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Review article

Regulation of sphingomyelin metabolism

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ABSTRACT

Sphingolipids (SFs) represent a large class of lipids playing diverse functions in a vast number of physiological and pathological processes. Sphingomyelin (SM) is the most abundant SF in the cell, with ubiquitous distribution within mammalian tissues, and particularly high levels in the Central Nervous System (CNS). SM is an essential element of plasma membrane (PM) and its levels are crucial for the cell function. SM content in a cell is strictly regulated by the enzymes of SM metabolic pathways, which activities create a balance between SM synthesis and degradation. The *de novo* synthesis *via* SM synthases (SMSs) in the last step of the multi-stage process is the most important pathway of SM formation in a cell. The SM hydrolysis by sphingomyelinases (SMases) increases the concentration of ceramide (Cer), a bioactive molecule, which is involved in cellular proliferation, growth and apoptosis. By controlling the levels of SM and Cer, SMSs and SMases maintain cellular homeostasis. Enzymes of SM cycle exhibit unique properties and diverse tissue distribution. Disturbances in their activities were observed in many CNS pathologies. This review characterizes the physiological roles of SM and enzymes controlling SM levels as well as their involvement in selected pathologies of the Central Nervous System, such as ischemia/hypoxia, Alzheimer disease (AD), Parkinson disease (PD), depression, schizophrenia and Niemann Pick disease (NPD).

Contents

Abbreviations: α-syn, α-synuclein; Aβ, amyloid β; AD, Alzheimer disease; APP, amyloid precursor protein; a-SMase, acid sphingomyelinase; alk-SMase, Alkaline SMase; Cer, ceramide; CERT, ceramide transfer protein; CSF, cerebrospinal fluid; D609, tricyclodecan-9-yl-xanthogenate; DAG, diacyglicerol; ER, endoplasmic reticulum; FasL, Fas ligand; FIASMA, Functional Inhibitor of Acid SphingoMyelinAse; GSH, glutathione; IR, ischemia/reperfusion; l-SMaze, lysosome sphingomyelinase; MA-nSMase, mitochondrial sphingomyelinase; MUFA, monounsaturated fatty acid; n-SMase, neutral sphingomyelinase; NPD, Niemann–Pick disease; PC-PLC, specific phospholipase C; PD, Parkinson disease; PM, plasma membrane; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; SAFA, saturated fatty acids; SAM, sterile motif; SF, sphingolipid; SM, sphingomyelin; SMase, sphingomyelinase; s-SMase, secretory sphingomyelinase; SMS, sphingomyelin synthase; SPT, serine palmitoyltransferase; START, protein-related lipid transfer domain; TNF-α, tumor necrosis factor-α; TNFR1, tumor necrosis factor receptor 1.

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Physiological roles of sphingomyelin (SM) and enzymes of SM cycle

SM – structure and function

SM is the most abundant eukaryotic sphingolipid (SF) which constitutes one of the major components of the plasma membrane (PM). The structural function of SM in a cell is determined by chemical structure of a phospholipid. Specifically, the hydrophilic head and the hydrophobic tail of the phospholipid molecules enable them to form a double layer structure, known as a lipid bilayer. SM (N-acyl-sphingosine-1-phosphorylcholine) is composed of ceramide which comprises a sphingoid backbone, an 18-carbon aminoalcohol with one trans-double bond in position 4 [1] with an attached hydrophobic fatty acid chain, and polar phosphocholine or, less frequently, phosphoethanolamine residues [2]. The naturally occurring SMs vary in their length of fatty acid chain (usually from 16 to 24 carbons) and the level of their saturation and hydrogenation. Thus, SM can contain the saturated fatty acids (SAFA), monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) [3,4]. The specific roles of the diverse SM species in PM are poorly established, although it seems that SM containing different fatty acids may regulate membrane fluidity. There are some findings validating this statement, however, obtained mostly in the studies of artificial model systems. For example, it was observed that MUFA-containing species of SMs form more liquid domains than those with SAFA [5]. Furthermore, hydrogenation of the SM double bond results in an increase in membrane raft melting temperature [6].

