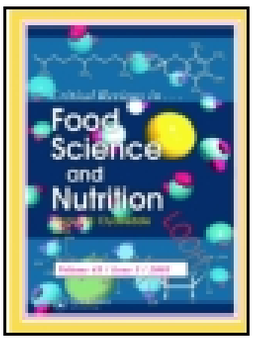

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REVIEW

Sphingolipids in food and their critical roles in human health

Xiaoxu Wang[a], Yuming Wang[a,b], Jie Xu[a], and Changhu Xue[a,b]

[a]College of Food Science and Engineering, Ocean University of China, Qingdao, Shandong, China; [b]Qingdao National Laboratory for Marine Science and Technology, Qingdao, Shandong, China

ABSTRACT

Sphingolipids (SLs) are ubiquitous structural components of cell membranes and are essential for cell functions under physiological conditions or during disease progression. Abundant evidence supports that SLs and their metabolites, including ceramide (Cer), ceramide-1-phosphate (C1P), sphingosine (So), sphingosine-1-phosphate (S1P), are signaling molecules that regulate a diverse range of cellular processes and human health. However, there are limited reviews on the emerging roles of exogenous dietary SLs in human health. In this review, we discuss the ubiquitous presence of dietary SLs, highlighting their structures and contents in foodstuffs, particularly in sea foods. The digestion and metabolism of dietary SLs is also discussed. Focus is given to the roles of SLs in both the etiology and prevention of diseases, including bacterial infection, cancers, neurogenesis and neurodegenerative diseases, skin integrity, and metabolic syndrome (MetS). We propose that dietary SLs represent a "functional" constituent as emerging strategies for improving human health. Gaps in research that could be of future interest are also discussed.

KEYWORDS

dietary sphingolipids; structure; digestion; metabolism; metabolic syndrome; human diseases

Introduction

The enigmas of sphingolipids (SLs) began with the initial naming of "sphingosin" in the 1880s, when sphingosine (So) was isolated from the brain by Thudichum (1884). SLs, one of the eight major categories of lipids (fatty acyls, glycerolipids, glycerophospholipids, SLs, sterol lipids, prenol lipids, saccharolipids, and polyketides), are defined by the presence of a sphingoid base backbone (Fahy et al. 2010). Normally, So, sphinganine (dihydrosphingosine, Sa) or 4-hydroxysphinganine (phytosphingosine) serve as the backbones. Attachment of fatty acid (FA) to carbon-2 (C-2) on backbones via an amide bond yields ceramide (Cer) in the endoplasmic reticulum. Further attachment of the hydrophilic head groups to the OH-group at C-1 yields complex SLs in the Golgi (Futerman and Riezman 2005). The major headgroup categories of SLs include Cer, sphingomyelins (SM), glucosylceramides (GluCer), galactosylceramides (GalCer), and more complex glycosphingolipids with a few to dozens of sugar residues, such as ganglioside (GLS) (Merrill 2011). Additionally, Cer can be converted to So by ceramidase, or to ceramide-1-phosphate (C1P) by ceramide kinase (CERK). So can be further phosphorylated to sphingosine-1-phosphate (S1P) by sphingosine kinase (SPHK) (Hanada et al. 2003). All of the above SLs, such as Cer, So, S1P and C1P, are reservoirs of natural SLs or bioactive metabolites that are profoundly important to a myriad of cell signaling and pathological functions, including regulation of cell growth, death, senescence, adhesion, migration, inflammation, angiogenesis, and intracellular trafficking (reviewed in Hannun and Obeid 2008).

Researches in the past decade have made significant progresses on SLs in serval key aspects. First, with the rapid development of mass spectrometry (MS) technologies (Murphy and Merrill 2011), a large number of novel molecular species are taken into account when both headgroup and backbone variables are considered, especially when SL metabolites are tracked with stable isotope-labeled precursors (Shaner et al. 2009; Merrill and Sullards 2017; Wigger et al. 2019). Tissue-imaging MS of SLs has been proven to be useful in identifying specific molecular subspecies and histological locations of SLs under a wide range of normal and abnormal physiological conditions, since imaging MS minimizes *in vivo* loss of information on compounds of interest after homogenization and extraction (Chen et al. 2008; Jones et al. 2014; Prentice et al. 2019). Second, great progresses have been made in elucidating SL metabolism in physiology and disease. Particularly, major advances have been achieved over the past several years in defining enzymes in SL metabolism, and their acting mechanisms and structures (reviewed in Hannun and Obeid 2018). For example, it has been documented that So, Cer, C1P and S1P act on distinct protein targets, including kinases, phosphatases, lipases and other enzymes and membrane receptors, to exert distinct cellular functions. There is no doubt that, at the tissue and organ level, a plethora of cell biological processes are critically modulated by these bioactive SLs (Boini et al. 2017; Hla and Dannenberg 2012). Regardless,

CONTACT Jie Xu xujie9@ouc.edu.cn; Changhu Xue xuech@ouc.edu.cn College of Food Science and Engineering, Ocean University of China, Qingdao, Shandong, China.

challenges remain in defining their biochemical and molecular underpinnings, especially lipid-protein interactions and the development of cellular probes, suitable biomarkers and therapeutic approaches (Olsen and Faergeman 2017). Last but not least, the pathways of SL synthesis and metabolism have emerged as important therapeutic targets. The development of SL analogs and inhibitors brings more possibility to this research (reviewed in Ogretmen 2018). The publicly developed among these targets is FTY720, an analog of So base. It has been used in clinical medicine for the treatment of multiple sclerosis through the action of SPHK2 (Lee, Choi, and Chun 2010; Li et al. 2017; Vessey et al. 2007). Also developed is myriocin, a serine palmitoyltransferase (SPT) inhibitor, can decrease plasma SM and Chol levels in mice (Li et al. 2009). The recent chemoenzymatically synthesized GM3 analogs have therapeutical potential on recovering nervous functionality in PC12 cells after injury (Zheng et al. 2018) and inhibiting tumor cell growth and migration *in vitro* (Zheng et al. 2019).

There is no doubt that endogenous SLs play crucial roles at multiples stages in cell biological processes and human health (Wennekes et al. 2009). Importantly, early studies have shown beneficial effects of dietary SLs on nutrition (Vesper et al. 1999). A recent review summarized preclinical and clinical studies examining dietary SL intake and prevention of dyslipidemia and nonalcoholic fatty liver disease (NAFLD) (Norris and Blesso 2017a). Dietary SLs have been shown to exert hypolipidemic effects in both rodents and humans. Such hypolipidemic effects may be related to the reduced intestinal absorption of cholesterol (Chol), triglyceride (TG) and FAs, which help prevent hepatic lipid uptake and accumulation in rodents. In addition, dietary SLs may prevent the translocation of lipopolysaccharide derived from gut bacteria and/or inhibiting its proinflammatory effects, invoking the gut-liver axis (Norris and Blesso 2017a). Although current researches suggest dietary SLs have lipid-lowering and anti-inflammatory properties *in vitro* and in rodent models, as well as in human clinical trials (Maceyka and Spiegel 2014; Norris and Blesso 2017b), their effects on endogenous SL metabolism and metabolism-related disorders have not been fully examined. Here in the current review, we introduce the important involvement of SLs in physiological and pathophysiological pathways. We highlight the structures, absorption and functions of dietary SLs (including marine bioactive SLs), the development of their therapeutic potentials for improving intestinal immunity, reducing cancer risk, regulating neural development, enhancing skin protection, and alleviating lipid disorders and metabolic syndrome (MetS).

Sphingolipids in foods

Contents of sphingolipids in foods

Distributions and amounts of dietary SL in various foods vary considerably, from low content in fruit and vegetables to high content in dairy products and soybeans (Vesper et al. 1999). Although they are not commonly considered as dietary nutrient lipids due to their low contents, SLs are important components in most foods, as summarized in Table 1. Animal products, e.g. meat, egg and dairy products, contain a higher level of SM than others. Both human and bovine milk are rich in GLS, but the content and profile of milk GLS vary among bovine milk, human colostrum and human mature milk (reviewed in German and Dillard 2006). Legumes are also considered a good source of SLs in plant-derived foods, such as full-fat soy flakes (Ahn and Schroeder 2002). Additionally, the species and contents of SLs in aquatic products are relatively abundant (Table 1), including SM (Duan, Sugawara, and Hirata 2010), cerebroside (Sugawara et al. 2006), GLS and some novel SLs such as ceramide 2-aminoethylphosphonate (CAEP) and deoxysphingolipids (deoxySLs) (Wan et al. 2019). Our study found that squid *Loligo chinensis* had the highest CAEP content and the most complex molecular species composition, whereas starfish *Asterias amurenis* had the lowest CAEP content, among five aquatic products (squid, mussel, oyster, neptunea and starfish) (Wang et al. 2020). Meanwhile, SL contents in vegetables and fruits are relatively lower than in other foods, containing mostly cerebrosides or glycosyl inositol phospho-ceramides (G-IPC) (Blaas and Humpf 2013). Five major glycolipid classes have been detected in 48 edible plants available in Japan including acylated steryl glucoside, steryl glucoside, ceramide monohexoside, monogalactosyldiacylglycerol, and digalactosyldiacylglycerol (Sugawara and Teruo 1999). When considering SL supplementation by adjusting dietary composition, in addition to the type of food that has higher SL content, the SL existing forms and other components of food, such as calories, should also be taken into account (Vesper et al. 1999). For example, Cer, as a class of hydrophobic lipids, is particularly abundant in the skin. Most animal-derived foods do not include skin when they are consumed (except chicken and duck) (Hellgren 2001). Additionally, in a typical Japanese diet, high- (3,000 kcal) and low- (1600–1700 kcal) calorie meals, respectively, contain 128, 292 mg cerebrosides and 45, 81 mg SM per day, mostly from cereals, vegetables, pulses and fruit (Yunoki et al. 2008). These issues put forward a more far-reaching requirement for future research on food-derived SLs, that is, a more comprehensive and integrated analysis of the composition of food SLs (Lai et al. 2016).

Structures of sphingolipids in foods

The structure of SLs consists of 3 building blocks: a FA, a sphingoid base and a head moiety. SLs are characterized by a common SL backbone, sphingoid, but their FAs and head moieties differ. Cer is generated through amide linkage of a FA to a sphingoid base (also known as long-chain base, LCB). Further head group, as the hydrophilic portion of SLs, is bound to the C-1 atom of the LCB moiety of the Cer (Chen et al. 2009). SLs can be classified into three categories, depending on their polar parts of the molecule being alkaline, neutral or acidic. Alkaline SLs include LCB, Cer, and SM; neutral SLs include cerebrosides, such as GluCer, GalCer, lactosylCer (LacCer), trisaccharide and tetraglycosyl

Table 1. Content of sphingolipids in various dietary sources.

Sphingolipids	Dietary sources	Content (mg/100g)	Latin name and references
Sphingomyelin	**Egg**	82.0[b]	(Norris and Blesso 2017b)
	Soybeans		
	Full-fat soy flakes	45.7[ac]	(Ahn and Schroeder 2002)
	Livestock and poultry meat		
	Chicken	41.8[bc]	(Hellgren 2001)
	Turkey	35.0[bc]	(Hellgren 2001)
	Lamb	33.2[bc]	(Hellgren 2001)
	Beef	28.6-69.0[bc]	(Hellgren 2001; Norris and Blesso 2017b)
	Pork	20.3[bc]	(Hellgren 2001)
	Ham	17.8[bc]	(Hellgren 2001)
	Dairy products		
	Cheese	24.3-365.7[ac]	(Rombaut, Koen, and John Van 2007)
	Milk	23.4-47.3[ac]	(Rombaut, Koen, and John Van 2007)
	Butter (Batch, continuous)	29.2-44.4[ac]	(Rombaut, Koen, and John Van 2007)
	Nonfat dry milk	15.2[ac]	(Ahn and Schroeder 2002)
	Yogurt	10.4[ac]	(Ahn and Schroeder 2002)
	Aquatic products		
	Plaice	9.6[bc]	(Hellgren 2001)
	Herring	7.2[bc]	(Hellgren 2001)
	Cod	6.5[bc]	(Hellgren 2001)
	Turbot	6.4[bc]	*Scophthalmus maximus* (Wang et al. 2019)
	Trout	4.2[bc]	*Oncorhynchus keta* (Wang et al. 2019)
	Mackerel	3.9[bc]	*Scomberomorus niphonius* (Wang et al. 2019)
	Grass carp	1.7[bc]	*Ctenopharyngodon idellus* (Wang et al. 2019)
	Shellfish	0.8[bc]	*Ruditapes philippinarum* (Li et al. 2020)
	Fruits		
	Peanuts	5.9[bc]	(Vesper et al. 1999)
	Orange	1.8[bc]	(Vesper et al. 1999)
	Banana	1.5[bc]	(Vesper et al. 1999)
Ceramide	**Aquatic products**		
	Mussel	21.9[bc]	*Mytilus edulis* (Li et al. 2020)
	Clam	19.3[bc]	*Ruditapes philippinarum* (Li et al. 2020)
	Scallop	16.7[bc]	*Chlamys farreri* (Li et al. 2020)
	Oyster	12.1[bc]	*Ostrea gigas* (Li et al. 2020)
	Mackerel	5.5[bc]	*Scomberomorus niphonius* (Wang et al. 2019)
	Turbot	2.9[bc]	*Scophthalmus maximus* (Wang et al. 2019)
	Trout	2.5[bc]	*Oncorhynchus keta* (Wang et al. 2019)
	Grass carp	1.7[bc]	Ctenopharyngodon idellus (Wang et al. 2019)
	Soybeans	11.5[a]	(Norris and Blesso 2017b)
Deoxy-ceramide	**Aquatic products**		
	Clam	4.6[bc]	*Ruditapes philippinarum* (Li et al. 2020)
	Mussel	2.0[bc]	*Mytilus edulis* (Li et al. 2020)
	Oyster	1.4[bc]	*Ostrea gigas* (Li et al. 2020)
	Scallop	0.8[bc]	*Chlamys farreri* (Li et al. 2020)
	Turbot	0.3[bc]	*Scophthalmus maximus* (Wang et al. 2019)
	Trout	0.1[bc]	*Oncorhynchus keta* (Wang et al. 2019)
Cerebroside	**Aquatic products**		
	Clam	7.4[bc]	*Ruditapes philippinarum* (Li et al. 2020)
	Scallop	6.8[bc]	*Chlamys farreri* (Li et al. 2020)
	Oyster	2.2[bc]	*Ostrea gigas* (Li et al. 2020)
	Mussel	1.4[bc]	*Mytilus edulis* (Li et al. 2020)
	Grass carp	0.3[bc]	*Ctenopharyngodon idellus* (Wang et al. 2019)
	Turbot	0.3[bc]	*Scophthalmus maximus* (Wang et al. 2019)
	Dairy products		
	Cheese	13.6-175.2[ac]	(Rombaut, Koen, and John Van 2007)
	Milk	12.22-27.9[ac]	(Rombaut, Koen, and John Van 2007)
	Butter	18.7-19.9[ac]	(Rombaut, Koen, and John Van 2007)
	Soybeans	11.1-38.3[ac]	(Gutierrez, Wang, and Walter 2004)
	Defatted soy flakes	19.2-23.9[ac]	(Gutierrez and Wang 2004)
	Cereal and nuts products		
	Corn	11.5[b]	(Norris and Blesso 2017b)
	Soybeans	5.3[a]	*Glycine max* (Fang et al. 2010)
	Pine nut	4.2[a]	*Pinus edulis* (Fang et al. 2010)
	Cashew nut	3.9[a]	*Anacardium occidentale* (Fang et al. 2010)
	Pumpkin	3.1[a]	*Cucurbita pepo* (Fang et al. 2010)
	Peanut	2.6[a]	*Arachis hypogaea* (Fang et al. 2010)
	Walnut	2.5[a]	*Juglans regia* (Fang et al. 2010)
	Hazelnut	2.1[a]	*Corylus avellane* (Fang et al. 2010)
Ceramide 2-aminoethylphosphonate	**Aquatic products**		
	Squid	492.0[a]	*Loligo chinensis* (Wang et al. 2020)
	Oyster	350.0[a]	*Ostrea gigas* (Wang et al. 2020)
	Neptunea	310.0[a]	*Neptunea cumingi* (Wang et al. 2020)
	Mussel	210.0[a]	*Mytilus edulis* (Wang et al. 2020)

(*continued*)

Table 1. Continued.

Sphingolipids	Dietary sources	Content (mg/100g)	Latin name and references
	Starfish	190.0[a]	*Asterias amurenis* (Wang et al. 2020)
	Clam	74.0[bc]	*Ruditapes philippinarum* (Li et al. 2020)
	Scallop	40.5[bc]	*Chlamys farreri* (Li et al. 2020)
Ganglioside	**Aquatic products**		
	Island mackerel	6.6[b]	*Rastrelliger faughni* (Fong et al. 2016)
	King salmon	1.1[b]	*Oncorhynchus tshawytscha* (Fong et al. 2016)
	Snapper	0.8[b]	*Chrysophrys auratusc* (Fong et al. 2016)
	Regular canned tuna	0.1[b]	(Pham et al. 2011)
	Turbot fish	0.9 [b]	*Scophthalmus maximus* (Fong et al. 2016)
	Large egg yolk	1.7[b]	(Pham et al. 2011)
	Livestock and poultry meat		
	Regular fat cooked ground beef	1.7[b]	(Pham et al. 2011)
	Regular fat raw ground beef	1.6[b]	(Pham et al. 2011)
	Chicken thigh	1.4[b]	*Gallus domesticus* (Fong et al. 2016)
	Beef blade steak	1.0[b]	*Bos Taurus* (Fong et al. 2016)
	Chicken breast	1.0[b]	*Gallus domesticus* (Fong et al. 2016)
	Dairy products		
	Regular fat cheddar cheese	0.07[b]	(Pham et al. 2011)
	Regular fat yogurt	0.07[b]	(Pham et al. 2011)
	1% milk	0.05[b]	(Pham et al. 2011)

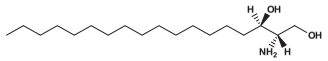
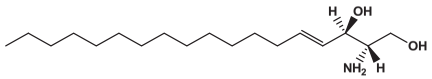
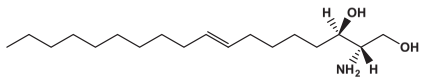
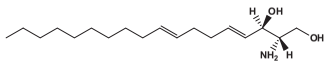
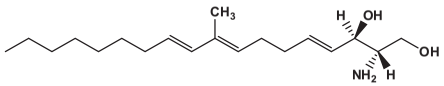
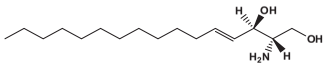
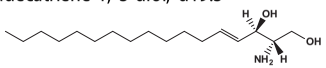
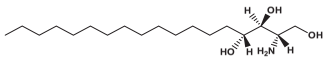
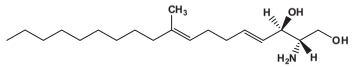
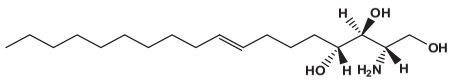
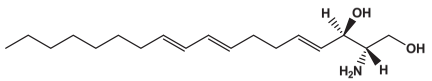
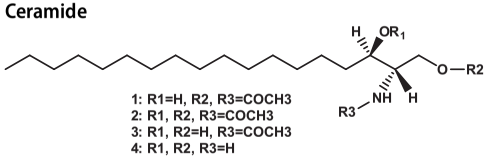
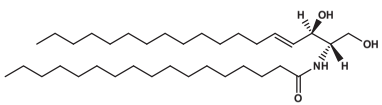
[a]Represents dry weight.
[b]Represents wet weight.
[c]Estimation based on reported sphingolipid content (g/mol) using an average molecular weight for the following: sphingomyelin 751, ceramide 587, deoxyceramide 606, ceramide 2-aminoethylphosphonate 676, cerebroside 779.

cerebroside; acidic SLs mainly include sulfatide and GLS (reviewed in Zhang and Frederick 2004).

