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Review

The metabolism and function of sphingolipids and glycosphingolipids

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Abstract. Sphingolipids and glycosphingolipids are emerging as major players in many facets of cell physiology and pathophysiology. We now present an overview of sphingolipid biochemistry and physiology, followed by a brief presentation of recent advances in translational research related to sphingolipids. In discussing sphingolipid biochemistry, we focus on the structure of sphingolipids, and their biosynthetic pathways – the recent identification of most of the enzymes in this pathway has led to significant advances and better characterization of a number of the biosynthetic steps, and the relationship between them. We then discuss some roles of sphingolipids in cell physiology, particularly those of ceramide and sphingosine-1-phosphate, and mention current views about how these lipids act in signal transduction pathways. We end with a discussion of sphingolipids and glycosphingolipids in the etiology and pathology of a number of diseases, such as cancer, immunity, cystic fibrosis, emphysema, diabetes, and sepsis, areas in which sphingolipids are beginning to take a central position, even though many of the details remain to be elucidated.

Keywords. Sphingolipid, glycosphingolipid, ceramide, sphingosine-1-phosphate, apoptosis, cancer.

Introduction

All eukaryotic cells are surrounded by a membrane composed of a lipid bilayer, whose chemical nature and essential role in cell permeability were first proposed around a hundred years ago. Today it is known that there are three major classes of lipids in eukaryotic cell membranes, namely glycerolipids, sphingolipids (SLs), and sterols, whose biochemical and biophysical properties vary considerably and impact upon their function. Progress over the past two or three decades in elucidating the components of lipid bilayers and their roles in signaling, and over the past few years in 'lipidomics', as well as advances in understanding the biophysical properties of lipids, has led to a major rethink of the structural and functional complexity of lipid bilayers and the role that specific lipids play in defined biological events. Clearly, the classical and simplistic cartoon of a membrane, containing a hydrophilic head group (often depicted as a ball) with two fatty acyl chains attached (depicted as two sticks) does not do justice to the intricacies of bilayer structure. Indeed, the number of possible lipid species, as well as the number observed experimentally to date (see for instance 'Lipid Maps' at http://www.lipidmaps.org) implies previously unsuspected complexity [1]. Moreover, since many of these lipids

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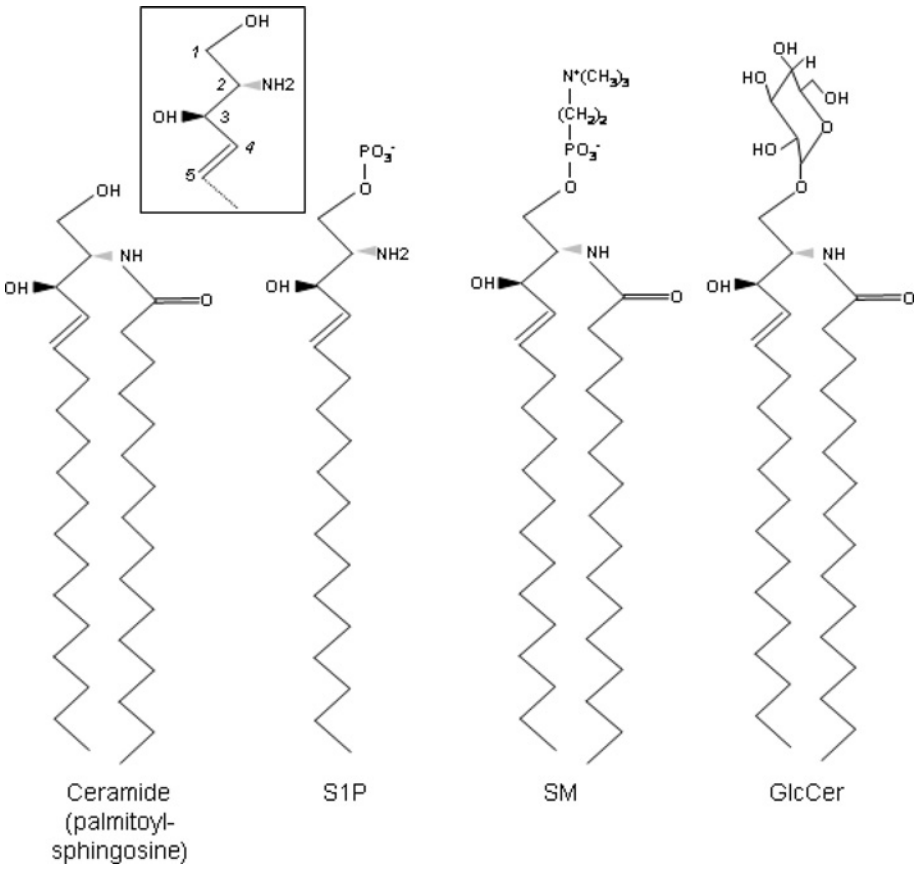

Figure 1. The structure of SLs and GSLs. S1P, sphingosine 1-phosphate; SM, sphingomyelin; GlcCer, glucosyl ceramide. The inset shows the numbering of the first five carbon atoms of the sphingoid long chain base. The sphingoid base is in the D-*erythro* (2*S*, 3*R*) conformation.

are bioactive and turn over in signaling pathways, combinatorial aspects of lipid structure and function are bound to play increasingly important roles in models of membrane structure.