Being a major SF in PM, SM has the ability of binding cholesterol [7]. This feature of SM is particularly important in the formation of lipid rafts, which are cholesterol-enriched PM domains. The specific composition of a lipid raft determines its gel ordered structure, which is separated from other parts of the membrane, thicker than the surroundings [8] and resistant to detergents [9]. From 40% to 70% of cell SFs are gathered in lipid rafts [10], where SM represents approximately 2% of the total SF content. Interestingly, SM accounts for 2%–15% of the total concentration of SFs in the cell [11]. Localization of a double bond in the SM fatty acid chain influences the interactions of this lipid with cholesterol. Therefore, while double bonds at Δ^{13} or Δ^{15}positions do not affect the SM binding with cholesterol, the double bond at Δ^{9} position weakens this reaction. On the other hand, cholesterol does not seem to favor any SM species on the basis of their specific acyl chain length [12]. In addition, the interactions of cholesterol with the NH_2 group of SM protect this lipid from oxidative degradation [13]. It has been reported that SM species with N-acyl branched chains form more fluid and disordered lipid rafts compared to domains composed of unbranched SMs. Furthermore, the interaction of cholesterol with SM is impaired when SM N-acyl chains are branched at Δ^{10} position [14]. Natural SM is optically active and occurs in two isomers, d-erythro SM and l-threo SM. Monolayers containing only one isomer are tighter, more ordered, exhibit stronger binding with cholesterol and form larger domains in comparison with racemic layers [15]. Importantly, SMs with different fatty acid chains are not equally distributed in mammalian tissues [3], which results in unique compositions of lipid rafts. It is worth noting that a myriad of signaling, cytoskeletal, mitochondrial [16] and GPI-anchored proteins have been discovered within lipid rafts [17].

The *de novo* synthesis of SM is a multi-stage process which begins on the cytosolic side of the endoplasmic reticulum (ER) with the condensation of palmitoyl-CoA and serine through the action of serine palmitoyltransferase (SPT). This reaction results in the production of 3-ketosfinganine which is subsequently transformed into dihydrosphingosine (sphinganine) by 3-ketosphinganine reductase. Next, the fatty acid chain is attached to sphinganine by dihydroceramide synthase to produce dihydroceramide. The reduction of a double bond in a molecule of dihydroceramide by dihydroceramide desaturase leads to the formation of ceramide (Cer) [18]. For SM synthesis, Cer is transferred from ER to the Golgi apparatus [19] by both vesicular and non-vesicular transport [20]. The latter is mediated by the ceramide transfer protein (CERT), which contains a steroidogenic acute regulatory protein-related lipid transfer domain (START), the site of Cer binding [21]. Studies on the role of CERT in SM formation showed a significant reduction in SM levels in CERT-deficient mouse embryos [22]. These findings point to a conclusion that the *de novo* synthesis is the most important pathway of SM creation in the cell. Moreover, transport of Cer to the Golgi is considered as the rate limiting factor of the *de novo* SM synthesis [21]. In the Golgi network, the phosphorylocholine group from phosphatidylocholine is transferred to Cer by sphingomyelin synthase 1 (SMS1), which eventually results in the formation of SM along with the production of diacyglycerol (DAG) [23]. Thereafter, newly synthetized SM reaches PM in transport vesicles [24]. In the cell membrane, SM takes part in the lipid raft formation [5] or undergoes hydrolysis. The common degradation process of SM occurs in the lysosome, where SM, transported mainly from the PM, is hydrolysed to Cer by the acidic SMase (a-SMase) [25]. The PM-localized SM can also be enzymatically degraded to Cer and phosphocholine by the hydrolysis of phosphodiester bond by two sphingomyelinases (SMases): secretory (s-SMase) or neutral (n-SMase) SMase [26], which is often observed in pathological processes. Interestingly, Cers derived from SM hydrolysis can be reutilized for SM synthesis by sphingomyelin synthase 2 (SMS2) [27].

Since SM is an essential modulator of PM properties which influences the membrane gathering of proteins involved in cellular proliferation, growth and apoptosis as well as being an important source of ceramide, its levels are critical for cell function. The SM content in a cell is strictly regulated by the enzymes of SM metabolic pathways whose activities create a balance between SM synthesis and degradation. This manuscript will characterize the physiological roles of these enzymes as well as their involvement in selected pathologies of the Central Nervous System.