Some naturally occurring SLs found in different foods are summarized in Table 2. The structures of SLs vary considerably with the type of food, and even more structural diversity is achieved by variations in the sphingoid base backbone. For example, a novel So, 2-acetamido-3-hydroxyoctadecyl acetate, which is characterized by replacement of the terminal hydroxyl group on the So and the hydrogen on the amino group with an acetyl group (Choi et al. 2013), can be extracted from the edible mushroom *Grifola gargal*. Another triene type of sphingoid base (sphingatrienine, d18:3) is found in rice and maize (Sugawara et al. 2019). SL species show profound diversity. On the one hand, the amino group of the sphingoid base is usually substituted with a long-chain FA to produce Cer. Further modifications of Cer are through changes in chain length, methylation, hydroxylation and/or degree of desaturation of LCB and FA (Lynch and Dunn 2004). In terms of LCB, the most common LCB in mammalian animals contains 18 carbon atoms and an unsaturated double bond, followed by saturated dihydrosphingosinol and hydrodihydrosphingosinol (i.e. phytosphingosine). In buttermilk, the most abundant Cer species are d18:1-C22:0, d17:1-C23:0 and d16:1-C24:0, while d18:1-C23:0 and d17:1-C24:0 are the most abundant ones in butter serum (Bourlieu et al. 2018). In particular reference to marine organism, the LCB of sea cucumber cerebrosides mainly contain d17:1. We have identified three GluCer series from sea cucumber *Cucumaria frondosa* and the most dominant molecular species were d17:1-C24:1, d18:2-C24:1, d18:2-C24:1h and t17:0-C24:1h (Jia et al. 2015, 2016). The fatty acyl chain varies in carbon number (typically 14 to 26), degree of unsaturation, and presence or absence of a hydroxyl group on the α-carbon atom. The common and most abundant FA moieties in starfish are saturated C16, C18, and C22-C24 2(R)-hydroxylated FA, while sea cucumber is characterized by C23 and C24 unsaturated FAs together with saturated C18 and C22-C24 2R-hydroxylated FAs (reviewed in Careaga and Maier 2014). Most of them are 2(R)-hydroxylated, generally unbranched and saturated, while unsaturated and branched (*iso*- and *anteiso*-types) 2-hydroxy FAs are found as minor constituents (Careaga and Maier 2014).

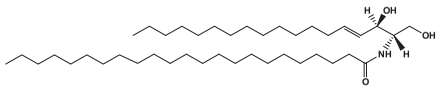
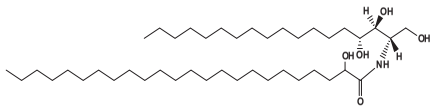
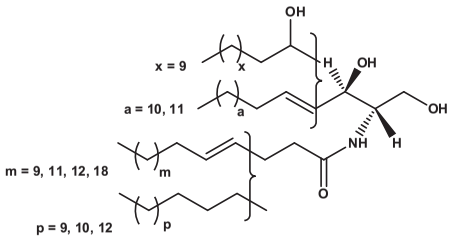
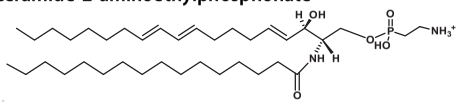
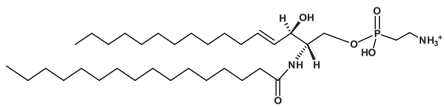
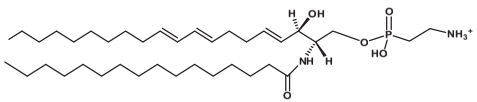
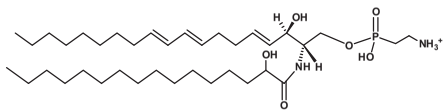
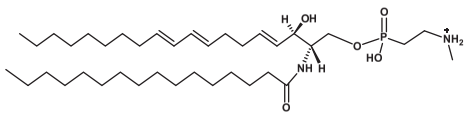
On the other hand, further addition of a hydrophilic head group, including sugar units and/or sulfate groups, gives rise to a broad range of SLs. GalCer and neuraminic (sialic) acid-containing Cer are typical mammalian SLs, which have not been found in higher plants (reviewed in Sperling and Heinz 2003). In rice and maize, GluCer containing 4,8-sphingadienine (d18:2) acylated to hydroxy-FAs are the predominant molecules (Sugawara et al. 2019). Most cerebrosides of fungi contain two main residues, including glucosyl or galactosyl residues, and glycosyl inositol phosphorylceramide with mannosyl residues (reviewed in Dickson and Lester 1999). More complex SLs, e.g. GLS, an acidic SL containing sialic acid, is composed of hydrophilic oligosaccharide chain and lipophilic Cer. The complexity of GLS is mainly due to the variety of their basic sugar moiety and the numbers and types of sialic acids (reviewed in Ledeen and Yu 1982). Mammalian SLs always contain N-acetyl-neuraminic acid (Neu5Ac), whereas numerous echinoderm GLS have unique structures, containing Neu5Ac, N-glycolyl-neuraminic acid (Neu5Gc) and sulfated Neu5Gc (Higuchi et al. 2007; Inagaki 2008; Kaneko et al. 2007). Two types of sulfated and non-sulfated monosialogangliosides were isolated from sea urchin and were identified with reversed-phase chromatography coupled to MS (Cong et al. 2015). We have also identified and isolated four special GLS series including HSO_3-NeuAc-Glc-Cer, HSO_3-NeuAc-NeuAc-Glc-Cer, NeuGc-NeuGc-Glc-Cer, and NeuAc-NeuAc-Glc-Cer, and named them as GM4(1S), GD4(1S), GD4(2G), and GD4(2A), respectively (Wang et al. 2017).

Table 2. Structures of some natural and novel sphingolipids from various dietary sources.

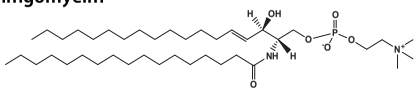
Structures	Dietary sources	Latin name and references	Structures	Dietary sources	Latin name and references
Sphingoid base					
 Sphinganine, d18:0	naturally occurring sphingoid base	(Sugawara et al. 2006)	 Sphingosine, d18:1	naturally occurring sphingoid base	(Sugawara et al. 2006)
 8-Sphingenine, d18:1			 4, 8-Sphingadienine, d18:2		
			 2-Amino-9-methy-4, 8, 10-octadecatriene-1, 3-diol, d19:3		
 8-Sphingenine, d16:1	jumbo flying squid	*Dosidicus gigas* (Tomonaga et al. 2019)	 8-Sphingenine, d17:1	sea cucumber	*Cucumaria frondosa* (Jia et al. 2016)
 Phytosphingosine, t18:0	potatoes and sweet potatoes	*Solanum tuberosum* L., *Ipomoea batatas* L. (Lynch and Dunn 2004)	 9-Methyl-4, 8-sphingadienine, d19:2	rice, mushroom, sea cucumber	(Sugawara et al. 2010)
 Phytosphingosines 8-enine, t18:1			 2-Amino-4, 8, 10-octadecatriene-1, 3-diol, d18:3		
Ceramide					
 1: R1=H, R2, R3=COCH3 2: R1, R2, R3=COCH3 3: R1, R2=H, R3=COCH3 4: R1, R2, R3=H	mushroom	*Grifola gargal* (Choi et al. 2013)	 N-(heptadecanoyl)-sphing-4-enine, Cer(d18:1/17:0)	meat and fish products	(Hellgren 2001)

(*continued*)

Table 2. Continued.

Structures	Dietary sources	Latin name and references	Structures	Dietary sources	Latin name and references
 N-(tricosanoyl)-sphing-4-enine, Cer (d18:1/23:0)	milk	(Norris et al. 2017a)	 N-(2-hydroxytetracosanoyl)-4R-hydroxysphinganine, Cer (t18:0/24:0h)	plants	(Lynch and Dunn 2004)
	sea cucumber	*Cucumaria frondosa* (Jia et al. 2016)			
Ceramide 2-aminoethylphosphonate					
 CAEP (d19:3/16:0)	jumbo flying squid	*Dosidicus gigas* (Tomonaga et al. 2019)	 CAEP (d16:1/16:0)	squid	*Loligo chinensis* (Wang et al. 2020)
 CAEP (d20:3/16:0)	mussel	*Mytilus edulis* (Wang et al. 2020)	 CAEP (d19:3/16:0h)	oyster	*Ostrea gigas* (Wang et al. 2020)
 Me-CAEP (d19:3/16:0)	starfish	*Asterias amurenis* (Wang et al. 2020)			

Sphingomyelin

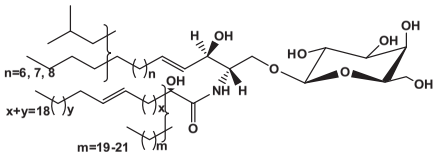


N-(heptadecanoyl)-sphinganine-1-phosphocholine
SM (d18:1/17:0)

meat and fish products (Hellgren 2001)

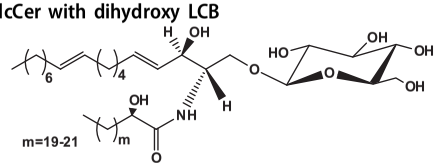
Cerebroside

GalCer

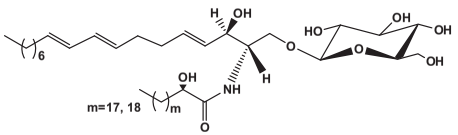


sea cucumber — *Bohadschia argus* (Careaga and Maier 2014)

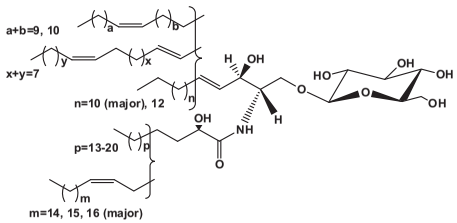
GlcCer with dihydroxy LCB



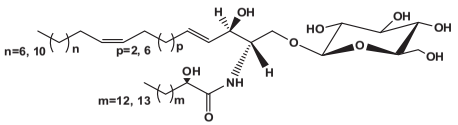
starfish — *Acanthaster planci* (Tan and Chen 2003)



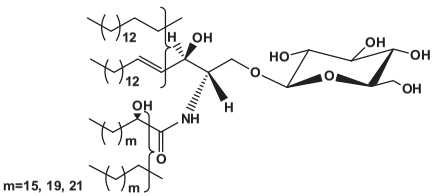
starfish — *Ophidiaster ophidiamus* (Tan and Chen 2003)



sea cucumber — *Cucumaria frondosa,* (Jia et al. 2016; Xu et al. 2013) *Apostichopus japonicus* (Guo et al. 2012)

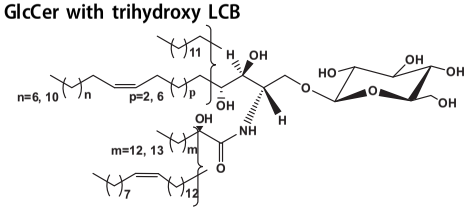


starfish, sea anemone, maryllidaceae — *Asterias aumrensis, Oreaster reticulatus, Metridium senile, Allium sativum* (Careaga and Maier 2014; Tan and Chen 2003)

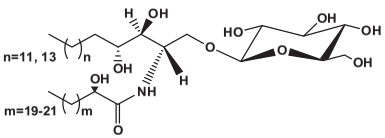


bullfrog — *Rana catesbeiana* (Tan and Chen 2003)

GlcCer with trihydroxy LCB



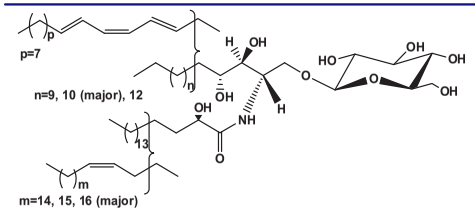
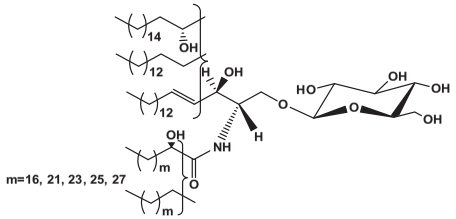
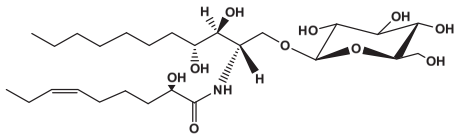
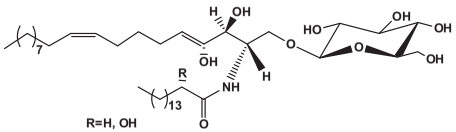
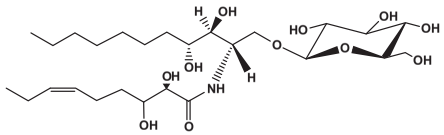
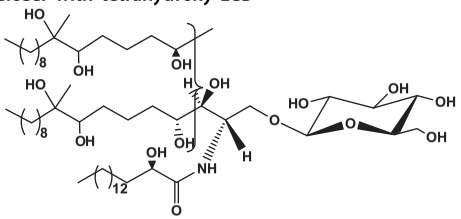
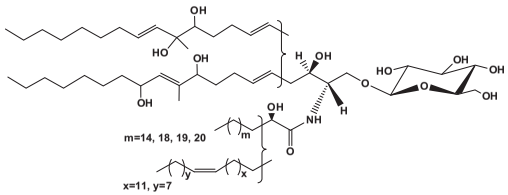
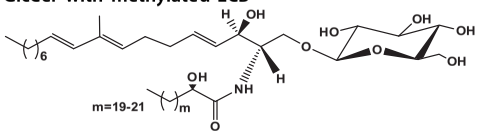
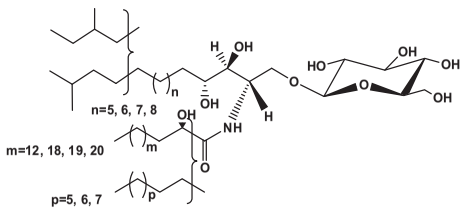
starfish — *Asterias aumrensis, Acanthaster planci* (Tan and Chen 2003)

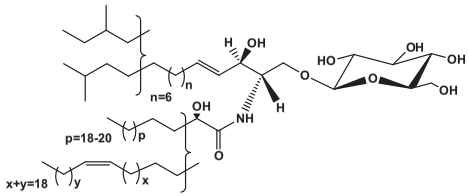
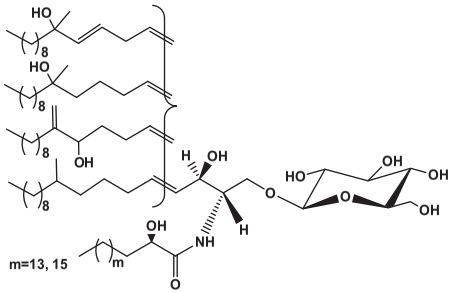
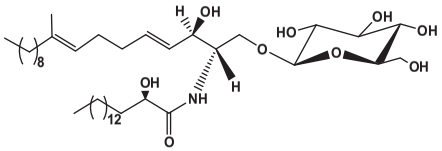
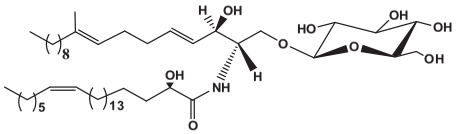


sea urchin, starfish — *Acanthaster planci, Pentaceraster regulus, Mnopleurus toreumaticus* (Tan and Chen 2003)

(*continued*)

Table 2. Continued.