Having briefly introduced the enormous combinatorial diversity of lipids, we will focus in this review on one particular class of lipids, the SLs, and their glycosylated derivatives, the glycosphingolipids (GSLs). Our rationale is that a reductionist approach to understanding lipid complexity is the most reasonable lead-in, and a required first step, to appreciate the complexity of lipid bilayers and how this complexity impacts upon their biological functions. Thus, we will first describe the structure and biosynthesis of SLs, and then discuss their major cellular functions, particularly those of two important bioactive SLs, ceramide and sphingosine-1-phophate (S1P). We will then discuss some aspects of translational research concerning SLs and GSLs; this latter issue is rapidly developing and moving toward clinical manipulation of SL levels as a novel therapeutic approach in human diseases.

SL structure

The backbone of all SLs, and the compound from which SLs derive their name, is the sphingoid long-chain base, the most common of which are sphinganine and sphingosine (Fig. 1). Sphinganine differs from sphingosine inasmuch as the latter contains a *trans* 4–5 double bond, which is essential for some of the bioactive roles in which sphingosine-based SLs are involved. A number of other sphingoid long-chain bases exist, such as phytosphingosine (4-hydroxy-sphinganine) with a hydroxyl group at C-4, and the less common methylsphingosine, which has a methyl group at C-15, and sphingoid bases containing 20 carbon atoms which are found at high levels in brain gangliosides. In rare cases, sphingoid bases containing 14 carbons have been described [2].

Ceramide, the simplest SL, consists of a sphingoid base to which a fatty acid is attached at C-2 via *N*-acylation (Fig. 1). SLs usually contain saturated fatty acids of varying chain length and degree of hydroxylation, although monounsaturated fatty acids, particularly with very long chains, can also be found in SLs [3]. Ceramide is the backbone of all complex SLs, which are formed by attachment of different head groups at C-1. Attachment of phosphorylcholine

forms sphingomyelin (SM), and attachment of glucose or galactose is the first step in the formation of GSLs (Fig. 1). The GSLs are the most structurally diverse class of complex SLs, and are normally classified as acidic or neutral. More than 500 different carbohydrate structures have been described in GSLs [4, 5], with the main sugars being glucose, galactose, fucose, *N*-acetylglucosamine (GlcNAc), *N*-acetylgalactosamine (GalNAc) and sialic acid (*N*-acetylneuraminic acid). GSLs containing sialic acid are the major class of acidic GSLs, but other acidic GSLs exist, such as those that contain glucuronic acid or sulfatides [6].

The complexity of SLs is thus based on three structural components, the sphingoid base, the fatty acid, and the head group. The reason for such a variety of SL structures is not known, but implies an as-yet unknown degree of functional complexity. It is not clear whether each particular SL or GSL structure has a unique role of its own, or whether the roles of SLs and GSLs are defined by their combinatorial patterns at any one time and their distribution (or segregation) over the plasma membrane (PM) surface. In addition, although the basic pathways of SL synthesis have been established (see below), little is known about how these pathways are regulated at the transcriptional, translational or post-translational levels, each of which could determine the SL pattern of a cell or tissue at any one time.

SL metabolism and intracellular transport

The biochemical pathways of SL metabolism are well described [7, 8], and the intracellular sites of synthesis and degradation, in the endoplasmic reticulum (ER)/Golgi apparatus and lysosomes, respectively, have been characterized extensively over the past couple of decades [7, 9]. As might be expected from the lipidic nature of their substrates, the enzymes in the SL biosynthetic pathway are integral membrane proteins that span the membrane bilayer one or multiple times; in contrast, many of the lysosomal hydrolases involved in SL degradation are peripheral membrane proteins that require the presence of activating proteins for maximal activity *in vivo* [7, 10].

SL synthesis begins with the condensation of serine and palmitoyl CoA by serine palmitoyl transferase [11] to form 3-ketosphinganine, which is subsequently reduced by 3-ketosphinganine reductase to produce sphinganine. Dihydroceramide synthase (sphinganine *N*-acyl transferase) [12] next acylates sphinganine to form dihydroceramide. Recently, a mammalian gene family of (dihydro)ceramide synthases [the ceramide synthase (CerS) genes, formerly known as longevity assurance (Lass) genes] has been described. The proteins encoded by these genes are integral membrane proteins that span the membrane lipid bilayer multiple times. Each member of the family has a unique tissue distribution and uses a unique subset of acyl CoAs for dihydroceramide synthesis [12]. Ceramide is subsequently formed by dihydroceramide desaturase/reductase, which inserts a *trans* 4–5 double bond. All of these reactions occur at the cytosolic leaflet of the ER [13–15].

Ceramide is the key hub in the SL biosynthetic pathway, and is the precursor of at least five different products (Fig. 2):

a) Ceramide is glycosylated to galactosylceramide (GalCer) at the lumenal leaflet of the ER by the transfer of galactose from a UDP-galactose donor [16].

b) Ceramide can be phosphorylated by ceramide kinase to produce ceramide-1-phosphate. The subcellular localization of this enzyme is unresolved, and has been suggested to be the PM [17, 18], Golgi apparatus [19], and the cytoplasm [18].

c) Ceramide can be deacylated to sphingosine and free fatty acid by ceramidases, of which various forms are known, acting at either neutral, alkaline, or acidic pH. Neutral ceramidase is located at the PM [20, 21], acid ceramidase is lysosomal [22], and the alkaline ceramidase is located at the ER/Golgi complex [23–25]. Ceramidase activity has also been reported in mitochondria [21].

