of the ceramide levels in ER (i.e., preventing ceramide accumulation) [42].

Since the major SMS activity is found in the luminal *trans* Golgi and the plasma membranes, it is not surprising that SM is enriched in membranes derived from *trans* Golgi and in the plasma membrane (including the endosomal recycling compartment) [15]. The sidedness of SMS activity (luminal *trans* Golgi and outer leaflet of the plasma membrane) also could explain the asymmetric (exoleaflet) distribution of SM in plasma membranes [43]. The spontaneous transmembrane movement of phospholipids is known to be slow, and no SM translocase in the plasma membrane has been reported. However, ceramide delivery to the Golgi via the CERT pathway may cause local scrambling, as seen in model membrane systems [44,45], and thus influence the transmembrane distribution of SM across Golgi membranes. Because of this, it may not be surprising that an equinatoxin-based assay has revealed a cytoplasmic exposure of SM in the Golgi apparatus in MDCK cells [46]. An equinatoxin II-GFP construct co-localized with markers for Golgi membranes, but not with markers for mitochondria, the nucleus or the ER, and also did not stain the endoleaflet of plasma membranes [46]. The findings that endogenously expressed equinatoxin failed to stain mitochondria or the nuclear envelope does not preclude a possible presence of SM in these organelles (SM could still be present in endoleaflets or internal membranes not accessible to the toxin).

Even though the endogenously expressed SM-binding toxins did not detect cytosolically exposed SM in mitochondria, the organelle is known to express SMase activity (both murine and zebrafish cells) [47,48]. While SM may not normally be present in mitochondria, or is present at low abundance or in internal membranes non-accessible to equinatoxin, mitochondrial SM has been suggested to be involved in TNFα-induced Bax translocation to mitochondria [49]. Mitochondrial SM (and ceramide) levels have also been shown to increase markedly after UV irradiation of HeLa cells [50], so apparently SM can be transferred to mitochondria by some mechanisms, and participate in e.g., initiation of apoptosis via ceramide generation.

SM has been reported to be present in rat liver cell nuclei, possibly being part of the nuclear matrix and chromatin structures [51]. In the nuclear membranes, SM is believed to associate with