Structures	Dietary sources	Latin name and references	Structures	Dietary sources	Latin name and references
	sea cucumber	*Cucumaria frondosa* (Jia et al. 2016; Xu et al. 2013) *Apostichopus japonicus* (Guo et al. 2012)		pig epidermis	(Tan and Chen 2003)
	basidiomycete	*Catathelasma ventricosa* (Hirsch and Kashman 1989)		solanaceae	*Lycium chinese* (Tan and Chen 2003)
		*Pholiota nameko* (Senik et al. 2011)			
GlcCer with tetrahydroxy LCB					
	black poplar mushroom, Chinese mushroom	*Agrocybe aegerita* (Diyabalanage et al. 2008) *Rmitomyces albuminosus* (Gao et al. 2010)		sea cucumber	*Stichopus japonicus* (Careaga and Maier 2014)
GlcCer with methylated LCB					
	starfish	*Pentaceraster regulus*, *Oreaster reticulatus* (Tan and Chen 2003) (Careaga and Maier 2014)		starfish	*Luidia maculate*, *Pentaceraster regulus, Linckia laevigata, Culcita novaeguineae, Protoreaster nodosus* (Careaga and Maier 2014; Tan and Chen 2003)

	sea cucumber	*Acaudina molpadioidesm, Holothuria leucospilota* (Careaga and Maier 2014)		black poplar mushroom Chinese mushroom	*Agrocybe aegerita* (Diyabalanage et al. 2008) *Termitomyces albuminosus* (Diyabalanage et al. 2008)
	edible fungus	*Tuber indicum, Termitomyces albuminosus, Hericium erinaceus* (Gao et al. 2010; Lee, Jung, et al. 2015)		fungus, basidiomycete	*Catathelasma ventricosa* (Hirsch and Kashman 1989), *Pholiota nameko* (Senik et al. 2011)
Glycosyl-inositol-phosphoceramides					
Galpα-3(Fucpα-2)Galpβ-6Manp(α)−2/(4)Ins1-PO_4-Cer Galpα-3(Fucpα-2)(Fucpα-6)Galpα-2(Galpα-3)Galpβ-6Manp(α)-2/(4)Ins1-PO_4-Cer	mushroom	*Amanita virosa* (Jennemann et al. 2001)	Manpα-2/(4)Ins1-PO_4-Cer Galpβ-6Manpα-2/(4)Ins1-PO_4-Cer Glcpα-6Galpβ-6Manpα-2/(4)Ins1-PO_4-Cer Galpα-3(Galpα-6)(Fucpα-2)Galpβ-6Manpα-2/(4)Ins1-PO_4-Cer	mushroom	*Calvatia exipuliformis* (Jennemann et al. 2001)
Manpα-3 or -6Manpα-2/(4)Ins1-PO_4-Cer Manpα-3(Manpα-6)Manpα-2/(4)Ins1-PO_4-Cer	mushroom	*Cantharellus cibarius* (Jennemann et al. 2001)	Manpα-2/(4)Ins1-PO_4-Cer Manpα-6Galpα-3(Fucpα-2)Galpβ-6Manpα-2/(4)Ins1-PO_4-Cer Manpα-2Manpα-6Galpα-3(Fucpα-2)Galpβ-6Manpα-2/(4)Ins1-PO_4-Cer	mushroom	*Lentinus edodes* (Jennemann et al. 2001)
Manpα-3Fucpα-2(Galpα-6)Galpα-6Galpβ-6Manp(α)-2/(4)Ins1-PO_4-Cer	mushroom	*Leccinum scabrum* (Jennemann et al. 2001)	Manpα-2/(4)Ins1-PO_4-Cer Galpα-3(Galpα-6)(Fucpα-2)Galpβ-6Manpα-2/(4)Ins1-PO_4-Cer	mushroom	*Pleurotus ostreatus* (Jennemann et al. 2001)
Ganglioside					
Monosialoganglioside					
NeuGc(Me)α2-6Glcβ1-1Cer	sea urchin	*Diadema setosum* (Yamada et al. 2008) (Hoda et al. 2006)	Fucβ1-4Galα1-4NeuAcα2-3Galβ1-4Glcβ1-1Cer	starfish	*Acanthaster planci* (Higuchi et al. 2007)
Fucβ1-11NeuG cα2-6Glcβ1-2Cer	sea cucumber	*Stichopus chloronotus* (Yamada et al. 2003)	Galβ1-3Galβ1-4NeuAcα2-3Galβ1-3Glc1-1Cer		
4-OAc-Fucβ1-11NeuGcα2-6Glcβ1-Cer	sea cucumber	*Cucumaria echinate* (Kisa et al. 2006)	Galβ1-3Galα1-3Galα1-4NeuAcα2-3Galβ1-4Glcβ1-1Cer		
Fucβ1-11NeuGcα2-6Glcβ1-1Cer			Galα1-4Galα1-4NeuAcα1-3Galβ1-4Glcβ1-1Cer	starfish	*Astropecten latespinosus* (Higuchi et al. 2007)
NeuGcα2-3Galβ1-4Glcβ1-1Cer	starfish	*Linckia laevigata* (Inagaki et al. 2009)	Ara1-6Galβ1-4[Galβl-8]NeuGcα2-3Galβ1-4Glcβ1-1-Cer	starfish	*Asterina pectinifera* (Higuchi et al. 2006)
Disialoganglioside					
NeuAcα2-8NeuAcα2-3Galβ1-4Glcβ1-1 Cer	starfish	*Luidia maculate* (Kawatake et al. 2002)	NeuGc(Me)α2-3GalNAcβ1-3Galβ1-4Glcβ1-1Cer	starfish	*Evasterias retifera* (Smirnova 1990)

(*continued*)

Table 2. Continued.

Structures	Dietary sources	Latin name and references	Structures	Dietary sources	Latin name and references
NeuGcα2-4NeuAcα2-6Glcβ1-1 Cer	starfish	*Evasterias echinosoma* (Smirnova 2003)	NeuGc(Me)α2-3[NeuAcα2-6]GalNAcβ1-3Galβ1-4Glcβ1-1Cer		
Fucβ1-11NeuGcα2-4NeuAcα-6Glcβ1-1 Cer	sea cucumber	*Holothuria leucospilota* (Higuchi et al. 2007)	NeuAcα2-9NeuAcα2-3GalNAcβ1-3Galβ1-4Glcβ1-1Cer		
Fucα1-11NeuG cα2-4NeuA cα2-6Glcβ1-1 Cer	sea cucumber	*Cucumaria echinata* (Kisa et al. 2006)	Fucα1-8NeuGcα2-4NeuGcα2-6Glcβ1-1Cer	starfish	*Evasterias echinosoma* (Smirnova 2003)
Araβ1-3Galα1-4NeuAcα2-6Galβ-4Galα1-4NeuAcα2-Galβ1-4Glcβ1-1Cer	starfish	*Asterina pectinifera* (Higuchi et al. 2006)	NeuAc(Me)α2-3[NeuAc(Me)α2-6]GalNAcβ1-3Galβ1-4Glcβ1-1Cer	starfish	*Evasterias echinosoma* (Smirnova 2003), *Asterias amurensis* (Higuchi et al. 2007)
NeuAcα2-11NeuGcα2-3Galα1-4Glc1-1 Cer	starfish	*Linckia laevigata* (Inagaki et al. 2009)			
Trisialoganglioside					
Fucβ1-4NeuAcα2-11NeuGcα2-4NeuA cα2-4Glcβ1-1Cer	sea cucumber	*Holothuria pervicax* (Kisa et al. 2006)	NeuAcα2-4[NeuAcα2-3]Galβ1-8Neu Acα2-3GalNAcβ1-3Galβ1-4Glcβ1-1Cer	sea cucumber	*Stichopus japonicus* (Higuchi et al. 2007)
NeuGc(Me)α2-11NeuGcα2-11NeuGcα2-3Galβ1-4Glcβ1-1Cer	starfish	*Linckia laevigata* (Inagaki et al. 2009)			
Sulfated ganglioside					
NeuGc8(SO_3H)2-6Glc-Cer	sea urchin	*Strongylocentrotus nudus* (Cong et al. 2015)	NeuAc(SO_3H)α2-6Glcβ1-1Cer	sea urchin, sea cucumber	*Echinocardium cordatom*, *Cucumaria echinata* (Kisa et al. 2006; Kochetkov, Smirnova, and Chekareva 1976)

Abbreviation: LCB, long-chain base; SM, sphingomyelin; Cer, ceramide; GalCer, galactosylceramide; GluCer, glucosylceramide; CAEP, ceramide 2-aminoethylphosphonate; GLS, ganglioside.

Digestion and utilization of dietary sphingolipids

Humans can digest and utilize most types of SL in a normal diet, although not completely. Intestinal tract, a major organ for digestion of food SLs, is rich in SLs which account for about 30% of total villous apical lipids (Duan 2011). Previous radioisotope labeling studies confirmed that dietary So, GluCer and GalCer could be digested in the small intestinal of rats and 55–60% So portion was digested to FAs in the mucosal cells (Nilsson 1969). Forty-three percent of dietary cerebrosides were found in feces, 40–70% as intact molecules and 25–60% as Cer. Dietary SLs are predominantly digested in the intestinal lumen (Nilsson 1969; Wehrmuller 2007). Following digestion, the hydrolysates are absorbed by intestinal cells where they are further broken down or converted to complex SLs (Schmelz et al. 1994).

As shown in Figure 1, SLs are hardly hydrolyzed in the stomach, and their hydrolysis occurs mainly in mucosal cells in the small intestine and colon. Orally ingested labeled So (^{3}H- or $^{13}C_2$, D_2-So) is absorbed through the digestive tract and distributed on the skin in the form of So, GluCer and Cer (Ueda, Uchiyama, and Nakashima 2010). So and probably Cer can be taken up directly by intestinal cells in human intestinal epithelial cell models, possibly through bathing on the mucosal enterocyte surface via the unstirred water layer, followed by penetrating into the enterocyte brush border membrane (Nicolas et al. 2005). Most complex SLs need to be digested before they can be absorbed, they are catalyzed by high levels of enzymes expressed in the gut, such as SPHK, S1P lyase and S1P phosphatases (reviewed in Duan and Nilsson 2009). For example, digestion of SM is mechanically caused by alkaline sphingomyelinase (alk-SMase) in human intestinal tract and bile (Duan 1998). Alk-SMase hydrolyzes SM into Cer and cholinephosphate (Nilsson 1968), while Cer is further hydrolyzed by ceramidase to So. SM from animal products such as eggs and dairy products are mainly digested in the lower and middle part of the small intestine in rats (Nyberg et al. 1997). Additionally, pancreas plays an important role in SM digestion, as pancreatic phospholipase A2 enhances the activity of intestinal alk-SMase by hydrolyzing PC and PE, although SMase is not secreted by the pancreas (Liu, Nilsson, and Duan 2000). We have identified and quantified CAEP species from different aquatic products (Wang et al. 2020) and CAEP can be digested to free sphingoid bases by mouse small intestinal mucosa. This hydrolysis process is catalyzed by the alk-SMase and affected by pH (Tomonaga, Manabe, and Sugawara 2017). Digestion and absorption of more complex SLs, such as cerebroside and GLS, have also been reported. For example, Sugawara et al. (2003) reported dietary GluCer originating from maize can be hydrolyzed into Cer and free sphingoid bases in rat digestive tract, and the degradation products 2-hydroxy fatty acids and Cer can be found in the lymph. Because most of the dietary So is converted to palmitic acid in the intestinal mucosa and is incorporated into chylomicron triacylglycerol and then transport to the lymph (Ishikawa et al. 2009; Sugawara et al. 2010), probably with the help of adenosine triphosphate-binding cassette (ABC) transporters (Yang et al. 2013; Zhang et al. 2015). Meanwhile, dietary SM from milk also can be transported to lymph as molecular species of Cer hydrolyzed SM such as d18:1, d17:1 and d16:1 So. Co-ingestion of dietary SM with other glycerophospholipids, compared with purified SM, enhances lymphatic absorption of milk SM and further enhances the bioavailability of dietary SM (Morifuji et al. 2015). Additionally, GLS are taken up from the lumen by either receptor-mediated endocytosis or dissociation of micelle GLS, and then insert into the brush border membrane. GLS (such as GD3) is further taken up across the brush border membrane into the enterocyte and is transferred across the basolateral membrane into the blood in human Caco-2 cells probably with the help of endosomes or glycolipid transport proteins (Schnabl et al. 2009). The final step of SL degradation is the conversion of So into S1P by SPHK, followed by cleavage by S1P lyase into phosphoethanolamine and 2-hexadecena (reviewed in Serra and Saba 2010).

Digestion and utilization of dietary SLs *in vivo* is affected by coexistence of other food substances. It is found that consumption together with other glycerophospholipids increased the bioavailability of milk SM in lymph duct-cannulated rats (Morifuji et al. 2015). Co-ingestion of fermented milk increased absorption of dietary SM more effectively than nonfat milk in rats, possibly because the polysaccharide composition of fermented milk inhibited SM crystallization (Morifuji et al. 2017). Meanwhile, ingestion of SLs also affects the absorption of other lipids. Hydrolyzation of dietary SM to Cer inhibited the absorption of Chol in Caco-2 cells (Feng et al. 2010) and in animal models (Chung et al. 2013), through reducing thermodynamic activity of Chol monomers, such as the rate of luminal lipolysis, micellar solubilization, and transfer of micellar lipids to the enterocyte (Eckhardt et al. 2002; Sang and Sung 2004). Although SLs are not utilized efficiently, these findings are helpful in identifying factors that can promote the absorption and utilization of dietary SLs and there is no denying the importance of SLs in human health.

Metabolism of sphingolipids

The bioactivities of SLs are closely related to their metabolism and intermediate metabolites. Metabolism of SLs is an important cellular event and a highly coordinated process. The overall metabolism of SLs (Hannun and Obeid 2018), especially complex GLS (Sandhoff and Sandhoff 2018; Sandhoff, Schulze, and Sandhoff 2018), has been well reviewed, and is not discussed in detail here. Instead, we mainly discuss the influence of SL metabolism on human health and the regulation of SL metabolism by food-borne substances. A series of metabolic pathways are triggered by serine and palmitoyl coenzyme A through SPT in endoplasmic reticulum, which is the rate-limiting step of SL *de novo* synthesis. The following steps are mediated by a series of related enzymes (Futerman and Riezman 2005) and lipid transfer proteins such as Cer transfer protein (CERT) (Wong, Čopič, and Levine 2017). CERT is involved in the delivery of Cer for SM synthesis, and altering the

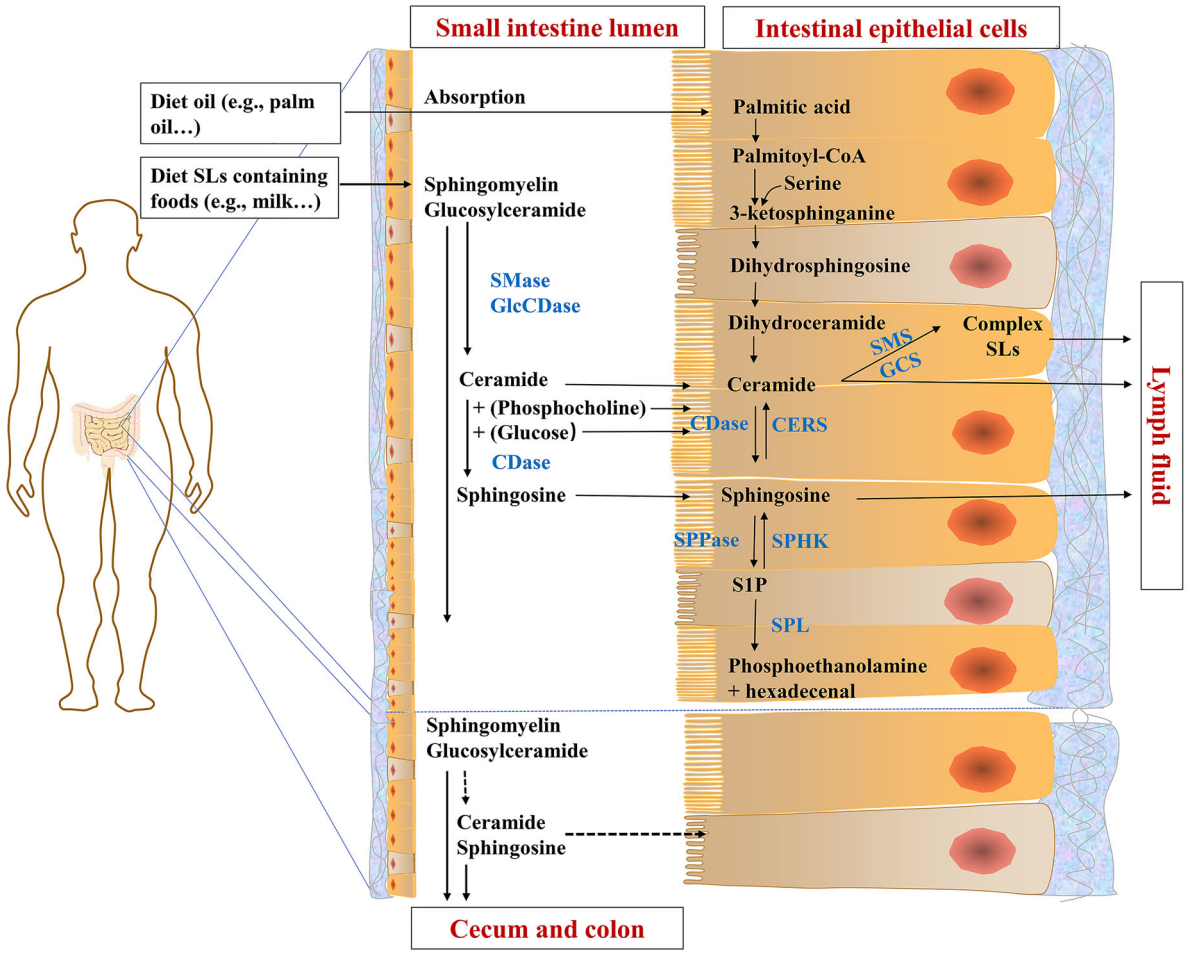


Figure 1. The fate of dietary sphingolipids consisting of different sphingoid bases from sphingosine. Dietary SLs can be hydrolyzed by intestinal enzymes. Digestion products are taken up by intestinal epithelial cells. Following absorption, Cer can be further used for synthesis of complex SLs. A large portion of sphingosine is converted to S1P. S1P finally is cleavage by S1P lyase into phosphoethanolamine and hexadecena. Abbreviation: SMase, sphingomyelinase; GlcCDase, glucosyl ceramidase; CDase, ceramidase; CERS, ceramide synthase; SPHK, sphingosine kinase; SMS, sphingomyelin synthase; GCS, glucosylceramide synthase; SPPase, sphingosine 1-phosphate phosphatase; SPL, S1P lyase.

activity of CERT directly affects SM synthesis and disturbs the balance between glycosphingolipid and SM levels (Hanada 2014). Cer is a product of *de novo* biosynthesis of SLs, and can be used as a substrate for synthesis of other complex SLs (Castro, Prieto, and Silva 2014). It is therefore not surprising that Cer plays a vital role in various pathophysiological conditions by altering signaling and metabolic pathways. Disruption of SL homeostasis in human results in metabolic stresses and therefore increase the risk of the MetS. For example, aberrant Cer accumulation contributes to the development of the deleterious clinical manifestations associated with some MetS with a hallmark of insulin resistance (Summers and Nelson 2005). Inhibition of Cer biosynthesis may combat insulin resistance in rodent models resulting from nutrient excess or glucocorticoid (Holland et al. 2007). Dietary components that structurally resemble SLs can interfere with endogenous SLs metabolism. For instance, food-borne fumonisins are common contaminants of corn, and their risks to human have been studied (Arranz et al. 2004). The most prevalent fumonisin B1 can inhibit CerS activity, disrupting synthesis of Cer and complex SLs, and causing accumulation of bioactive intermediates of SL metabolism (Sa and other sphingoid bases and derivatives) (reviewed in Riley and Merrill 2019). Fumonisin B1 also interferes with the function of some membrane proteins. For example, fumonisin B1 interferes with folate-binding protein and disrupts the transport of folate causing neural tube and craniofacial defects in mouse embryos in culture (Marasas et al. 2004; Riley et al. 2006). Another naturally occurring SL inhibitor is So-like ISP-1/myriocin, from a fungi *Isaria sinclairii* used in Chinese traditional medicine, which inhibits the proliferation of mouse cytotoxic T cell by inhibiting SPT activity (Miyake et al. 1995). Once consumed by human, myriocin can disrupt SL metabolism, cause organ damage, alter immune function, and result in developmental defects. In general, although it is recognized that endogenous SLs and their metabolism are important to human physiology and disease (Pralhada et al. 2013), the roles of exogenous SLs in human health remain elusive.