d) The synthesis of SM from ceramide occurs at the lumenal leaflet of the Golgi apparatus [26, 27] by transfer of phosphorylcholine from phosphatidylcholine (PC) to ceramide, with diacylglycerol formed as a by-product [28]. Recently two SM synthases (SMs) have been identified; SMS1 is located at the Golgi apparatus, and SMS2 at the PM [29, 30]. Since ceramide is synthesized in the ER, a mechanism must exist for transferring ceramide to the Golgi apparatus for its metabolism to SM. It was earlier assumed that vesicular transport would be responsible for ceramide transfer; however, a ceramide transport protein, CERT, which transfers ceramides of relatively short acyl chain length (C16–20) from the ER specifically for SM synthesis in the Golgi apparatus [31], has recently been discovered and is absolutely required for SM synthesis [32] by SMS1.

e) The final fate of ceramide is its glycosylation to glucosylceramide (GlcCer), which unlike glycosylation to GalCer, occurs in the Golgi apparatus. Moreover, and in contrast to the topology of SM synthesis, GlcCer is synthesized on the cytosolic leaflet of the Golgi apparatus [33, 34]. Furthermore, and again in contrast to SM synthesis, the ceramide used for GlcCer synthesis is delivered to the Golgi apparatus by vesicular transport, which is independent of the

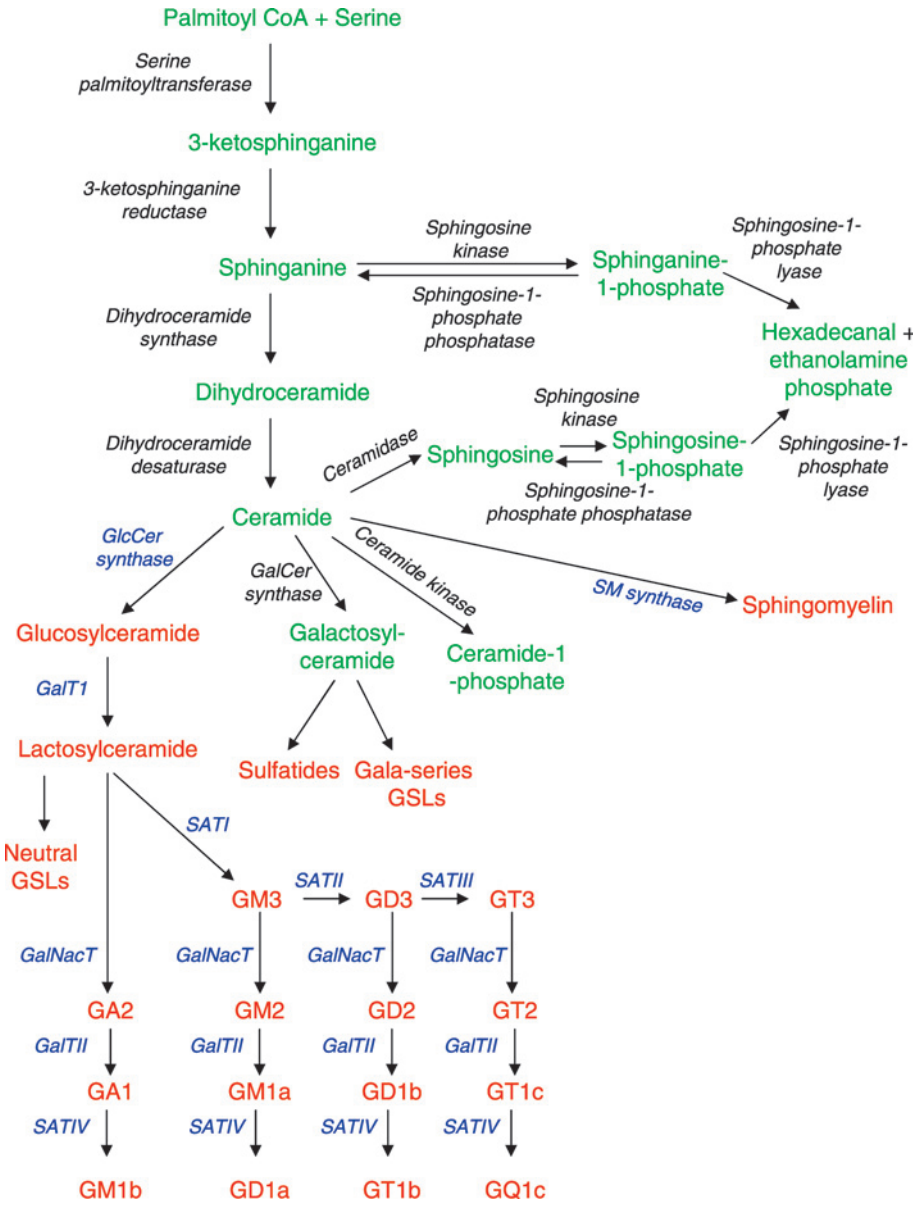

Figure 2. The metabolism of SLs in the ER and Golgi apparatus. SLs synthesized in the ER are in green, and those synthesized in the Golgi apparatus are in red. Enzymes are shown in italics, with those that reside in the ER in black and those that reside in the Golgi apparatus in blue. GalNacT, *N*-acetylgalactosamine transferase; GalT, galactosyltransferase; SAT, sialyl transferase.

activity of CERT [32, 35]. Thus, even though the same ceramide is substrate for both GlcCer synthase and SM synthase, the mechanism of transport of ceramide, and the topology of synthesis, differ.

Little is known about the modes of regulation that channel ceramide into these distinct pathways. Presumably, the compartmentalized nature of ceramide metabolism in the ER and Golgi apparatus allows additional levels of regulation of, for example, GlcCer and SM synthesis (by regulating vesicular transport and CERT, respectively), but the details of this regulation are not known. With the exception of ceramide-1-phosphate and SM, which are metabolic end-products, the metabolites produced in the pathways outlined above are all metabolized further. Thus, GalCer and GlcCer are the precursors of the hundreds of known GSLs, which are formed by the sequential transfer of sugars by galactosyltransferases, sialyltransferases, GalNAc transferases and GalCer sulfotranferase (Fig. 2), all of which are located in the Golgi apparatus [5]. After their synthesis, GSLs move by vesicular transport to the PM, where they reside. The topology and intracellular modes of transport of SLs have been recently reviewed [7].

The sphingosine produced from ceramide by ceramidases can be phosphorylated to S1P by sphingosine kinase (SK). Two mammalian isoforms of SK are known, SK1 which is predominantly cytosolic [36], and SK2 which is cytosolic and also associated with the nucleus [37]. SK1 can be secreted [38, 39], although the physiological relevance of secreted SK1 is not clear. Since S1P is an important first and second

messenger, regulation of its levels is critical, and this is also achieved by the activity of a microsomal S1P phosphatase [40]. Alternatively, S1P can be degraded by S1P lyase [41, 42], which yields two non-SL products, hexadecanal and ethanolamine phosphate. The production of these two compounds is the only known exit route from the pathways of SL metabolism, since lysosomal degradation of SLs produces SL metabolites that are recycled back into the SL pathway [43], some of which can be subsequently reutilized in the salvage pathway of SL synthesis [44]. Thus, sphingosine formed from ceramide can be recycled back into the pathway of SL synthesis [45] via the action of ceramide synthase, which can use either sphingosine or sphinganine [46].

Study of the lysosomal hydrolysis of SLs and GSLs has been motivated by their involvement in a number of human inherited diseases, the lysosomal storage diseases. Indeed, a disease is associated with essentially every enzyme in the pathway of GSL degradation, and for acid SMase [47]. It should be emphasized that the pathways leading from lysosomal accumulation of SLs to disease have not been well established, although it appears highly likely that signaling functions of SLs will be implicated in the etiology of these diseases [48]. Non-lysosomal hydrolysis of SLs also occurs, by hydrolases that work at neutral or alkaline pH. For example, a neutral SMase is located at the PM [49], an alkaline SMase is found in the Golgi apparatus and in endosomes [50, 51], and a neutral β-glucosidase has been recently reported [52] whose deficiency leads to impaired male fertility [53].

In summary, the biochemical pathways of SL and GSL metabolism have been fully described, and most of the enzymes have been identified, as have, for the most part, their intracellular locations. The next challenge in this area is to understand how these pathways are regulated and integrated in metabolism [54, 55] and in signaling: the age of combinatorial sphingolipidomics is truly upon us.

Role of SLs in cell physiology

The past couple of decades have proved beyond reasonable doubt that SLs, and for that matter, many other membrane lipids, are not merely structural components of biological membranes, but also play other vital roles, particularly in signaling. Moreover, a large variety of specific SLs have been shown to function in intracellular signaling pathways, and some conflict has arisen as researchers attempt to grapple with the new roles applied to simpler SLs, such as ceramide and S1P, compared to the more classical roles ascribed to complex GSLs, such as the gangliosides. The field has swung from opinions stating that only the GSLs are important, to those that state that only the simpler SLs are important. Neither of these extreme views is correct, and current opinion would support the notion that both simple SLs and more complex GSLs play roles in signaling, sometimes in the same cell type even under similar conditions. Determining the relationship between roles of specific SLs and GSLs in signaling pathways is one of the current challenges in the field of SL and GSL biology. Of the simple SLs, ceramide, ceramide-1-phosphate, sphingosine, and S1P have been shown to be involved in a number of cellular events such as proliferation, differentiation, motility, growth, senescence, and apoptosis, and ceramide and S1P have been proposed to have opposite roles in these processes (Fig. 3), with entrance into one or other of these pathways being determined by the balance between ceramide and S1P, which are metabolically interconnected (Fig. 2). Complex GSLs are involved in cell physiology by acting as antigens, as mediators of cell adhesion, binding agents for microbial toxins and growth factors, and as modulators of signal transduction.

Functions of ceramide as an apoptotic mediator

Much work on SLs in signal transduction pathways has focused on the role of ceramide in apoptosis (Fig. 3). A large number of extracellular signals or stimuli elevate intracellular ceramide levels and induce apoptosis, including heat shock, ionizing radiation, oxidative stress, progesterone, vitamin D3, daunorubicin, tumor necrosis factor (TNF)-α, interleukin (IL)-1α, IL-1β, interferon-γ, Fas ligand, fenretinide, oxidized low-density lipoprotein (LDL) and nitric oxide [56, 57]. When the ceramide pathway was first discovered, there was considerable debate about the mechanism by which ceramide is formed, but it is now agreed that intracellular ceramide levels can be elevated as a result of either *de novo* synthesis [58, 59], or of SM hydrolysis by acid [60] or neutral [61] SMase. However, there is no evidence that ceramide formed by GSL degradation acts in signaling pathways.