Function of dietary sphingolipids in human physiology and disease

Function of dietary sphingolipids in bacterial toxins and intestinal immunity

As described in section "Digestion and utilization of dietary sphingolipids," the digestion and absorption of dietary SLs

mainly take place in intestinal tract. The gut, besides its role in nutrient digestion and absorption, is also considered as an immune organ (Kunisawa and Kiyono 2010). Thus, SLs may influence immunocompetent cells in the gastrointestinal tract and affect the progress of inflammation. SLs involvement in inflammatory bowel disease (IBD) mechanically relate to their mucosal integrity, barrier and receptor functions and formation of SL messengers in epithelium and inflammatory cells. For example, GluCer showed an important barrier role in apical membrane, and its transfer to the apical membrane was regulated by the multidrug resistance protein 1 (MDR1) (Duan and Nilsson 2009). Microorganisms of the normal gut microbiota and probiotics affect the functions of SLs, such as augmented activity of alk-SMase and elevated levels of Cer, which in turn mediates the crosstalk between intestinal immunity and microorganisms (Bryan et al. 2016).

SLs and their metabolites may promote or inhibit infections, depending on the nature of the intracellular pathogen, and how and where Cer is produced. For example, Cer and its metabolic products, particularly their phosphorylated forms, are increased in IBD of mice. Loss of SPHK 1 appears to protect against IBD severity, which mediates IBD through lack of SPHK 1 activity and downregulation of S1P levels in colons of SPHK1$^{-/-}$ mice (Snider et al. 2009). S1P is also produced by neutral ceramidase (nCDase), whereas nCDase$^{-/-}$ mice are not protected from this disease model. This is due to the loss of nCDase resulting in increases in both local and circulating levels of S1P in nCDase$^{-/-}$ model, suggesting that nCDase-derived So is not the source of So for S1P in circulation (Snider et al. 2012). All these evidences suggest that S1P is essential for immune-cell trafficking and has primarily proinflammatory properties. Its concentration is increased in many inflammatory conditions, such as asthma and autoimmunity (Rivera, Proia, and Olivera 2008). A drug that targets S1P receptors, FTY720, approved by U.S. Food and Drug Administration (FDA) shows immunomodulating therapy for multiple sclerosis (Strader, Pearce, and Oberlies 2011) and potently downregulates lymphocyte S1P receptor 1 (Matloubian et al. 2004; Cyster and Schwab 2012).

Dietary SLs have been shown to possess antimicrobial effect and intestinal immunity. Study in rats suggests that SLs in bovine milk may enhance the resistance to certain types of food-borne gastrointestinal infections (Sprong, Hulstein, and van der Meer 2002). So may act as a natural antimicrobial barrier of the human skin (Arikawa et al. 2002). The application of dietary So is limited to specific environments due to its sensitivity to inhibition, such as the presence of bovine serum albumin, stearic acid and surfactants (Possemiers et al. 2005). Exogenous GLS can inhibit the infection of *Giardia lamblia* in the small intestine of mice (Suh, Belosevic, and Clandinin 2004). Dietary GLS such as that in milk may protect breast-fed infants from infections because GLS-supplemented infant formula modifies the intestinal ecology of preterm newborns, increases *bifidobacteria* and lowers *E. coli* (Rueda et al. 1998). Some microorganisms and microbial toxins from food or in the gut may exert their pathogenic effects through binding to host cells via glycosphingolipid (Ofek, Hasty, and Sharon 2003). Recent researches reported that some toxins from food can bind to glycosphingolipids on cell membrane. Tetrodotoxin (Qiao et al. 2008) and AB5 toxins cholera toxin (Patry et al. 2019) specifically target GLS-like glycoconjugates, resulting in inhibiting the growth of gut bacteria. Botulinum neurotoxin type B (Flores et al. 2019) and Botulinum neurotoxin DC (Zhang et al. 2017) can use cell membrane GLSs as co-receptors with a unique recognition mechanism. Noroviruses also can use GLS as ligand (Han et al. 2014). In this way, dietary SLs may compete for the binding sites and promote elimination of pathogenic organisms and toxins from the intestine (Duan and Nilsson 2009). SLs can also alter membrane organization in terms of fluidity and segregation of host cell proteins including viral receptors (Utermohlen et al. 2008). Additionally, SLs may affect intestinal physiology and mediate the activity of related intestinal enzymes such as sucrase and maltase (Barrenetxe et al. 2006). Therefore, SLs can be used to prevent the interaction of viruses with their host and play an important role in essential steps of viral replication. Collectively, dietary SLs have promising therapeutic potentials toward inhibiting infections, ameliorating IBD and preventing certain pathological conditions.

Roles and function of dietary sphingolipids in cancer

In terms of the relationship between cancer and SLs, an important concept "sphingolipid rheostat" was proposed in 1996 (Cuvillier et al. 1996). It means that Cer and S1P have the capability to regulate cell fate determination and the initiation, progression, and drug sensitivity of cancer by modulation of opposing signaling pathways (Newton et al. 2015). As showed in Figure 2 (adapted from Hanahan and Weinberg 2000; Colacios et al. 2015), S1P, acting as a tumor promoting lipid, plays a role in influencing cancer cell growth, drug resistance and tumor metastasis mainly through S1P receptor-dependent or independent signaling (Takabe et al. 2008). In MCF-7 cells, S1P increases the population of cancer stem cells with enhanced Notch signaling via S1P receptor 3; and overexpressing SPHK1, an S1P-producing enzyme, increases tumor development in nude mice (Hirata et al. 2014). Conversely, Cer functions as a tumor-suppressing lipid due to its ability to induce apoptosis, and C16-Cer is a natural small molecule that activates p53 tumor suppressor through direct binding (Fekry et al. 2018). Cer and Cer-generating agents, such as fenretinideis, are regarded as promising anti-cancer agents (Morad and Cabot 2013). Alterations in both glycan- and Cer moieties are clinically useful in screening of such distinct molecular species of cancer-associated glycolipids (Yin et al. 2010). Above all, Cer and S1P, and their related multiple enzymes have prognostic implications in cancer (Beckham et al. 2012; Brizuela et al. 2012; Flowers et al. 2012). Other certain SL molecules have also been reported to play critical roles in cancer development and progression, such as GLS and So. These diverse effects are illustrated in Figure 2. For example,

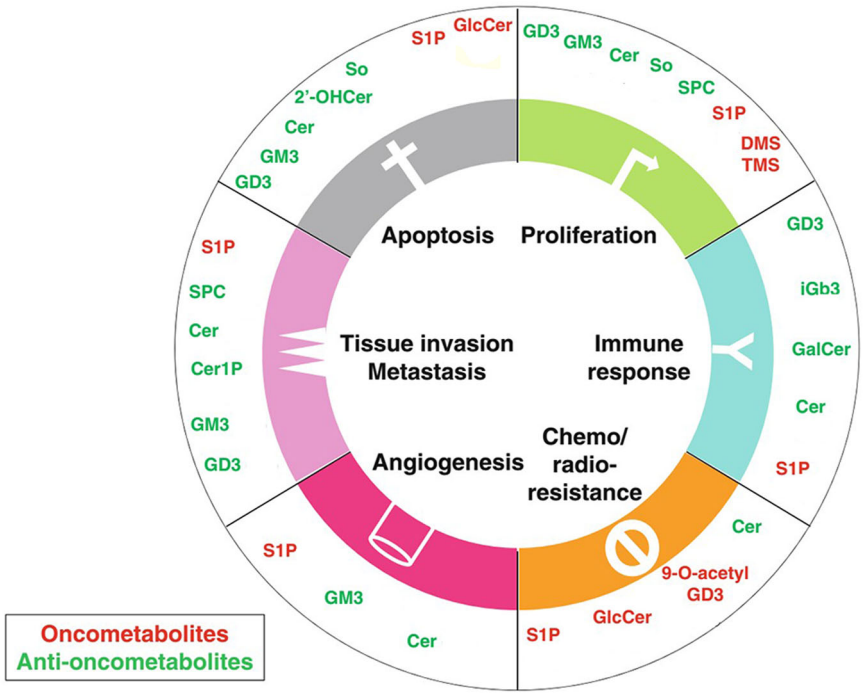


Figure 2. Biological effects and the manners of specific sphingolipids on the mediation of cancer development (adapted from Colacios et al. 2015; Hanahan and Weinberg 2000). "Red" represents promoting tumor development whereas "green" notes anti-tumor SLs. Abbreviation: Cer, ceramide; Cer1P, ceramide 1-phosphate; 2'-OHCer, 2'-hydroxyceramide; DMS, N, N-dimethyl-sphingosine; GalCer, galactosylceramide; GlcCer, glucosylceramide; S1P, sphingosine 1-phosphate; So, sphingosine; SPC, sphingosylphosphocholine; TMS, N, N, N-trimethyl-sphingosine.

in breast cancer, low expressions of ganglioside GD3-synthase (ST8SIA1), not only abnormal expression of CERK and Cer galactosyl transferase (UGT8) were observed (Eugen et al. 2009).

Therefore, modulation of SL levels and metabolisms has been recently demonstrated to bear exciting potential to augment the efficacy of anti-cancer therapeutics (Lewis et al. 2018). In particular, the modulation of the fine balance between swinging the ceramide-SPHK/S1P pendulum is important for cancer prevention/treatment (Guillermet-Guibert et al. 2009). A recent research confirmed the promising predictive value of SPHK in non-small cell lung cancer patients treated with adjuvant platinum-based chemotherapy (Gachechiladze et al. 2019). Dietary SLs also open the doors to new therapy against cancer. First, sphingoid bases hydrolyzed from wheat-flour cerebroside showed apoptotic effects on human colorectal cancer DLA-1 cells by leading to condensed chromatin fragments (Sugawara et al. 2002). Enigmol, a sphingoid base analog, lacks the C-1 hydroxyl group and cannot be phosphorylated. This analog is more persistent than natural sphingoid bases and exhibited anti-cancer activity in HT29 cells (a colon cancer cell) and in mice by normalizing aberrant accumulation of β-catenin in the nucleus (Symolon et al. 2011). Furthermore, addition of dietary SM to rodents with carcinogen-induced cancer led to suppression of the number of aberrant crypt foci (ACF) (Schmelz et al. 2000), and with longer feeding markedly reduced the number of colonic adenocarcinomas (Exon and South 2003). GluCer and GLS from animal food sources also decreased the risk of ACF in mice with colon cancer (Schmelz et al. 2000). Oral administration of cerebrosides from sea cucumber alleviates cancer-associated cachexia in mice, such as suppressing body weight loss through alleviating adipose atrophy. Especially LCB hydrolyzed from this cerebroside exhibit more potent anti-tumor effects than cerebrosides (Du et al. 2015).

How do these above-mentioned exogenous SLs mediate the progression of specific cancers, especially colon cancer? There are several possible mechanisms of actions of SL in suppressing colon carcinogenesis. Firstly, digestion of dietary SLs takes place predominantly in the middle and lower small intestine and the colon where most biologically active metabolites are available, and hydrolyzed SLs have the ability of regulating tumor development (as described in Section "Digestion and utilization of dietary sphingolipids"). Second, exogenously supplied SLs bypass a SL signaling defect that is important in cancer (Berra et al. 2002). Thirdly, uptake of dietary SLs may improve the microenvironment of intestinal tract via modulating the intestinal microbiota (Schmelz, Zhou, and Roberts 2015). Collectively, dietary SLs effectively display preventive and chemotherapeutic effects on colon cancer in animal models; however, clinical trials are urgently needed to examine the response of colon carcinogenesis to dietary SLs in the future.

Function of dietary sphingolipids in neuroprotection and neurogenesis

Another prominent function of SLs relates to neurogenesis and neurodegeneration. SLs can participate many signaling pathways controlling the development of neuronal survival, migration, differentiation, responsiveness to trophic factors, and are involved in synaptic stability, synaptic transmission,

as well as neuronal-glial interactions and myelin stability (Piccinini et al. 2010).

The neural functions of and mechanism of Cer, GluCer, S1P and GLS have been studied *in vitro*, indicating they may act as second messengers or regulating the Ca^{2+} homeostasis (reviewed in Buccoliero and Futerman 2003). Changes of SLs occur in the progress of neurological diseases, such as the significant alterations of SM and Cer in Alzheimer's disease (AD) and Parkinson's disease (PD) (Hussain et al. 2019). SM was found to be increased in the serum of AD patient, indicating their role in early AD stages (Toledo et al. 2017). Han et al. (2002) found a marked decrease in sulfatides in patients with AD, which was associated with early events in the pathological process of AD. We have demonstrated significantly lower levels of sulfatide and higher levels of Cer and cerebrosides in an AD animal model (SAMP8 mice) than in normal mice (SAMR1 mice) (Song et al. 2017). Interestingly, levels of Cer and sulfatide in hippocampus of SAMP8 mice were adjusted to near normal levels by sea cucumber GluCer treatment, which indicated that dietary GluCer had potential ameliorative effects in AD mice (Song et al. 2017). The mechanism of this function may be due to the regulation of mitochondria-dependent apoptotic pathway, because this GluCer can increase the survival rate of PC12 cells, recover the cellular morphology and protect against oxidative stress in SAMP8 mice (Che et al. 2017). And we found cerebrosides from starfish also prevented PC12 cells from oxidative damage (Wu et al. 2013). Mutation in the key enzyme in *de novo* SL biosynthesis, serine palmitoyltransferase (SPT), in fruit flies resulted in defects in axonal morphology and pathologies. SPT mutations in humans caused hereditary sensory and autonomic neuropathy type 1 (HSAN1), a neurodegenerative disorder (Goyal et al. 2019). Although the implications of altered lipid profile depend mostly on the specific diseases, one general mechanism may exist. Aberrant conversion of different SL molecules, such as SM to Cer, as well as pronounced changes of GLS patterns have been documented in the development and progression of AD, Parkinson's disease (PD), Huntington's disease (HD) and Human immunodeficiency virus (HIV) 1-related dementia (reviewed in Chaves 2006).

Consistent with the therapeutic potential of dietary SLs in neurogenesis and neuroprotection, our previous study demonstrated the benefits of sea cucumber GluCer in protecting PC12 cells from oxidative damage and ameliorating AD (Wu et al. 2013). GluCer also possess a marked neurogenic effect in undifferentiated PC12 on enhancing the signaling pathway downstream of TrkA, likely via the MEK-ERK1/2-CREB/BDNF pathway (Wang et al. 2018). Of note, sialic acid-containing complex glycosphingolipid GLS are particularly abundant in the nervous system. GLS is essential for the development of a stable CNS, possibly through promoting interactions between axon and glia, thus interruption of the synthesis of the major GLS class (GM3 and GM2) in mouse CNS resulted in a marked degeneration of myelinated axons and interfered with axon–glial interactions (Yamashita et al. 2005). Intraperitoneal administration of a GLS mixture was shown to accelerate functional recovery of damaged nerves (Ceccarelli, Aporti, and Finesso 1976). We have demonstrated that sea urchin GLS promoted resistance to AD in a dose-dependent and structure-selective manner via reducing the loss of neurites and blocking the mitochondrial apoptosis pathway (Wang et al. 2017). Meanwhile, dietary GLS, such as GLS from human milk, are essential to the development of utero and early neonatal brain (McJarrow et al. 2009). We also found that GLS from sea urchin exhibited neurogenic effect on undifferentiated PC12 cells and newborn mice. In this study, dietary GLS may serve as neurotrophic factors that activates the signaling pathway downstream of Trks, likely via the MEK1/2-ERK1/2-CREB and PI3K-Akt-CREB pathways (Unpublished results).