Two major possibilities have been proposed concerning the mechanism by which ceramide induces apoptosis [62]. In the first, ceramide would act as a typical second messenger, inasmuch as upon its production in the PM, it would bind to proteins whose activity it regulates. Among the proteins shown to be regulated by ceramide are a ceramide-activated protein phosphatase [63, 64], protein kinase Cζ [65, 66], kinase suppressor of Ras [67, 68], phospholipase A_2 [69, 70], cathepsin D [71, 72], Jun-N-terminal kinases (JNKs) [68, 73], c-Raf-1 [74, 75], the small G-proteins Ras [76] and Rac [77, 78], and Src-like tyrosine kinases [79, 80]. In the second possibility, the unique biophysical

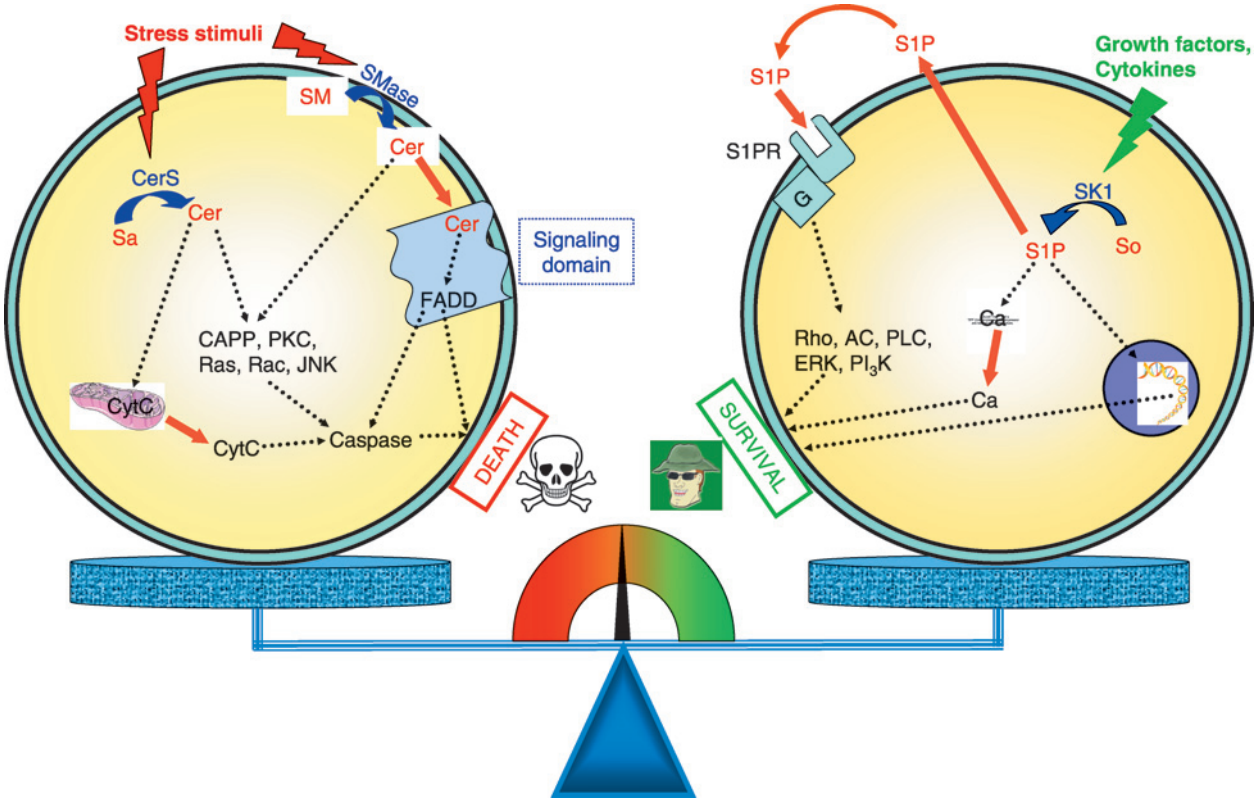

Figure 3. A simplified view of the role of ceramide and S1P in cell death and survival. A number of different signaling mechanisms regulated by ceramide (Cer) and S1P are depicted. Whether a cell dies or survives depends, among other things, on the balance between ceramide-activated and S1P-activated signaling pathways. For simplicity, the schemes do not show all the signaling and metabolic pathways involving ceramide and S1P. Blue arrows are metabolic interconversions, orange arrows are transport steps, and black dotted arrows are signaling interactions. AC, adenylate cyclase; Ca, calcium; CAPP, ceramide-activated protein phosphatase; CerS, ceramide synthase; CytC, cytochrome c; G, G-proteins; ERK, extracellular signal-regulated kinase; FADD, Fas-associated death domain-containing protein; JNK, Jun-N-terminal kinase; PI_3K, phosphatidylinositol 3-kinase; PLC, phospholipase C; PKC, protein kinase C; S1PR, S1P receptors; Sa, sphinganine; So, sphingosine; SMase, sphingomyelinase; TNF, tumor necrosis factor.

properties of ceramide would be responsible for its ability to act as a signaling lipid. Ceramide can self-associate in the plane of the membrane lipid bilayer [81], and by so doing provide the driving force that results in the fusion of GSL- and cholesterol-containing rafts into large signaling macrodomains (signaling platforms) [82]. For example, many of the above stimuli activate A-SMase at the PM resulting in formation of ceramide-enriched membrane platforms that trap and cluster signaling proteins, thus allowing for signal initiation and amplification via concentration and oligomerization of proteins associated with apoptotic signaling mechanisms [83]. Such clustering has been shown for Fas receptors, which become concentrated in these macrodomains, for downstream effecter proteins such as Fas-associated death domain-containing protein (FADD), and for caspase 8 [83]. Another mechanism by which ceramide might induce apoptosis is via its direct interaction with, and modulation of, the properties of mitochondria. Ceramide can form membrane channels in mitochondria which are large enough to transport cytochrome c and small proteins [84, 85], leading to activation of the caspase-dependent apoptotic pathway. Whether ceramide is transported to mitochondria from its site of synthesis in the ER is currently unknown [9], but recent work has suggested that some lipids can be transported between ER and mitochondria [86] at zones of apposition and contact between the two membranes. Interestingly, there is some evidence suggesting that ganglioside GD3 can be trafficked to mitochondria, and that its arrival at the mitochondria can also induce apoptosis [87].

Functions of S1P and ceramide-1-phosphate

S1P is the most intriguing SL inasmuch as it acts as both a first and second messenger [88] (Fig. 3). As a first messenger (or paracrine agent), S1P regulates processes such as cytoskeletal rearrangement [89], cell migration [90, 91], angiogenesis [92], vascular maturation [93], embryonic development of the heart [88], and immunity and lymphocyte trafficking [94]. As an

intracellular second messenger, S1P mediates calcium homeostasis [88], cell growth [88], tumorogenesis [95] and suppression of apoptosis [88]. S1P can trigger signal transduction pathways by acting on the same cell from which it is secreted, by acting in an autocrine manner [96].

Inducers of cell proliferation and differentiation, including growth factors, GPCR agonists, cytokines, phorbol esters, vitamin D3, and antigens, increase intracellular S1P levels by activation of SK [96, 97]. The downstream effectors of S1P in intracellular pathways include IP_3-independent calcium mobilization and DNA synthesis [88, 98].

S1P is secreted from a variety of cells, such as platelets, monocytes, and mast cells, perhaps via ATP-binding cassette (ABC) transporters [99], and subsequently binds a family of G-protein-coupled receptors, the S1P receptors (S1PRs) [88, 100, 101] (formerly known as Edg receptors). Five S1PRs have been identified and are expressed in a wide variety of tissues [96, 102]. Some downstream effectors have been identified, such as adenylate cyclase, phospholipase C, extracellular-signal-regulated kinase (ERK), JNK, phosphatidylinositol 3-kinase (PI3K), Rac, and Rho [88, 102].

S1P appears to have opposite effects to ceramide in many of the pathways in which it is involved, particularly in those relating to cell growth and survival, with ceramide implicated in growth-inhibitory and pro-apoptotic effects, and S1P implicated in cell growth and inhibition of ceramide-mediated apoptosis. Moreover, sphingosine appears to act in a similar fashion to ceramide, whereas ceramide-1-phosphate shares similar functions with S1P [103]. This suggests that the balance between survival and death may depend on a delicate equilibrium (Fig. 3) between intracellular levels of each of these interconvertible SLs, the equilibrium itself being controlled by the enzymes that either produce or degrade specific SLs. SK1 may be a vital player in this pathway, as it increases levels of S1P, a pro-survival molecule, and reduces levels of ceramide and sphingosine, which are pro-apoptotic. Thus, SK1-over-expressing cells not only have higher growth rates but are also protected from apoptosis induced by serum withdrawal, TNF-α, or exogenously added ceramide [104, 105]. Ceramide-1-phosphate is also anti-apoptotic, via its inhibitory action on protein phosphatase 1 [103], which has been attributed to ceramide-induced apoptosis [106]. Thus both ceramide kinase and SK1 are emerging as key determinants of the balance between cell death and survival.

Functions of GSLs

Early studies on complex GSLs were mainly devoted to attempting to understand their roles in the nervous system where GSLs, particularly gangliosides, are expressed at different levels in different regions of the brain during development, suggesting functional roles for gangliosides in brain development [107]. For example, during embryogenesis, and during the postnatal period, the hemato-series gangliosides, GM3, GD3, and 9-O-acetyl GD3, are highly expressed in the brain. In adult tissue, these gangliosides are found at much lower levels, so that the ganglioside composition of adult brain differs significantly from that of embryonic brain, with adult brain expressing a much wider range of complex gangliosides, GM1, GD1a, GD1b, and GT1b being predominant [108]. However, it was not until the cloning of the glycosyltransferases responsible for GSL synthesis, and subsequent availability of genetically engineered mice, that specific functions for specific gangliosides, or at least classes of gangliosides, began to emerge.

The essential nature of GSLs for sustaining life was first shown in knock-out mice lacking GlcCer synthase, the first enzyme in the pathway of GSL biosynthesis (Fig. 2); these mice showed embryonic lethality [109], but whether this was caused by ceramide accumulation, or due to lack of complex GSLs, is unclear. Mice lacking the GM2/GD2 synthase gene contain high levels of GM3 and GD3, but no complex gangliosides [110]. Surprisingly, these mice are viable and the nervous system is only mildly affected, although male fertility is severely disrupted due to aspermatogenesis [111]. A number of other knock-out mice have been produced in the ganglioside biosynthetic pathway, and the overall consensus is that there is considerable functional redundancy between different gangliosides, and that there may be considerable overlap in the roles of individual gangliosides.