Mechanistic studies show that SLs can affect stem cell biology, membranes and organelles within neurons and glia via ion transport mechanisms (Ledeen and Wu 2002), receptor modulation including neurotrophic factor receptors, and effective replacement of endogenous neurotrophies (Rösner 1998). On one hand, a switch from globo- to ganglio-series, glycosphingolipid production occurs during neural development (Russo et al. 2018). Thus, supplement of dietary ganglio-series GLS (such as GM1 and GM2) promote neuritogenesis of neuroblastoma cells (Chiricozzi et al. 2017). Specifically, more complex carbohydrate moieties, GM1a, GD1a, GD1b and GT1b, are increased in expression during neuro- and astrocyto-genesis (Yu, Nakatani, and Yanagisawa 2009), although the regulation of which is incompletely understood. On the other hand, dietary SL modulation of neural functions mainly results from membrane reorganization and from lipid interaction with proteins within cellular membranes (Figure 3). GM1, for example, activates transport through appropriate signaling, either through direct association with ion transport channels (Ledeen and Wu 2018) or indirectly through association with neuronal receptors (Mutoh et al. 1995; Yates and Rampersaud 1998). Additionally, SM, Cer and GLS are highly dynamic lipids that modulate membrane composition and behavior through their reciprocal interconversion and the formation of specific lipid-protein interactions (reviewed in Chaves and Sipione 2010). SM can be converted to Cer and both of them can re-model the lipid raft (Cremesti, Goni, and Kolesnick 2002). This conversion at the membrane promotes the formation and increases membrane permeability through transmembrane Cer channels, causing neurodegenerative diseases associated with lysosomal abnormalities (Soreghan, Thomas, and Yang 2003). Thus, interventions with dietary SLs toward the prevention of early age-related dementias may be therapeutically effective. Although these data revealed the positive effect of exogenous GLS, especially of natural food, on neurogenesis and neural regeneration, their therapeutic applications and the specific mechanism of action are still being to define (Mocchetti 2005). Several semi-synthetic GLS have been characterized, such as a semisynthetic GM1 with N-dichloroacetyl sphingosine (LIGA 20). It shows the most effective action on attenuating glutamate-induced necrotic damage in cultured cerebellar granule cells among GM1, GD1a, GD1b, GT1b, and

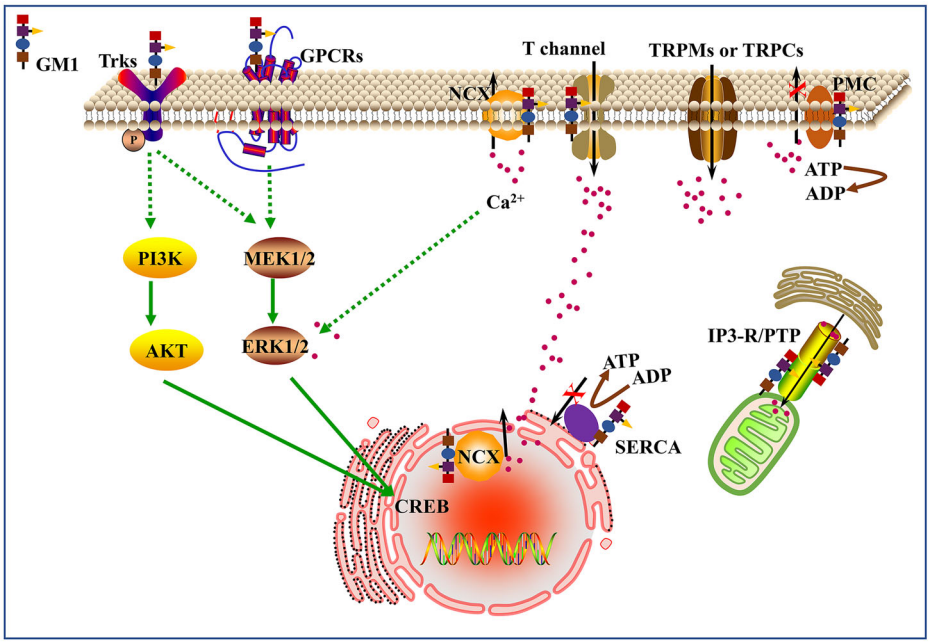


Figure 3. Mechanism of modulatory roles of exogenous GM1 in neuronal development. Exogenous GM1 can directly or indirectly interact with neuronal receptors (eg. GPCRs, Trks) to enhance downstream signaling to improve axon development. Alternatively, GM1 can mediate neuritogenesis and synaptic transmission via the virus ion channels, especially through modulation of Ca^{2+} via TRPC channels, T channels and Na^{+}/K^{+} exchanger (NCX). Abbreviation: GM1, monosialoganglioside GM1; Trks, tropomyosin receptor kinases; GPCRs, G-protein-coupled receptors; NCX, Na^{+}/K^{+} exchanger; T channel, T type channels; TRPMs, transient receptor potential melastatins; TRPCs, transient receptor potential channels; PMCA, plasma-membrane Ca^{2+}-ATPase; SERCA, sarco/endoplasmic reticulum Ca^{2+}-ATPase; IP3-R, inositol 1,4,5-trisposphate (IP3) receptor; PTP, permeability transition pore; CREB, cAMP-response element binding protein.

semisynthetic derivatives of SLs (Manev et al. 1990; Polo et al. 1994; Seren et al. 1994; Saito et al. 1998). These findings highlight the important roles of SLs, especially complex glycosphingolipids, in neurogenesis and neurodegeneration.

Functions of dietary sphingolipids in skin protection

Epidermis is composed of underlying dermis and overlying epidermis called stratum corneum. Since the lipid domains form the only continuous structure in the stratum corneum, the desiccation and penetration of xenobiotics have to pass these regions. This lipid regions, mainly composed of Cer, Chol and free fatty acid (FFA), are considered as the important skin barrier (Bouwstra et al. 2003). Therefore, Cer is an important component of mammalian epidermis and participates in the process of skin protection. Large quantities of GluCer and SM precursors also can be produced in skin and delivered to the extracellular domains in stratum corneum, where they are hydrolyzed to corresponding Cer species (Holleran, Takagi, and Uchida 2006). If the lipid composition of stratum corneum is altered, their organization and epidermal function are impaired, resulting in disease such as Harlequin-type ichthyosis, psoriasis and atopic dermatitis (reviewed in Breiden and Sandhoff 2014). Low levels of Cer and GluCer in atherosclerosis-prone ($ApoE^{-/-}$) mice led to skin inflammation and hair discoloration and loss (Bedja et al. 2018).

It is therefore not surprising that studies have shown the potential of SLs to improve skin barrier function. First, dietary SLs can moisturize skin and be applied in cosmetic products. Dry skin or xerosis, a very common skin disorder, is associated with roughness, squamae, itching or inflammation and leads to unpleasant sensations and a dull appearance of the skin (Barco and Gimenez-Arnau 2008). Previous studies have confirmed that decreased Cer level in the stratum cornel areas is a major etiologic factor in dry skin conditions (Imokawa et al. 1991; Jungersted et al. 2010; Matsumoto et al. 1999). A wheat extract powder rich in Cer and digalactosyl-diglycerides promoted skin hydration in both *in vitro* tests and clinical studies (Guillou et al. 2011; Lee, Kim, et al. 2015). A radioisotope labeling study confirmed that orally administered Cer was gradually distributed in the dermis after gastrointestinal absorption, followed by transferring from the dermis to the epidermis (Ueda, Hasegawa, and Kitamura 2009). Milk SM also can improve water content of the stratum corneum in hairless mice (Haruta-Ono et al. 2012). Thus, SLs are capable of promoting the formation of skin barrier by enhancing skin hydration to ameliorate dry skin. Second, SLs are considered of great significance in the regulation of barrier function in damaged skin, especially on the distribution and function of Cer in the skin (reviewed in Choi and Maibach 2005). In the condition of ageing, photoaging, atopic dermatitis and other metabolic abnormalities, Cer in the stratum corneum decreased in levels with altered profiles (Coderch et al. 2003). Besides free Cer, a unique ω-O-acyl-Cer characterized by very long-chain amide-linked FAs with terminal ω-hydroxyl groups, was significantly reduced in both lesional and non-lesional areas of atopic epidermis in AD patients, compared with healthy control epidermis (Uchida and Holleran 2008; Macheleidt, Kaiser, and Sandhoff 2002). Both acyl-Cer and very-long chain FAs ($\geq$C 28) are required for the structure and function of epidermal permeability barrier in mice (Vasireddy et al. 2007). Additionally, dietary

supplementation of GluCer, derived from sea cucumber (Duan et al. 2016), rice bran and germ (Tsuji et al. 2006), and enhanced the recovery of chronic skin perturbation in hairless mice. Oral administration of GluCer from maize significantly reduced UVA-induced wrinkle formation in the skin as well as epidermal hypertrophy of hairless mice (Shimada et al. 2011). These studies support that oral intake of GluCer is useful for preservation and recovery of epidermal barrier functions, regardless of it being from plants, fruits or other food sources. So is known as a natural antimicrobial agent, protecting the human skin from bacterial colonization (Possemiers et al. 2005). Orally administrated SM also helps prevent disruption of skin barrier function, mainly through suppressing an increase in trans epidermal water loss and a decrease in water content induced by UV-B irradiation (Oba et al. 2015). Mechanistically, SL intake increases Cer in the epidermis and further participates in biological modulation of keratinocytes and immune cells of the skin (reviewed in Kleuser and Japtok 2013), which is also related to changes in SL metabolism-related enzymes in the epidermis (Duan et al. 2012). Taken together, dietary SLs are essential for the formation of a well-organized epidermal permeability barrier.

Functions of dietary sphingolipids on metabolism related diseases

Herein, we discuss the roles of endogenous SLs in metabolism related diseases, and mainly explore the possibility of dietary SLs as a good nutritional support to alleviate MetS, including obesity, type 2 diabetes mellitus (T2DM), atherosclerosis, and nonalcoholic fatty liver disease (NAFLD) (Table 3).

Obesity, especially abdominal obesity, is a primary contributor to the rising prevalence of MetS (Grundy et al. 2004). It is well known that plasma FFA levels in obese animal models (Turpin et al. 2009) and patients with adiposity (Unger et al. 2010) are significantly higher than those in normal subjects. Excessive FFA cause mitochondrial dysfunction and this process is called as "lipotoxicity" (Turpin et al. 2009). Obesity is defined by excessive lipid accumulation. Expansion of adipose tissue mass is most healthfully accomplished via adipocyte hyperplasia, which occurs through adipogenesis. This process contains the formation of preadipocytes by expression of preadipocyte factor 1 (PREF1) and CCAAT/enhancer binding proteins (C/EBPs), and maturation related to the peroxisome proliferator-activated receptor gamma (PPARγ) adiponectin, FA binding protein 4 (FABP4), leptin, and others factors (Otto and Lane 2005). An emerging role of SLs in adipogenesis strongly relates to these factors in adipogenesis (reviewed in Lambert, Anderson, and Cowart 2018). For instance, in 3T3-L1 cells, dihydroceramide stimulation induced the adipogenesis and reduced expression of PPARγ, the master regulator of adipogenesis (Barbarroja et al. 2015). Not only are endogenous SLs involved in adipose tissue function and obesity-related pathologies (Walls et al. 2013; Le Barz et al. 2020), but exogenous SLs may be beneficial in prevention or treatment of obesity (as shown in Table 3). Dietary cerebrosides also reduced lipid accumulation by modulating the PPARγ and C/EBPα expression in our previous study (Xu et al. 2015). Norris et al. (2016, 2017) proved that dietary SM lowered hepatic TG and Chol via regulating lipid metabolism-related genes such as PPARγ, SREBP1c, LXRa, ACOX and PPARα, and furher improved metabolic complications associated with diet-induced obesity.

Additionally, "lipotoxicity" is found in T2DM patients (Ross et al. 2014). Accumulation of lipid-derived metabolites (such as esterified FAs) results from mitochondrial dysfunction are diverted away from carnitine palmitoyl transferase 1 toward TG and other lipid metabolites, such as diacylglycerol (DG) and Cer; thus, inhibition of Cer *de novo* synthesis enhanced mitochondrial function in high-fat diet (HFD) and *db/db* mice (Ussher et al. 2010). Bellini et al. (2015) proposed that strengthening the S1P formation from Cer is a potential way to reduce the toxicity of Cer. Pushing Cer metabolism toward the synthesis of less harmful lipid, such as S1P, may represent a potential target to counteract lipotoxicity (Bellini et al. 2015). Therefore, specific exogenous SLs can alleviate the symptoms of obesity and diabetes in recent studies (Table 3). For example, supplementation of milk SM significantly increased fecal lipids, and reduced the levels of hepatic total cholesterol (TC), plasma Chol and TG in obese/diabetic (KK-A^{y}) mice (Yamauchi et al. 2016). Additionally, exogenous S1P can activate the phospholipase C-Ca^{2+} system to increase non-glucose-stimulated insulin secretion from HIT-T15 cells and isolated mouse islets (Shimizu et al. 2000). S1P can reduce cytokine-mediated apoptosis of pancreatic β-cells (Laychock et al. 2006). In addition to studies in animal models, clinical studies have also shown beneficial effects of dietary SLs on plasma lipid levels. In MetS patients, supplementation of phytosphingosine (1 g/day) reduced levels of plasma TC, low-density lipoprotein-cholesterol (LDL-C) and glucose, and increased glucose disappearance rate (Snel et al. 2010).

In terms of the relationship of SLs and atherosclerosis, increased levels of some SLs in plasma and the aortic vascular wall are associated strongly with atherosclerosis both in patients and experimental models, such as GluCer, LacCer and SM (reviewed in Rekhter and Karathanasis 2006). Importantly, plasma SM levels have been implicated as a risk factor for coronary artery disease and correlated with subclinical atherosclerosis (Jiang et al. 2000). Because SLs overload may lead to the generation of SL-enriched lipoproteins. These circulating lipoproteins interact with the vascular wall and further facilitates plaque development (Rekhter and Karathanasis 2006). Therefore, inhibiting SPT and/or other enzymes involved in Cer and SM production may be a promising therapeutic approach for atherosclerosis. For instance, myriocin treatment of ApoE-knockout mice in a Western diet lowered SM and Sa levels in the plasma, liver and aorta (Park et al. 2004). And reduction in SM levels by knockout SM synthase 2 in ApoE-deficient mice also lowered the plasma lipoprotein SM levels as well as lowered SM, Cer, Chol, and cholesteryl ester (CE) in the brachiocephalic arteries (Fan et al. 2010). All these treatments reduce the atherosclerotic plaque area in the aortic root and brachiocephalic artery. Importantly, as summarized in Table 3,

Table 3. Effects of dietary sphingolipids on metabolic diseases.

Diseases	Exogenous SL ingredients	Model	Treatment and duration	Outcomes	References
Obesity	Phytosphingosine	DES2 KO mice fed with HFD	0.2% (wt/wt) phytosphingosine 18 weeks	— plasma TG, TC levels ↓ body weight, plasma neutral lipids (plasma TG, TC) ↓ markers of hepatic damage (GOT, GPT)	(Murakami et al. 2013)
	SM (milk and egg)	HFD-induced C57BL/6J obesity mice (6 weeks old)	0.1% (wt/wt) SM 10 weeks	↓ hepatic steatosis (hepatic TG, Chol) ↓ PPARγ-related genes (Scd1, Pparg2, Cd36, Fabp4, Ccl2) ↓ skeletal muscle TG	(Norris et al. 2017)
	Bovine milk SM Chicken egg SM	C57BL/6J mice fed with HFD (8 weeks old)	0.25% wt milk SM, or 0.25% wt egg SM 4 weeks	↓ milk SM: weight, serum Chol, hepatic TG, serum LPS ↑ egg SM: Chol, TG, phospholipids, SM, hepatic TG ↓ Chol-regulated genes: hepatic IDOL — lipid metabolism (SREBP1c, LXRa, ACOX, PPARα), lipoprotein uptake (LDLr, PCSK9), or inflammation (MCP-1), fatty acid oxidation (ACAD, ACOX, PGC-1α, LPL)	(Norris et al. 2016a)
	Cerebrosides (sea cucumber)	3T3-L1 cells	250 μg/mL cerebrosides 24 hours	↓ lipid accumulation (PPARγ and C/EBPα) ↑ anti-adipogenic activity, WNT/β-catenin pathway (β-catenin, CCND1, c-myc)	(Xu et al. 2015)
	LCB (sea cucumber)	3T3-L1 cells	100 μg/mL LCB 24 hours	↓ adipocyte differentiation (C/EBPs, PPARγ) ↑ target factors of β-catenin (c-myc D1, LRP5/6) ↑ WNT/β-catenin pathway (LRP5, LRP6, FZI, β-catenin, CCND1, c-myc mRNA, LRP6 protein, total β-catenin protein, nuclear β-catenin protein) ↑ FFA levels and the expressions of lipidolytic factors — WNT10b, GSK3β	(Tian et al. 2016)
	Cerebrosides (sea cucumber) LCB (sea cucumber)	HFD-induced obese C57BL/6J mice (6 weeks old)	0.025% wt cerebrosides or LCB 5 weeks	↓ epididymal adipose tissue weights, lowered hepatic TG levels, and serum glucose, insulin levels and HOMA-IR index ↓ hepatic lipogenetic enzymes (FAS, ME, SREBP-1c) ↓ hepatic SREBP-1c mediated lipogenesis (FAS, ACC, ATGL, HS) ↓ TG catabolism ↑ lipid uptake — hepatic lipolysis pathway	(Liu et al. 2015)
Diabetes	Phytosphingosine	Twelve men with MetS (aged 18 and 65 years; body mass index 27–40 kg/m^2; and HOMA-IR $>$ 2.0)	500 mg phytosphingosine twice daily (1 g/day) 4 weeks	↓ serum Chol, LDL-C ↓ fasting plasma glucose level ↑ glucose disappearance rate — TG, HDL-C	(Snel et al. 2010)
	Phytosphingosine	DES2 KO mice fed with HFD	0.2% wt phytosphingosine 18 weeks	↑ glucose tolerance ↓ epididymal adipose gene expression (↓ F4/80, MCP-1, TNF-α; ↑ adiponectin)	(Murakami et al. 2013)
	LCB (sea cucumber)	Male C57BL/6J mice (6 weeks old) fed with an HFD and injected with a single low dose of STZ (40 mg/kg)	10 mg/kg LCBs 23 weeks	↓ OGTT ↓ intraperitoneal insulin tolerance test ↓ urinary and blood parameters (UACR, blood glucose, TC, TG) ↓ tubular atrophy and lipid droplet in glomerulus areas ↓ renal inflammation (TNF-α, IL-1β, IL-6) ↓ renal fibrosis (fibronectin, TGF-β1, Smad3) apoptosis kidneys (↓ caspase 3, Bax;	(Hu et al. 2018)

(*continued*)

Table 3. Continued.

Diseases	Exogenous SL ingredients	Model	Treatment and duration	Outcomes	References
				↑ Bcl-2, PI3K, p-Akt, Akt, p-ERK, ERK)	
	SM (milk)	Obese/diabetic male KK-A^y mice (4 weeks old)	1% wt SM 4 weeks	↓ TC, non-HDL-C of blood lipid — neutral lipids, HDL-C of blood lipid; lipid metabolism gene expression (SREBP-2, HMG-CoA, Cyp7a1, CPT1a, FAS, Fads1) ↑ blood lipid (LDL-C); liver lipid (TAG, Chol, TL, NL); fecal lipids (TL, Chol, total bile acid, PL) ↑ lipid metabolism gene expression (SREBP-2, HMG-CoA, and Cyp7a1) ↓ lipid metabolism gene expression (SCD1, Elov2, Elov5, Fads2)	(Yamauchi et al. 2016)
	S1P	Cytokine-Induced rat pancreatic islet β-cells INS-1 cells	100-400 nM *D-erythro*-S1P and *D-erythro*-dihydro-S1P 4.5-5 hours	↓ TUNEL analysis; caspase-3 activity ↑ PKC activity ↓ cytochrome c release ↓ nitric oxide synthase	(Laychock et al. 2006)
	S1P	HIT-T 15 cells Mouse Islet from 8 weeks ICR mouse (cultured medium containing 7 mM D-glucose, 24-hour preincubation)	10 µM S1P 10 minutes	↑ insulin secretion ↓ intracellular cyclic AMP levels	(Shimizu et al. 2000)
	Cerebroside (sea cucumber)	HFD-fructose diet C57BL/6J mice (6–8 weeks old);	0.03%, 0.06% wt cerebroside 8 weeks	↓ OGTT (serum glucose, insulin) ↓ serum lipid levels (TC, TG, LDL-C) ↓ hepatic lipid levels (TC, TG)	(Zhang et al. 2018)
	GM1	Female non-obese diabetic mice	intraperitoneal dose injection of 100 mg/kg/d GM1 24 weeks	↑ infiltrating insular cell phenotype (CD4+, CD8+, CD11+) ↑ β cell survival (GFAP, S100-b, NGF, TrkA) pancreatic islets (↑ IL-12, TNF-α; ↓ IFN-γ, IL-1β spleen cells (↓ IL-12, TNF-α, IFN-γ; ↑IL-1β)	(Vieira et al. 2008)
Atherosclerosis	Phytosphingosine	ApoE*3 Leiden mice (female heterozygous, 6 months old)	1% wt phytosphingosine with Western type diet 5 weeks	↓ plasma Chol and TG ↓ absorption of dietary Chol and FFA — intestinal TG lipolysis, plasma VLDL lipolysis ↑ hepatic lipid synthesis, VLDL and LDL ↓ liver parameters (liver weight, TG, free Chol, CE)	(Nieuwenhuizen et al. 2007)
	Phytosphingosine	Twelve men with MetS (aged 18 and 65 years; body mass index 27–40 kg/m^2; and HOMA-IR > 2.0)	500 mg phytosphingosine, twice daily 4 weeks	↓ serum TC and LDL-C — body weight and fat mass — serum TG and HDL-C	(Snel et al. 2010)
	SM (milk)	Ten healthy adult males and females (aged 32.7 ± 4.1 years; height 170 ± 11 cm; body weight 66.2 ± 9.5 kg and BMI 23 ± 2 kg/m)	1 g/d milk SM 14 days	— serum TG, TC, LDL-C and VLDL-C, Chol absorption, Chol fractional synthesis rate — intraluminal Chol solubilization ↑ HDL-C	(Ramprasath et al. 2013)
	SM (egg)	HFD induced male C57BL/6 mice (4 weeks old)	HFD containing 0.3%, 0.6% or 1.2% wt SM 4 weeks	↓ TMAO — choline and betaine levels	(Chung et al. 2017)
		$ApoE^{-/-}$ mice with HFD (5 weeks old)	HFD + 1.2% wt SM 16 weeks	— aortic lesions — serum lipid levels (Chol, TG, non-esterified FA, SM)	
		$ApoE^{-/-}$ mice with normal chow diet (5 weeks old)	Normal chow diet +1.2% wt SM 19 weeks	↓ aortic lesions ↓ lesion composition — serum lipid, TMAO, choline and betaine levels	
	Ox brain SLs (67.5% ceramide-monosaccharide, 28.7% SM, and 2.5% Chol)	LDL receptor knockout female mice (12 weeks old)	1% SLs 1 month	↑ serum lipid (SM, Chol, SM/PC ratio, non-HDL-SM, non-HDL-Chol, and non-HDL-SM/non-HDL-PC ratio)	(Li et al. 2005)

(*continued*)

Table 3. Continued.

Diseases	Exogenous SL ingredients	Model	Treatment and duration	Outcomes	References
				— HDL-lipids ↑ atherosclerotic lesion area	
	Cerebroside (sea cucumber)	ApoE$^{-/-}$ male mice (18–19 weeks old)	0.06% cerebroside 8 weeks	↓ Chol levels in serum and liver ↓ atherosclerotic lesion formation and Chol accumulation in the aorta (Foam cells (HE), Chol crystals (Masson), college fibers (Masson), atherosclerotic lesions (ORO)) ↓ serum TC, LDL-C, hepatic TG and TC, VLDL ↑ serum HDL-C, — Chol metabolism genes (SREBP2, HMGCR, ACAT, ABCA1) ↑ Chol metabolism genes (ABCG5, ABCG8, CYP7A1) ↑ fatty acid β-oxidation (PPARα, CPT-1a, ACOX1) ↓ lipogenesis gene (↓ G6PDH, ME) (↑ SREBP-1c, FAS, SCD1)	(Zhang et al. 2018)
NAFLD	SM (egg)	C57BL/6 male mice fed with Western-type diet (21% milk-fat; 0.15% Chol) (4–5 weeks old)	0.3, 0.6 or 1.2% wt SM 4 weeks	↓ intestinal Chol absorption ↓ hepatic lipid (total lipid, Chol, TG, DG, SM, [^{14}C] Chol, [^{3}H] sitostanol) ↑ feces lipid (total lipid, Chol, TG, [^{14}C] Chol, [^{3}H] sitostanol) ↓ hepatic gene expression (Chol efflux, Chol uptake, Chol synthesis, other LXR-regulated gene, fatty acid synthesis, TG synthesis, fatty acid oxidation, *de novo* Cer synthesis, Cer generation from SM, transcription factor)	(Chung et al. 2013)
	SM	C57Bl/6J male mice fed an HFD (4 weeks old)	0.42% wt SM 5 weeks	↓ TG synthesis ↓ liver palmitoleic to palmitic acid ratio	(Reis et al. 2013)
	SM and Cer (milk)	Female KK-A$_y$ mice (3 weeks old)	1.7% (wt/wt) of lipid-concentrated butter serum (0.13% SM; 0.18% Cer) or 0.5% (wt/wt) Cer-fraction (0.34% Cer) or 0.5% (wt/wt) SM-fraction (0.25% SM) 4 weeks	Lipid-concentrated butter serum: ↓ TG, — TC Cer-fraction: ↓ TG, TC, stearoyl-CoA SM-fraction: — TG, TC	(Watanabe et al. 2011)
	Cerebrosides (sea cucumber)	Sprague-Dawley male rats administrated with 1% orotic acid (5 weeks old)	0.03%, 0.006% g/kg diet cerebrosides 10 days	↓ hepatic and serum TG, TC ↓ liver weight ↓ fatty acid endogenous synthesis gene ↓ hepatic lipogenic enzymes FAS, malic enzyme and G6PDH ↓ triglyceride transfer protein (MTP) activity	(Xu et al. 2011; Zhang et al. 2012)
	SM (animal origin) GluCer (plant origin)	Zucker fatty rats (5 weeks old)	0.5% wt SM (SM group) and 0.5% wt GluCer (GluCer group) 45 days	↓ hepatic lipid and plasma non-HDL-C ↓ plasma insulin levels ↑ hepatic gene expression (Adipor2, PPARα, and Pdk4) ↓ Scd1	(Yunoki et al. 2010)

Abbreviations: SM, sphingomyelin; LCB, long-chain base; S1P, sphingosine-1-phosphate; Cer, ceramide; SLs, sphingolipids; DES2, δ(4)- desaturase/C4-hydroxylase isoform 2; HFD, high feed diet; wt, weight; TC, total cholesterol; TG, triglyceride; DG, diglyceride; PC, phosphatidylcholine; GM1, monosialoganglioside GM1; OGTT, oral glucose tolerance test; CE, cholesteryl ester; FA, fatty acid; FFA, free fatty acid; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; VLDL-C, very low-density lipoprotein-cholesterol; TMAO, trimethylamine oxide; HOMA-IR, homeostatic model assesment-Insulin resistance; NAFLD, nonalcoholic fatty liver disease; GluCer, glucosylceramide.
"↓" represents the significantly decreasing index, "↑" represents the significantly increasing index, and "—" represents no significant changes.

dietary SM may be atheroprotective via inhibiting Chol absorption, influencing lipoprotein formation and mucosal growth in the gut (Eckhardt et al. 2002; Nilsson and Duan 2006). Kobayashi et al. (1997) found that long-term supplementation of SL mixture from bovine brain to a Chol-rich diet reduced Chol absorption in rat. In a randomized cross-sectional study in ten healthy men and women, milk SM supplementation (1 g/day) for 14 days increased serum high-density lipoprotein-cholesterol (HDL-C) levels, without affecting the levels of plasma TGs, TC, LDL-C and very low-density lipoprotein-cholesterol (VLDL-C) (Ramprasath et al. 2013). Additionally, S1P receptor agonists FTY720

and CYM5442 may exert atheroprotective effects under conditions of increased Chol burden exacerbating vascular inflammation, but not in moderately hypercholesterolemic LDL receptor deficient mice (Poti et al. 2012). Dietary SM actually did not affect circulating SM levels or increase atherosclerosis in HFD mice, but were anti-atherogenic in chow-fed ApoE$^{-/-}$ mice, possibly due to SM-mediated alterations in gut flora (Chung et al. 2017). Additionally, we have found that sea cucumber cerebroside treatment of ApoE$^{-/-}$ mice for 8 weeks reduced atherosclerotic plaques, serum TC, hepatic free Chol, serum glucose and insulin (Ding et al. 2018; Zhang et al. 2018). This SL was also shown to act as an anti-adipogenesis factor via WNT/β-catenin pathway (Xu et al. 2015).

Development of NAFLD begins with excess fatty accumulation in the liver and progresses to nonalcoholic fatty hepatitis and nonalcoholic steatohepatitis (NASH), which may eventually lead to cirrhosis of the liver (Manne, Handa, and Kowdley 2018). A tight relationship between adipose tissue dysfunction and NASH pathogenesis has been suspected (Duval et al. 2010). Progression of steatosis to NASH may be stimulated by cellular lipotoxicity mediated by lipotoxic FAs, Chol, and/or Cer. For example, plasma elevated Cer, dihydroceramide (DHCer), and 1-deoxy-DHCers are also associated with NASH in clinical research (Gorden et al. 2015). Cer and SM concentrations of obese human are higher in the liver compared to subcutaneous and intra-abdominal adipose tissue (Chung et al. 2017). Therefore, all these results indicate a relationship between NAFLD and Cer levels, and specific Cer blockers may offer potential therapeutic values for NAFLD (Nikolova-Karakashian 2018). Myriocin, an inhibitor of *de novo* Cer synthesis, robustly protects against hepatic steatosis on mice with diet induced obesity. And the acute depletion of Cer in hepatocytes or adipocytes also prevent the development of NAFLD in acid ceramidase transgenic mice overexpressing acid ceramidase to trigger the deacylation of Cer (Xia et al. 2015). The deficiency of acid SMase (ASMase), generating Cer by hydrolysis of SM, can prevent the lipid accumulation in the liver (Deevska et al. 2009). Importantly, some dietary SLs also show effects on alleviating NAFLD (summarized in Table 3). For example, dietary phytoshphingosine, So, Sa, cerebroside, or SM dose-dependently lower both plasma Chol and TG and protect the liver from fat- and Chol-induced steatosis in ApoE deficient mice. We found that treating orotic acid-fed rats with AMC-2, a novel cerebroside from sea cucumber, significantly reduced the levels of TG and TC in the liver, and alleviated NAFLD by inhibiting the activity of total stearyl coenzyme A desaturase (Xu et al. 2011).

SLs in various foods may have different effects on metabolism related diseases. Norris et al. (2016) compared the effects of milk SM and egg SM on lipid metabolism in C57BL/6J HFD-fed mice; serum Chol, TG, phospholipids and SM were increased in mice fed with egg SM, whereas these indices decreased in mice fed with milk SM. Compared with mammalian and plant SLs, our research shows that marine SLs are different in content and structure, and may have different effects on metabolic diseases. For example, sea cucumber cerebroside and the key structural unit LCB are efficacious in suppressing hepatic SREBP-1c-mediated lipogenesis, inhibiting lipid uptake and increasing TG catabolism in adipose tissue (Liu et al. 2015). Meanwhile, LCB from *Cucumaria frondosa* can inhibit adipogenesis and regulate lipid metabolism through the WNT/β-catenin and AMPK signaling pathways (Tian et al. 2016; Hu et al. 2018). These studies highlight the importance of the sources of sphingolipids. Further, the effect of SL is structure-selective, thus absent or presence of double bond of Cer promoted lipid uptake and storage and impaired glucose utilization, none of which could be recapitulated by DHCers that lacked the critical double bond (Chaurasia et al. 2019).

Collectively, some dietary SLs indeed show the beneficial effects of on MetS (Table 3), although higher levels of endogenous SL are always observed in MetS than healthy physiological conditions, such as a positive correlation between hepatic Cer levels and the degree of steatosis in *ob/ob* mice (Greco et al. 2008). Therefore, it's necessary to recognize the ameliorative effects of dietary SLs on MetS (shown in Table 3), and the mechanism of exogenous SLs actions still needs further research.

Conclusion and perspectives

There is no doubt that endogenous and exogenous SLs continue to surprise us today and there are exciting times for the field. SLs are a chemically complex group of substances, widely existing in plasma, brain and some foodstuffs. In this review, we summarized the importance of SLs under physiological conditions and during disease progression. Importantly, we drawn attention to dietary SLs, including their content and novel structures in various foods. Their digestion, absorption and metabolism were also discussed. We particularly focused on the biological roles of dietary SLs and their metabolites and the possible implications in health, including cancer, immunity, neural development, skin protection and metabolism related diseases (obesity, diabetes, atherosclerosis, and NAFLD). Collectively, SLs play important roles in human health, whereas more research is needed to elucidate the underlying mechanisms.

More work is required to explore the various bioactivities and functional mechanism of dietary SLs. How do dietary SLs regulate a variety of complex cellular processes remains a mystery? Future research is needed to determine the fate of the added exogenous SLs. We should determine whether they distribute focally or throughout specific tissue, or whether they are degraded or converted to other SLs or glycosphingolipid, in order to establish whether it is the metabolites or the actual SLs added that induce an effect. Understanding the mechanisms of action may provide novel potential for developing therapeutic strategies for the prevention and treatment of various human disorders. A broader assessment of the types of SLs in foods is needed because some diets may contain sufficient amounts of atypical or typical SLs that may have beneficial or deleterious effects on human health. Some special SLs should receive

particular attention; for example, 1-deoxysphingolipids (1-deoxySLs) (Lone et al. 2019) exists in some food materials, but their potential functions for human health are not clear.

In addition, whether intervention into a single metabolic pathway or multiple pathways will produce optimal results remains to be determined. It requires further animal studies and clinical trials to define the stage of disease at which modulation of lipid metabolism will have maximal efficacy. A key future challenge is to consider individual SL species or subgroups and their changes in different physiological and pathological context, which will give us a precise molecular mechanism of action for their specific roles and function. This field may benefit from the advanced sphingolipidomics, tissue-imaging MS for histological locations of SLs, and the use of click chemistry lipids (reviewed in McKay and Finn 2014). Another challenge is to characterize the complex effects of SLs on biophysical properties of biological membranes. It will help to clarify the structural mechanisms underlying the biological function of these bioactive compounds. Lastly, the differences between human disease and specific cellular or *in vivo* models should be recognized. Likewise, it is important to distinguish physiological from pharmacological effects of SLs when interpreting their mechanisms of action.

Disclosure statement

The authors declare no conflict of interest.

Abbreviations

SL	sphingolipid
Cer	ceramide
C1P	ceramide-1-phosphate
So	sphingosine
Sa	sphinganine
S1P	sphingosine-1-phosphate
MetS	metabolic syndrome
SM	sphingomyelin
MS	mass spectrometry
SPT	palmitoyltransferase
GLS	ganglioside
CAEP	ceramide 2-aminoethylphosphonate
G-IPC	glycosyl inositol phospho-ceramides
LCB	long-chain bases
GluCer	glucocerebroside
GalCer	galactocerebroside
LacCer	lactosylceramide
CERK	ceramide kinase
SPHK	sphingosine kinase
Neu5Ac	N-acetyl-neuraminic acid
Neu5Gc	N-glycolyl-neuraminic acid
SMase	sphingomyelinase
alk-SMase	alkaline sphingomyelinase
ASMase	acid sphingomyelinase
ACF	aberrant crypt foci
IBD	inflammatory bowel disease
AD	Alzheimer's disease
PD	Parkinson's disease
HD	Huntington's disease
HIV	human immunodeficiency virus
HFD	high-fat diet
PREF1	preadipocyte factor 1
C/EBPs	CCAAT/enhancer binding proteins
PPARγ	proliferator-activated receptor gamma
FABP4	fatty acid binding protein 4
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TG	triglyceride
DG	diacylglycerol
Chol	cholesterol
CE	cholesteryl ester
LDL-C	low-density lipoprotein-cholesterol
VLDL-C	very low-density lipoprotein-cholesterol
HDL-C	high-density lipoprotein-cholesterol
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
DHCer	dihydroceramide
1-deoxyDHCer	1-deoxydihydroceramide
deoxySL	deoxysphingolipid
FFA	free fatty acid
FA	fatty acid
ABC	adenosine triphosphate-binding cassette
MDR1	multidrug resistance protein 1

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References

Ahn, E. H., and J. J. Schroeder. 2002. Bioactive sphingolipids are constituents of soy and dairy products. *Journal of Food Science* 67 (2):522–4. doi: 10.1111/j.1365-2621.2002.tb10630.x.

Arikawa, J., M. Ishibashi, M. Kawashima, Y. Takagi, Y. Ichikawa, and G. Imokawa. 2002. Decreased levels of sphingosine, a natural antimicrobial agent, may be associated with vulnerability of the stratum corneum from patients with atopic dermatitis to colonization by *Staphylococcus aureus*. *Journal of Investigative Dermatology* 119 (2): 433–9. doi: 10.1046/j.1523-1747.2002.01846.x.

Arranz, I., W. R. G. Baeyens, G. Weken, S. Saeger, and C. Peteghem. 2004. Review: HPLC determination of fumonisin mycotoxins. *Critical Reviews in Food Science and Nutrition* 44 (3):195–203. doi: 10.1080/10408690490441604.

Barbarroja, N., S. Rodriguez-Cuenca, H. Nygren, A. Camargo, A. Pirraco, J. Relat, I. Cuadrado, V. Pellegrinelli, G. Medina-Gomez, C. Lopez-Pedrera, et al. 2015. Increased dihydroceramide/ceramide ratio mediated by defective expression of degs1 impairs adipocyte differentiation and function. *Diabetes* 64 (4):1180–92. doi: 10.2337/db14-0359.

Barco, D., and A. Gimenez-Arnau. 2008. Xerosis: A dysfunction of the epidermal barrier. *Actas Dermo-Sifiliográficas (English Edition)* 99 (9):671–82. doi: 10.1016/S1578-2190(08)70343-3.

Barrenetxe, J., P. Aranguren, A. Grijalba, J. M. Martinez-Penuela, F. Marzo, and E. Urdaneta. 2006. Effect of dietary quercetin and sphingomyelin on intestinal nutrient absorption and animal growth. *British Journal of Nutrition* 95 (3):455–61. doi: 10.1079/BJN20051651.

Beckham, T. H., P. Lu, J. C. Cheng, D. Zhao, L. S. Turner, X. Zhang, S. Hoffman, K. E. Armeson, A. Liu, T. Marrison, et al. 2012. Acid ceramidase-mediated production of sphingosine 1-phosphate promotes prostate cancer invasion through upregulation of cathepsin B. *International Journal of Cancer* 131 (9):2034–43. doi: 10.1002/ijc.27480.