Gangliosides can act as toxin receptors. In order for toxins to reach their intracellular targets, they bind to cell surface receptors, which are then internalized together with the toxins. Two toxins, namely cholera toxin from *Vibrio cholera*, and *Escherichia coli* heat-labile enterotoxin bind to ganglioside GM1 [112], and Shiga toxin from *Shigella dysenteriae* binds to the neutral GSL, globotriaosylceramide (Gb3) [113]. The B subunit of the toxins binds to their respective GSL receptors, and is internalized together with the A subunit, which carries the catalytic domain. Lipid rafts have been implicated in the internalization mechanism, and although there is some disagreement about the precise internalization itinerary undertaken by the toxins, they are eventually targeted to the Golgi apparatus and then to the ER, where the A subunit is released and initiates toxicity [114].

GSLs at the cell surface are also involved in recognition events that are beneficial, rather than the toxic effects caused by toxin binding. Thus, a large body of data has shown roles for GSLs as antigens [115], as mediators of cell adhesion, and as modulators of signal transduction [116]. The list of receptor functions of GSLs is extensive. For example, GSLs mediate E-selectin-dependent rolling and tethering [117], α-GalCer acts as a ligand recognized by a special group of immune T cells, known as invariant NKT cells (discussed in more detail below), and 9-O-acetyl GD3, expressed in regions of cell migration and neurite outgrowth in the developing and adult nervous system, plays a role in neuronal motility [118]. Together, these varied examples illustrate that the complex glycan structures of GSLs are involved in vital recognition events at the cell surface.

SLs and GSLs in disease: translational research

Translational research is typically described as research that allows scientific discoveries to be translated into practical applications. Within the past decade, real progress has been made in our understanding of how SLs and GSLs contribute to disease processes, which is leading to novel therapeutic approaches based on interventions in SL homeostasis. We will now summarize some of the areas in which particularly important advances have been made.

SLs and cancer

Recent advances in appreciating the complexity of cell death pathways, and specifically of apoptosis, have led to the realization that manipulating apoptosis could be a novel way of approaching cancer therapy. Since ceramide and S1P are both involved in regulating cell death and survival, they join the list of candidate molecules that might be amenable to manipulation in order to modify the growth rate of cancer cells [119]. A number of studies have shown that ceramide can have anti-carcinogenic activity. For example, direct administration of ceramide or ceramide analogs has been shown to have anti-tumor activity and to induce apoptosis in cancer cells and cancer cell lines [120–124], *de novo* ceramide synthesis is altered in human head and neck carcinomas and is implicated in caspase-dependent cancer cell death pathways [106, 125], and ceramide generation via SMase can alter cytotoxicity resistance [126, 127]. In addition, anti-carcinogenic effects have also been observed upon increasing ceramide levels by slowing its conversion to GlcCer via GlcCer synthase [128, 129], to SM via SM synthase [130], or to sphingosine via ceramidases [131], and the effectiveness of a number of chemotherapeutic agents appears to be related to their ability to activate ceramide-mediated apoptotic pathways [132, 133]. SK1 has also become a target for therapeutic manipulation in cancer. Thus, over-expression of SK1 protects cells from apoptosis [104], increases tumorogenicity [105], and SK1 activity is decreased during anti-cancer treatment [134]. Moreover, reduction of S1P levels induced apoptosis in several human tumor-derived cell lines [135].

About 50% of cancer patients receive radiation therapy, with radiation targeting, directly or indirectly [136], the acid SMase apoptotic system of microvascular endothelial cells in the lungs, intestines, and brain, as well as in oocytes, to initiate the pathogenesis of tissue damage [137]. Radiation-induced ceramide production results in the formation of ceramide-rich platforms in the PM, which induces the caspase-independent pathway of apoptosis [138].

Some studies have also suggested a relationship between ceramide and multidrug resistance (MDR). For example, removal of ceramide by its glycosylation to GlcCer has been identified as a novel MDR mechanism [139], and GlcCer synthase has emerged as a potential target to increase apoptosis and decrease drug resistance of tumor cells [140, 141]. Some MDR cell types exhibit abnormal SL composition or metabolism [142], and inhibition of GlcCer synthase causes downregulation of P-glycoprotein and resensitizes MDR breast cancer cells to anti-cancer drugs [128]. However, a recent study has suggested that inhibition of GlcCer synthase does not reverse MDR [143].

Finally, GSLs are also involved in cancer pathogenesis. For example, malignant transformation is associated with abnormal glycosylation, resulting in the synthesis and expression of altered carbohydrate determinants, including those on GSLs, and the increase of these determinants in malignant cells is an inevitable consequence of the malignant transformation of cells [144]. Indeed, therapies based on the use of anti-ganglioside antibodies have been suggested, particularly in neuroblastoma [145].

Gangliosides are also often found in tumor cells at high levels and can act as immunosuppressants. Tumor gangliosides are shed actively by tumor cells [146] and can inhibit the anti-tumor immune response implicated in tumor rejection. Thus mice model tumor cells with a pharmacologically decreased concentration of gangliosides produce fewer tumors, suggesting that pharmacologic depletion of gangliosides could be explored as a therapeutic approach to cancer [147].

Simple GSLs and immunity

α-GalCer, a glycolipid derived from marine sponge, has been identified as a ligand recognized by a special

subset of immune T cells, invariant NKT (iNKT) cells [148]. Activation of iNKT cells by α-GalCer causes rapid secretion of IL-4 and interferon-γ, downregulation of cell surface T cell receptors, and as a result, transactivation of various cells of the innate and adaptive immune system [149]. Based on this, a therapeutic role for α-GalCer has been proposed in various autoimmune diseases [150], such as type 1 diabetes [151], multiple sclerosis [152], systemic lupus erythematosus [153] and rheumatoid arthritis [154]. However, there are several concerns about using α-GalCer therapy for humans since some preclinical studies demonstrated that α-GalCer aggravated the diseases, and several adverse side-effects have been noted in mice, including liver toxicity and exacerbation of atherosclerosis [150].