Bedja, D., W. Yan, V. Lad, D. Iocco, N. Sivakumar, V. V. R. Bandaru, and S. Chatterjee. 2018. Inhibition of glycosphingolipid synthesis reverses skin inflammation and hair loss in apoe-/- mice fed western diet. *Scientific Reports* 8 (1):11463. doi: 10.1038/s41598-018-28663-9.

Bellini, L., M. Campana, R. Mahfouz, A. Carlier, J. Veret, C. Magnan, E. Hajduch, and H. L. Stunff. 2015. Targeting sphingolipid metabolism in the treatment of obesity/type 2 diabetes. *Expert Opinion on Therapeutic Targets* 19 (8):1037–50. doi: 10.1517/14728222.2015.1028359.

Berra, B.,. I. Colombo, E. Sottocornola, and A. Giacosa. 2002. Dietary sphingolipids in colorectal cancer prevention. *European Journal of Cancer Prevention* 11 (2):193–7. doi: 10.1097/00008469-200204000-00013.

Blaas, N., and H. U. Humpf. 2013. Structural profiling and quantitation of glycosyl inositol phosphoceramides in plants with Fourier transform mass spectrometry. *Journal of Agricultural and Food Chemistry* 61 (18):4257–69. doi: 10.1021/jf4001499.

Boini, K. M., M. Xia, S. Koka, T. W. B. Gehr, and P. L. Li. 2017. Sphingolipids in obesity and related complications. *Frontiers in Bioscience (Landmark Edition)* 22:96–116. https://www.ncbi.nlm.nih.gov/pubmed/27814604. doi: 10.2741/4474.

Bourlieu, C., D. Cheillan, M. Blot, P. Daira, M. Trauchessec, S. Ruet, J. Y. Gassi, E. Beaucher, B. Robert, N. Leconte, et al. 2018. Polar lipid composition of bioactive dairy co-products buttermilk and butterserum: Emphasis on sphingolipid and ceramide isoforms. *Food Chemistry* 240:67–74. doi: 10.1016/j.foodchem.2017.07.091.

Bouwstra, J. A., P. L. Honeywell-Nguyen, G. S. Gooris, and M. Ponec. 2003. Structure of the skin barrier and its modulation by vesicular formulations. *Progress in Lipid Research* 42 (1):1–36. doi: 10.1016/S0163-7827(02)00028-0.

Breiden, B., and K. Sandhoff. 2014. The role of sphingolipid metabolism in cutaneous permeability barrier formation. *Biochimica et Biophysica Acta* (*BBA*) - *Molecular and Cell Biology of Lipids* 1841 (3):441–52. doi: 10.1016/j.bbalip.2013.08.010.

Brizuela, L., I. Ader, C. Mazerolles, M. Bocquet, B. Malavaud, and O. Cuvillier. 2012. First evidence of sphingosine 1-phosphate lyase protein expression and activity downregulation in human neoplasm: Implication for resistance to therapeutics in prostate cancer. *Molecular Cancer Therapeutics* 11 (9):1841–51. doi: 10.1158/1535-7163.MCT-12-0227.

Bryan, P. F., C. Karla, M. T. Edgar Alejandro, E. P. Sara Elva, F. Gemma, and C. Luz. 2016. Sphingolipids as mediators in the crosstalk between microbiota and intestinal cells: Implications for inflammatory bowel disease. *Mediators of Inflammation* 2016:1–11. doi: 10.1155/2016/9890141.

Buccoliero, R., and A. H. Futerman. 2003. The roles of ceramide and complex sphingolipids in neuronal cell function. *Pharmacological Research* 47 (5):409–19. doi: 10.1016/S1043-6618(03)00049-5.

Careaga, V. P., and M. S. Maier. 2014. Cerebrosides from marine organisms. *Studies in Natural Products Chemistry* 42 (1):59–81. doi: 10.1016/B978-0-444-63281-400003-3.

Castro, B. M., M. Prieto, and L. C. Silva. 2014. Ceramide: A simple sphingolipid with unique biophysical properties. *Progress in Lipid Research* 54:53–67. doi: 10.1016/j.plipres.2014.01.004.

Ceccarelli, B., F. Aporti, and M. Finesso. 1976. Effects of brain gangliosides on functional recovery in experimental regeneration and reinnervation. *Advances in Experimental Medicine and Biology* 71:275–93. doi: 10.1007/978-1-4614-4614-9_17.

Chaurasia, B., T. S. Tippetts, R. M. Monibas, J. Liu, Y. Li, L. Wang, J. L. Wilkerson, C. R. Sweeney, R. F. Pereira, D. H. Sumida, et al. 2019. Targeting a ceramide double bond improves insulin resistance and hepatic steatosis. *Science* 365 (6451):386–92. doi: 10.1126/science.aav3722.

Chaves, E. P. D. 2006. Sphingolipids in apoptosis, survival and regeneration in the nervous system. *Biochimica et Biophysica Acta* 1758 (12):1995–2015. doi: 10.1016/j.bbamem.2006.09.018.

Chaves, E. P. D., and S. Sipione. 2010. Sphingolipids and gangliosides of the nervous system in membrane function and dysfunction. *FEBS Letters* 584 (9):1748–59. doi: 10.1016/j.febslet.2009.12.010.

Che, H. X., L. Du, P. X. Cong, S. Y. Tao, N. Ding, F. J. Wu, C. H. Xue, J. Xu, and Y. M. Wang. 2017. Cerebrosides from sea cucumber protect against oxidative stress in SAMP8 mice and PC12 cells. *Journal of Medicinal Food* 20 (4):392–402. doi: 10.1089/jmf.2016.3789.

Chen, M., E. B. Cahoon, M. Saucedo-García, J. Plasencia, and M. Gavilanes-Ruíz. 2009. Plant sphingolipids: Structure, synthesis and function. In *Lipids in photosynthesis: Essential and regulatory functions*, eds. H. Wada and N. Murata, 77–115. Dordrecht: Springer Netherlands.

Chen, Y., J. Allegood, Y. Liu, E. Wang, B. Cachon-Gonzalez, T. M. Cox, A. H. Merrill, Jr., and M. C. Sullards. 2008. Imaging MALDI mass spectrometry using an oscillating capillary nebulizer matrix coating system and its application to analysis of lipids in brain from a mouse model of Tay-Sachs/Sandhoff disease. *Analytical Chemistry* 80 (8):2780–8. doi: 10.1021/ac702350g.

Chiricozzi, E., D. Y. Pome, M. Maggioni, E. D. Biase, C. Parravicini, L. Palazzolo, N. Loberto, I. Eberini, and S. Sonnino. 2017. Role of the GM1 ganglioside oligosaccharide portion in the TrkA-dependent neurite sprouting in neuroblastoma cells. *Journal of Neurochemistry* 143 (6):645–59. doi: 10.1111/jnc.14146.

Choi, J. H., M. Yoshida, T. Suzuki, E. Harada, M. Kawade, K. Yazawa, S. Nishimoto, H. Hirai, and H. Kawagishi. 2013. A novel sphingosine with osteoclast-forming suppressing activity, from the edible mushroom *Grifola gargal*. *Tetrahedron* 69 (40):8609–11. doi: 10.1016/j.tet.2013.07.068.

Choi, M. J., and D. H. I. Maibach. 2005. Role of ceramides in barrier function of healthy and diseased skin. *American Journal of Clinical Dermatology* 6 (4):215–23. doi: 10.2165/00128071-200506040-00002.

Chung, R. W. S., Z. Wang, C. A. Bursill, B. J. Wu, P. J. Barter, and K.-A. Rye. 2017. Effect of long-term dietary sphingomyelin supplementation on atherosclerosis in mice. *PloS One* 12 (12):e0189523. doi: 10.1371/journal.pone.0189523.

Chung, R. W. S., A. Kamili, S. Tandy, M. Weir Jacquelyn, R. Gaire, G. Wong, J. Meikle Peter, S. Cohn Jeffrey, K. A. Rye, and L. Brennan. 2013. Dietary sphingomyelin lowers hepatic lipid levels and inhibits intestinal cholesterol absorption in high-fat-fed mice. *PloS One* 8 (2):e55949. doi: 10.1371/journal.pone.0055949.

Coderch, L., O. López, A. de la Maza, and J. L. Parra. 2003. Ceramides and skin function. *American Journal of Clinical Dermatology* 4 (2):107–29. doi: 10.2165/00128071-200304020-00004.

Colacios, C., F. Sabourdy, N. Andrieu-Abadie, B. Ségui, and T. Levade. 2015. Basics of sphingolipid metabolism and signalling. In *Bioactive sphingolipids in cancer biology and therapy*, eds. Y. A. Hannun, C. Luberto, C. Mao, and L. M. Obeid. Cham: Springer.

Cong, P. X., R. C. Gao, C. H. Xue, Z. J. Li, H. W. Zhang, M. N. Khan, Y. Xue, T. Sugawara, and J. Xu. 2015. Molecular species analysis of monosialogangliosides from sea urchin *Strongylocentrotus nudus* by RPLC-ESI-MS/MS. *Food Chemistry* 166:473–8. doi: 10.1016/j.foodchem.2014.06.028.

Cremesti, A. E., F. M. Goni, and R. Kolesnick. 2002. Role of sphingomyelinase and ceramide in modulating rafts: Do biophysical properties determine biologic outcome?. *FEBS Letters* 531 (1):47–53. doi: 10.1016/S0014-5793(02)03489-0.

Cuvillier, O., G. Pirianov, B. Kleuser, P. G. Vanek, O. A. Coso, J. S. Gutkind, and S. Spiegel. 1996. Suppression of ceramide-mediated programmed cell death by sphingosine-1-phosphate. *Nature* 381 (6585):800–3. doi: 10.1038/381800a0.

Cyster, J. G., and S. R. Schwab. 2012. Sphingosine-1-phosphate and lymphocyte egress from lymphoid organs. *Annual Review of Immunology* 30 (1):69–94. doi: 10.1146/annurev-immunol-020711-075011.

Deevska, G. M., K. A. Rozenova, N. V. Giltiay, M. A. Chambers, J. White, B. B. Boyanovsky, J. Wei, A. Daugherty, E. J. Smart, M. B. Reid, et al. 2009. Acid sphingomyelinase deficiency prevents diet-induced hepatic triacylglycerol accumulation and hyperglycemia in mice. *Journal of Biological Chemistry* 284 (13):8359–68. doi: 10.1074/jbc.M807800200.

Dickson, R. C., and R. L. Lester. 1999. Yeast sphingolipids. *Biochimica et Biophysica Acta* (*BBA*) - *General Subjects* 1426 (2):347–57. doi: 10.1016/S0304-4165(98)00135-4.

Ding, L., T. T. Zhang, H. X. Che, L. Y. Zhang, C. H. Xue, Y. G. Chang, and Y. M. Wang. 2018. Saponins of sea cucumber attenuate atherosclerosis in ApoE(-/-) mice via lipid-lowering and anti-

inflammatory properties. *Journal of Functional Foods* 48:490–7. doi: 10.1016/j.jff.2018.07.046.

Diyabalanage, T., M. Vanisree, M. Gary, L. D. David, and G. N. Muraleedharan. 2008. Health-beneficial qualities of the edible mushroom, *Agrocybe aegerita*. *Food Chemistry* 108 (1):97–102. doi: 10.1016/j.foodchem.2007.10.049.

Du, L., J. Xu, Y. Xue, K. Takahashi, C. H. Xue, J. F. Wang, and Y. M. Wang. 2015. Cerebrosides from sea cucumber ameliorates cancer-associated cachexia in mice by attenuating adipose atrophy. *Journal of Functional Foods* 17:352–63. doi: 10.1016/j.jff.2015.05.040.

Duan, J. J., T. Sugawara, and T. Hirata. 2010. Rapid quantitative analysis of sphingolipids in seafood using HPLC with evaporative light-scattering detection: Its application in tissue distribution of sphingolipids in fish. *Journal of Oleo Science* 59 (9):509–13. doi: 10.5650/jos.59.509.

Duan, J. J., M. Ishida, K. Aida, T. Tsuduki, J. Zhang, Y. Manabe, T. Hirata, and T. Sugawara. 2016. Dietary cerebroside from sea cucumber (*Stichopus japonicus*): Absorption and effects on skin barrier and cecal short-chain fatty acids. *Journal of Agricultural and Food Chemistry* 64 (37):7014–21. doi: 10.1021/acs.jafc.6b02564.

Duan, J. J., T. Sugawara, M. Hirose, K. Aida, S. Sakai, A. Fujii, and T. Hirata. 2012. Dietary sphingolipids improve skin barrier functions via the upregulation of ceramide synthases in the epidermis. *Experimental Dermatology* 21 (6):448–52. doi: 10.1111/j.1600-0625.2012.01501.x.

Duan, R. D., and A. Nilsson. 2009. Metabolism of sphingolipids in the gut and its relation to inflammation and cancer development. *Progress in Lipid Research* 48 (1):62–72. doi: 10.1016/j.plipres.2008.04.003.

Duan, R. D. 2011. Physiological functions and clinical implications of sphingolipids in the gut. *Journal of Digestive Diseases* 12 (2):60–70. doi: 10.1111/j.1751-2980.2011.00481.x.

Duan, R. D. 1998. Sphingomyelin hydrolysis in the gut and clinical implications in colorectal tumorigenesis and other gastrointestinal diseases. *Scandinavian Journal of Gastroenterology* 33 (7): 673–83. doi: 10.1080/00365529850171594.

Duivenvoorden, I., P. J. Voshol, P. C. N. Rensen, W. V. Duyvenvoorde, J. A. Romijn, J. J. Emeis, L. M. Havekes, and W. F. Nieuwenhuizen. 2006. Dietary sphingolipids lower plasma cholesterol and triacylglycerol and prevent liver steatosis in APOE*leiden mice. *The* American Journal of Clinical Nutrition 84 (2):312–21. doi: 10.1093/ajcn/84.1.312.

Eckhardt, E. R. M., Q. H. Wang, J. M. Donovan, and M. C. Carey. 2002. Dietary sphingomyelin suppresses intestinal cholesterol absorption by decreasing thermodynamic activity of cholesterol monomers. *Gastroenterology* 122 (4):948–56. doi: 10.1053/gast.2002.32539.

Eugen, R. B., K. Thomas, R. Achim, H. Lars, G. T. Regine, M. Dirk, H. Uwe, and K. Manfred. 2009. Gene expression of ceramide kinase, galactosyl ceramide synthase and ganglioside GD3 synthase is associated with prognosis in breast cancer. *Journal of Cancer Research & Clinical Oncology* 135 (8):1005–13. doi: 10.1007/s00432-008-0536-6.

Exon, J. H., and E. H. South. 2003. Effects of sphingomyelin on aberrant colonic crypt foci development, colon crypt cell proliferation and immune function in an aging rat tumor model. *Food and Chemical Toxicology* 41 (4):471–6. doi: 10.1016/S0278-6915(02)00297-1.

Fahy, E., S. Subramaniam, H. A. Brown, C. K. Glass, A. H. Merrill, Jr., R. C. Murphy, C. R. H. Raetz, D. W. Russell, Y. Seyama, and W. Shaw. 2010. A comprehensive classification system for lipids. *European Journal of Lipid Science and Technology* 107 (5):337–64. doi: 10.1002/ejlt.200405001.

Fan, Y., F. Shi, J. Liu, J. Dong, H. H. Bui, D. A. Peake, M. S. Kuo, G. Cao, and X. C. Jiang. 2010. Selective reduction in the sphingomyelin content of atherogenic lipoproteins inhibits their retention in murine aortas and the subsequent development of atherosclerosis. *Arteriosclerosis Thrombosis & Vascular Biology* 30 (11):2114–20. doi: 10.1161/ATVBAHA.110.213363.

Fang, F., C.-T. Ho, S. M. Sang, and R. T. Rosen. 2010. Determination of sphingolipids in nuts and seeds by a single quadrupole liquid chromatography-mass spectrometry method. *Journal of Food Lipids* 12 (4):327–43. doi: 10.1111/j.1745-452200028.x.

Fekry, B., K. A. Jeffries, A. Esmaeilniakooshkghazi, Z. M. Szulc, K. J. Knagge, D. R. Kirchner, D. A. Horita, S. A. Krupenko, and N. I. Krupenko. 2018. C16-ceramide is a natural regulatory ligand of p53 in cellular stress response. *Nature Communications* 9 (1):4149. doi: 10.1038/s41467-018-06650-y.

Feng, D., L. Ohlsson, W. Ling, A. Nilsson, and R. D. Duan. 2010. Generating ceramide from sphingomyelin by alkaline sphingomyelinase in the gut enhances sphingomyelin-induced inhibition of cholesterol uptake in Caco-2 cells. *Digestive Diseases and Sciences* 55 (12):3377–83. doi: 10.1007/s10620-010-1202-9.

Flores, A., J. Ramirez-Franco, R. Desplantes, K. Debreux, G. Ferracci, F. Wernert, M.-P. Blanchard, Y. Maulet, F. Youssouf, M. Sangiardi, et al. 2019. Gangliosides interact with synaptotagmin to form the high-affinity receptor complex for botulinum neurotoxin B. *Proceedings of the National Academy of Sciences* 116 (36):18098–108. doi: 10.1073/pnas.1908051116.

Flowers, M., G. Fabrias, A. Delgado, J. Casas, J. L. Abad, and M. C. Cabot. 2012. C6-ceramide and targeted inhibition of acid ceramidase induce synergistic decreases in breast cancer cell growth. *Breast Cancer Research and Treatment* 133 (2):447–58. doi: 10.1007/s10549-011-1768-8.

Fong, B. Y., L. Ma, G. L. Khor, Y. van der Does, A. Rowan, P. McJarrow, and A. K. MacGibbon. 2016. Ganglioside composition in beef, chicken, pork, and fish determined using liquid chromatography-high-resolution mass spectrometry. *Journal of Agricultural and Food Chemistry* 64 (32):6295–305. doi: 10.1021/acs.jafc.6b02200.

Futerman, A. H., and H. Riezman. 2005. The ins and outs of sphingolipid synthesis. *Trends in Cell Biology* 15 (6):312–8. doi: 10.1016/j.tcb.2005.04.006.

Gachechiladze, M., T. Tichy, V. Kolek, I. Grygarkova, J. Klein, G. Mgebrishvili, G. Kharaishvili, M. Janikova, P. Smickova, and L. Cierna. 2019. Sphingosine kinase-1 predicts overall survival outcomes in non-small cell lung cancer patients treated with carboplatin and navelbine. *Oncology Letters* 18 (2):1259–66. doi: 10.3892/ol.2019.10447.