SLs and cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, a member of the ABC transporter family [155]. Defects in CFTR result in CF [156], which is characterized by chronic and recurrent bacterial infections and inflammation, with major prevalence in pulmonary and intestinal epithelial tissues. SLs may be involved in CF pathogenesis by a number of mechanisms. First, ceramide produced from SM via SMase at the basolateral membrane augments CF pathogenesis by inhibiting cAMP-mediated anion transport by CFTR [157]. Another study demonstrated that fenretinide, which upregulates *de novo* ceramide synthesis, reduces IL-8-mediated inflammation of CF cells [158]. CFTR enhances uptake of S1P [159] and structurally related lipids, and this uptake modulates the response of cells to these lipids. This latter study might have important implications for the development of angiogenesis in response to chronic infection and inflammation in CF. As S1P mediates angiogenesis through S1PRs, and in CF no functional CFTR exists, the reduced uptake of S1P may allow S1P to be more available to stimulate excessive angiogenesis in response to inflammation.

SLs and emphysema and pulmonary cell apoptosis

Emphysema is a chronic lung disease characterized by destruction of pulmonary alveoli and capillaries, and is commonly associated with chronic bronchitis, together known as chronic obstructive pulmonary disease (COPD) [160]. Since COPD is directly related to cigarette smoking, it is the focus of much attention. Alveolar cell apoptosis is a key factor in the pathogenesis of emphysema, and recently, upregulation of ceramide levels has been shown to cause pulmonary cell apoptosis and onset of emphysema [161–163]. Moreover, inhibition of *de novo* ceramide synthesis prevented alveolar cell apoptosis. It was also observed that stimulation of S1P signaling prevents lung apoptosis, implying involvement of the balance between levels of ceramide and S1P in alveolar cell survival [163].

SLs in diabetes

A number of studies have demonstrated that ceramide inhibits insulin-stimulated glucose uptake, GLUT4 translocation, and glycogen synthesis [164], and thereby contributes to the development of insulin resistance resulting from lipid over-supply [165–167]. The inhibitory effect of ceramide on insulin signaling mainly results from its ability to block the phosphorylation and activation of Akt/protein kinase B, a serine/threonine kinase that is a central mediator of insulin action [168, 169]. A correlation also exists between an increase in insulin sensitivity and lowering of ceramide levels [164]. Increased levels of simple GSLs such as GlcCer [170], and increased synthesis of ganglioside GM3, have also been implicated in diabetes pathogenesis [171, 172].

SLs and pathogen invasion

Some pathogens activate acid SMase, and as a consequence, ceramide-enriched membrane platforms are formed, which are known to mediate internalization of bacteria, viruses and parasites [173]. Other pathogens exploit the SLs of host cells as membrane receptors. For example, sialic acid on gangliosides is involved in influenza virus internalization [174], and different components of the HIV fusion machinery interact with cell surface GSLs [175]. As a consequence, binding of some pathogens and toxins to human cells can be prevented by depleting host cells of their surface GSLs or by coating the binding sites of pathogens with GSL-like substances that compete with the pathogen for binding [176].

SLs and sepsis

Sepsis is a major cause of death in intensive care units worldwide [177], and the septic immune response is associated with changes in SL metabolism. Ceramide production by SM hydrolysis is involved in the onset of sepsis [178, 179], with a secreted form of SMase playing a critical role in the development of apoptosis and organ failure in sepsis. Sphingosine is involved in endotoxin-induced mitochondrial dysfunction, as inhibition of sphingosine production by the ceramidase inhibitor, N-oleoylethanolamine, prevents the latter [180].

SLs in neurological diseases

Much of the early work on SLs and GSLs was stimulated by their accumulation in a number of inherited metabolic diseases caused by defects in the lysosomal hydrolases responsible for their degradation [181], many of which have severe neurological components. However, more recently, SLs and GSLs have also been implicated in many other neurological diseases, such as dementia [182], Alzheimer's [183] and Parkinson's diseases [184]. The involvement of SLs and GSLs in these neurological diseases is perhaps not surprising, since GSLs are found at high levels in the brain.

Perspectives

In this brief review, we have attempted to give an overview of SL and GSL biology. With the explosion of interest in these molecules over the past two or three decades, we have only been able to touch upon a few examples in each case, and by so doing, have had to limit details in many cases. The main impressions that we would like to leave with the reader are, first, that SLs and GSLs are important bioactive lipids and, second, that the involvement of SLs and GSLs in multiple intracellular pathways, and in multiple disease states, renders an 'integrated' and 'unified' view of their functions almost impossible, at least at present. This is best illustrated by considering the diseases in which SLs and GSLs are involved. Are they the cause of the diseases? Clearly the answer to this question is 'yes' when discussing lysosomal storage diseases due to defective SL degradation, but 'no' in most other diseases, where altered SL and GSL metabolism is a result of alterations in other pathways. However, since SLs and GSLs are critically involved in the pathogenesis of a number of these diseases, intervention in SL and GSL metabolic pathways, and application of exogenous SLs and GSLs, may yet provide novel modes of therapeutic intervention.

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