Gao, J. M., W. M. Zhu, S. Q. Zhang, Z. Xing, A. L. Zhang, C. Hui, Y. Y. Sun, and T. Ming. 2010. Sphingolipids from the edible fungus *Tuber indicum*. *European Journal of Lipid Science and Technology* 106 (12):815–21. doi: 10.1002/ejlt.200401052.

German, J. B., and C. J. Dillard. 2006. Composition, structure and absorption of milk lipids: A source of energy, fat-soluble nutrients and bioactive molecules. *Critical Reviews in Food Science and Nutrition* 46 (1):57–92. doi: 10.1080/10408690590957098.

Gorden, D. L., D. S. Myers, P. T. Ivanova, E. Fahy, M. R. Maurya, S. Gupta, J. Min, N. J. Spann, J. G. McDonald, S. L. Kelly, et al. 2015. Biomarkers of nafld progression: A lipidomics approach to an epidemic. *Journal of Lipid Research* 56 (3):722–36. doi: 10.1194/jlr.P056002.

Goyal, G.,. J. Zheng, E. Adam, G. Steffes, M. Jain, K. Klavins, and T. Hummel. 2019. Sphingolipid-dependent dscam sorting regulates axon segregation. *Nature Communications* 10 (1):813doi: 10.1038/s41467-019-08765-2.

Greco, D., A. Kotronen, J. Westerbacka, O. Puig, P. Arkkila, T. Kiviluoto, S. Laitinen, M. Kolak, R. M. Fisher, A. Hamsten, et al. 2008. Gene expression in human NAFLD. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 294 (5):G1281–7. doi: 10.1152/ajpgi.00074.2008.

Grundy, S. M., H. B. Brewer, Jr., J. I. Cleeman, S. C. Smith, Jr., and C. Lenfant. 2004. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on scientific issues related to definition. *Circulation* 109 (3):433–8. doi: 10.1161/01.CIR.0000111245.75752.C6.

Guillermet-Guibert, J., L. Davenne, D. Pchejetski, N. Saint-Laurent, L. Brizuela, C. Guilbeau-Frugier, M.-B. Delisle, O. Cuvillier, C. Susini, and C. Bousquet. 2009. Targeting the sphingolipid metabolism to defeat pancreatic cancer cell resistance to the chemotherapeutic gemcitabine drug. *Molecular Cancer Therapeutics* 8 (4):809–20. doi: 10.1158/1535-7163.MCT-08-1096.

Guillou, S., S. Ghabri, C. Jannot, E. Gaillard, I. Lamour, and S. Boisnic. 2011. The moisturizing effect of a wheat extract food supplement on women's skin: A randomized, double-blind placebo-controlled trial. *International Journal of Cosmetic Science* 33 (2):138–43. doi: 10.1111/j.1468-2494.2010.00600.x.

Guo, S., C. H. Xue, J. Xu, Y. M. Wang, and P. X. Cong. 2012. Three glucocerebroside molecular species from the sea cucumber. *Apostichopus japonicus*. *Advanced Materials Research* 524–527: 2334–9. doi: 10.4028/www.scientific.net/AMR.524-527.2334.

Gutierrez, E., and T. Wang. 2004. Effect of processing on sphingolipid content in soybean products. *Journal of the American Oil Chemists' Society* 81 (10):971–7. doi: 10.1007/s11746-004-1009-1.

Gutierrez, E., T. Wang, and R. F. Walter. 2004. Quantification of sphingolipids in soybeans. *Journal of the American Oil Chemists' Society* 81 (8):737–42. doi: 10.1007/s11746-004-0971-y.

Han, L., T. Ming, X. Ming, E. N. Kitova, J. Xi, and J. S. Klassen. 2014. Gangliosides are ligands for human noroviruses. *Journal of the American Chemical Society* 136 (36):12631–7. doi: 10.1021/ja505272n.

Han, X. L., D. M. Holtzman, D. W. McKeel, J. Kelley, and J. C. Morris. 2002. Substantial sulfatide deficiency and ceramide elevation in very early Alzheimer' disease: Potential role in disease pathogenesis. *Journal of Neurochemistry* 82 (4):809–18. doi: 10.1046/j.1471-4159.2002.00997.x.

Hanahan, D., and R. A. Weinberg. 2000. The hallmarks of cancer. *Cell* 100 (1):57–70. doi: 10.1016/S0092-8674(00)81683-9.

Hanada, K. 2014. Co-evolution of sphingomyelin and the ceramide transport protein CERT. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1841 (5):704–19. doi: 10.1016/j.bbalip.2013.06.006.

Hanada, K., K. Kumagai, S. Yasuda, Y. Miura, M. Kawano, M. Fukasawa, and M. Nishijima. 2003. Molecular machinery for non-vesicular trafficking of ceramide. *Nature* 426 (6968):803–9. doi: 10.1038/nature02188.

Hannun, Y. A., and L. M. Obeid. 2008. Principles of bioactive lipid signalling: Lessons from sphingolipids. *Nature Reviews Molecular Cell Biology* 9 (2):139–50. doi: 10.1038/nrm2329.

Hannun, Y. A., and L. M. Obeid. 2018. Sphingolipids and their metabolism in physiology and disease. *Nature Reviews Molecular Cell Biology* 19 (3):175–91. doi: 10.1038/nrm.2017.107.

Haruta-Ono, Y., S. Setoguchi, H. M. Ueno, S. Higurashi, N. Ueda, K. Kato, T. Saito, K. Matsunaga, and J. Takata. 2012. Orally administered sphingomyelin in bovine milk is incorporated into skin sphingolipids and is involved in the water-holding capacity of hairless mice. *Journal of Dermatological Science* 68 (1):56–62. doi: 10.1016/j.jdermsci.2012.07.006.

Hellgren, L. I. 2001. Occurrence of bioactive sphingolipids in meat and fish products. *European Journal of Lipid Science and Technology* 103 (10):661–7. doi: 10.1002/1438-9312(200110)103:103.0.CO;2-8.

Higuchi, R., I. Masanori, Y. Koji, and M. Tomofumi. 2007. Biologically active gangliosides from echinoderms. *Journal of Natural Medicines* 61 (4):367–70. doi: 10.1007/s11418-007-0171-6.

Higuchi, R., S. Inoue, K. Inagaki, M. Sakai, T. Miyamoto, T. Komori, M. Inagaki, and R. Isobe. 2006. Biologically active glycosides from asteroidea, 42. Isolation and structure of a new biologically active ganglioside molecular species from the starfish *Asterina pectinifera*. *Chemical & Pharmaceutical Bulletin* 54 (3):287–91. doi: 10.1248/cpb.54.287.

Hirata, N., S. Yamada, T. Shoda, M. Kurihara, Y. Sekino, and Y. Kanda. 2014. Sphingosine-1-phosphate promotes expansion of cancer stem cells via S1PR3 by a ligand-independent notch activation. *Nature Communications* 5:4806. doi: 10.1038/ncomms5806.

Hirsch, S., and Y. Kashman. 1989. New glycosphingolipids from marine organisms. *Tetrahedron* 45 (12):3897–906. doi: 10.1016/S0040-4020(01)89249-8.

Hla, T., and A. J. Dannenberg. 2012. Sphingolipid signaling in metabolic disorders. *Cell Metabolism* 16 (4):420–34. doi: 10.1016/j.cmet.2012.06.017.

Hoda, K., I. Yuriko, K. Hideya, Y. Koji, H. Ryuichi, and S. Osamu. 2006. Mode of interaction of ganglioside Langmuir monolayer originated from echinoderms: Three binary systems of ganglioside/DPPC, ganglioside/DMPE, and ganglioside/cholesterol. *Colloids and Surfaces B: Biointerfaces* 52 (1):57–75. doi: 10.1016/j.colsurfb.2006.07.006.

Holland, W. L., J. T. Brozinick, L. P. Wang, E. D. Hawkins, K. M. Sargent, Y. Liu, K. Narra, K. L. Hoehn, T. A. Knotts, A. Siesky, et al. 2007. Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. *Cell Metabolism* 5 (3):167–79. doi: 10.1016/j.cmet.2007.01.002.

Holleran, W. M., Y. Takagi, and Y. Uchida. 2006. Epidermal sphingolipids: Metabolism, function, and roles in skin disorders. *FEBS Letters* 580 (23):5456–66. doi: 10.1016/j.febslet.2006.08.039.

Hu, S. W., J. H. Wang, J. F. Wang, H. C. Yang, S. J. Li, W. Jiang, Y. Liu, and J. L. Li. 2018. Long-chain bases from sea cucumber inhibits renal fibrosis and apoptosis in type 2 diabetic mice. *Journal of Functional Foods* 40:760–8. doi: 10.1016/j.jff.2017.12.013.

Hussain, G., H. Anwar, A. Rasul, A. Imran, M. Qasim, S. Zafar, M. Imran, S. K. S. Kamran, N. Aziz, and A. Razzaq. 2019. Lipids as biomarkers of brain disorders. *Critical Reviews in Food Science and Nutrition* 59 (20):1–24. doi: 10.1080/10408398.2018.1529653.

Imokawa, G., A. Abe, K. Jin, Y. Higaki, M. Kawashima, and A. Hidano. 1991. Decreased level of ceramides in stratum corneum of atopic dermatitis: An etiologic factor in atopic dry skin. *Journal of Investigative Dermatology* 96 (4):523–6. doi: 10.1111/1523-1747.ep12470233.

Inagaki, M. 2008. Structure and biological activity of glycosphingolipids from starfish and feather stars. *Yakugaku Zasshi* 128 (8):1187–94. doi: 10.1248/yakushi.128.1187.

Inagaki, M., T. Saito, T. Miyamoto, and R. Higuchi. 2009. Isolation and structure of hematoside-type ganglioside from the starfish *Linckia laevigata*. *Chemical & Pharmaceutical Bulletin* 57 (2):204–6. doi: 10.1248/cpb.57.204.

Ishikawa, J., S. Takada, K. Hashizume, Y. Takagi, M. Hotta, Y. Masukawa, T. Kitahara, Y. Mizutani, and Y. Igarashi. 2009. Dietary glucosylceramide is absorbed into the lymph and increases levels of epidermal sphingolipids. *Journal of Dermatological Science* 56 (3): 216–8. doi: 10.1016/j.jdermsci.2009.09.002.

Jennemann, R., R. Geyer, R. Sandhoff, R. M. Gschwind, S. B. Levery, H. J. Grone, and H. Wiegandt. 2001. Glycoinositolphosphosphingolipids (basidiolipids) of higher mushrooms. *European Journal of Biochemistry* 268 (5):1190–205. doi: 10.1046/j.1432-1327.2001.01963.x.

Jia, Z. C., S. Y. Li, P. X. Cong, Y. M. Wang, T. Sugawara, C. H. Xue, and J. Xu. 2015. High throughput analysis of cerebrosides from the sea cucumber *Pearsonothria graeffei* by liquid chromatography-quadrupole-time-of-flight mass spectrometry. *Journal of Oleo Science* 64 (1):51–60. doi: 10.5650/jos.ess14136.

Jia, Z. C., Y. Song, S. Y. Tao, P. X. Cong, X. X. Wang, C. H. Xue, and J. Xu. 2016. Structure of sphingolipids from sea cucumber *Cucumaria frondosa* and structure-specific cytotoxicity against human HepG2 cells. *Lipids* 51 (3):321–34. doi: 10.1007/s11745-016-4128-y.

Jiang, X. C., F. Paultre, T. A. Pearson, R. G. Reed, C. K. Francis, M. Lin, L. Berglund, and A. R. Tall. 2000. Plasma sphingomyelin level as a risk factor for coronary artery disease. *Arteriosclerosis, Thrombosis, and Vascular Biology* 20 (12):2614–8. doi: 10.1161/01.ATV.20.12.2614.

Jones, E. E., S. Dworski, D. Canals, J. Casas, G. Fabrias, D. Schoenling, T. Levade, C. Denlinger, Y. A. Hannun, J. A. Medin, et al. 2014. On-tissue localization of ceramides and other sphingolipids by MALDI mass spectrometry imaging. *Analytical Chemistry* 86 (16): 8303–11. doi: 10.1021/ac501937d.

Jungersted, J., L. I. Hellgren, J. K. Høgh, T. Drachmann, G. B. E. Jemec, and T. Agner. 2010. Ceramides and barrier function in healthy skin. *Acta Dermato Venereologica* 90 (4):350–3. doi: 10.2340/00015555-0894.

Kaneko, M., K. Yamada, T. Miyamoto, M. Inagaki, and R. Higuchi. 2007. Neuritogenic activity of gangliosides from echinoderms and their structure-activity relationship. *Chemical & Pharmaceutical Bulletin* 55 (3):462–3. doi: 10.1248/cpb.55.462.

Kawatake, S., M. Inagaki, R. Isobe, T. Miyamoto, and R. Higuchi. 2002. Isolation and structure of monomethylated GM3-type ganglioside molecular species from the starfish *Luidia maculata*. *Chemical & Pharmaceutical Bulletin* 50 (10):1386–9. doi: 10.1248/cpb.50.1386.

Kisa, F., K. Yamada, T. Miyamoto, M. Inagaki, and R. Higuchi. 2006. Constituents of holothuroidea, 17. Isolation and structure of biologically active monosialo-gangliosides from the sea cucumber *Cucumaria echinata*. *Chemical & Pharmaceutical Bulletin* 54 (7): 982–7. doi: 10.1248/cpb.54.982.

Kleuser, B., and L. Japtok. 2013. Sphingolipids and inflammatory diseases of the skin. *Handbook of Experimental Pharmacology* 2013 (216):355–72. doi: 10.1007/978-3-7091-1511-4_18.

Kobayashi, T., T. Shimizugawa, T. Osakabe, S. Watanabe, and H. Okuyama. 1997. A long-term feeding of sphingolipids affected the level of plasma cholesterol and hepatic triacylglycerol but not tissue phospholipids and sphingolipids. *Nutrition Research* 17 (1):111–4. doi: 10.1016/S0271-5317(96)00237-0.

Kochetkov, N. K., G. P. Smirnova, and N. V. Chekareva. 1976. Isolation and structural studies of a sulfated sialosphingolipid from the sea urchin *Echinocardium cordatum*. *Biochimica et Biophysica Acta* (*BBA*) - *Lipids and Lipid Metabolism* 424 (2):274–83. doi: 10.1016/0005-2760(76)90195-8.

Kunisawa, J., and H. Kiyono. 2010. Aberrant interaction of the gut immune system with environmental factors in the development of food allergies. *Current Allergy and Asthma Reports* 10 (3):215–21. doi: 10.1007/s11882-010-0097-z.

Lai, M. K., W. S. Chew, F. Torta, A. Rao, G. L. Harris, J. Chun, and D. R. Herr. 2016. Biological effects of naturally occurring sphingolipids, uncommon variants, and their analogs. *NeuroMolecular Medicine* 18 (3):396–414. doi: 10.1007/s12017-016-8424-8.

Laychock, S. G., S. M. Sessanna, M. H. Lin, and L. D. Mastrandrea. 2006. Sphingosine 1-phosphate affects cytokine-induced apoptosis in rat pancreatic islet β-cells. *Endocrinology* 147 (10):4705–12. doi: 10.1210/en.2006-0456.

Ledeen, R. W., and G. Wu. 2018. Gangliosides of the nervous system. In: *Gangliosides. Methods in molecular biology*, eds. S. Sonnino and A. Prinetti, vol. 1804. New York, NY: Humana Press.

Ledeen, R. W., and G. Wu. 2002. Ganglioside function in calcium homeostasis and signaling. *Neurochemical Research* 27 (7/8):637–47. doi: 10.1023/A:1020224016830.

Ledeen, R. W., and R. K. Yu. 1982. Gangliosides: Structure, isolation, and analysis. *Methods in Enzymology* 83:139–91. doi: 10.1016/0076-6879(82)83012-7.

Lee, C. W., J. W. Choi, and J. Chun. 2010. Neurological S1P signaling as an emerging mechanism of action of oral FTY720 (fingolimod) in multiple sclerosis. *Archives of Pharmacal Research* 33 (10):1567–74. doi: 10.1007/s12272-010-1008-5.

Lee, S., J.-E. Kim, S. Suk, O. W. Kwon, G. Park, T.-G. Lim, S. G. Seo, J. R. Kim, D. E. Kim, M. Lee, et al. 2015. A fermented barley and soybean formula enhances skin hydration. *Journal of Clinical Biochemistry and Nutrition* 57 (2):156–63. doi: 10.3164/jcbn.15-43.

Lee, S. R., K. Jung, H. J. Noh, J. P. Yong, H. L. Lee, R. L. Kang, K. S. Kang, and K. H. Kim. 2015. A new cerebroside from the fruiting bodies of hericium erinaceus and its applicability to cancer treatment. *Bioorganic & Medicinal Chemistry Letters* 25 (24):5712–5. doi: 10.1016/j.bmcl.2015.10.092.

Lewis, A. C., C. T. Wallington-Beddoe, J. A. Powell, and S. M. Pitson. 2018. Targeting sphingolipid metabolism as an approach for combination therapies in haematological malignancies. *Cell Death Discovery* 4 (1):72. doi: 10.1038/s41420-018-0075-0.

Li, H., Y. Song, H. W. Zhang, X. S. Wang, P. X. Cong, J. Xu, and C. H. Xue. 2020. Comparative lipid profile of four edible shellfishes by UPLC-Triple TOF-MS/MS. *Food Chemistry* 310:125947. doi: 10.1016/j.foodchem.2019.125947.

Li, Y., T. Zhou, Y. Wang, C. Ning, Z. Lv, G. Han, J. C. Morris, E. N. Taylor, R. Wang, H. Xiao, et al. 2017. The protumorigenic potential of FTY720 by promoting extramedullary hematopoiesis and MDSC accumulation. *Oncogene* 36 (26):3760–71. doi: 10.1038/onc.2017.2.

Li, Z., T. S. Park, Y. Li, X. Pan, J. Iqbal, D. Lu, W. Tang, L. Yu, I. J. Goldberg, and M. M. Hussain. 2009. Serine palmitoyltransferase (spt) deficient mice absorb less cholesterol. *Biochimica et Biophysica Acta* (*Bba*) - *Molecular and Cell Biology of Lipids* 1791 (4):297–306. doi: 10.1016/j.bbalip.2009.01.010.

Li, Z., M. J. Basterr, T. K. Hailemariam, M. R. Hojjati, S. Lu, J. Liu, R. Liu, H. Zhou, and X. C. Jiang. 2005. The effect of dietary sphingolipids on plasma sphingomyelin metabolism and atherosclerosis. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1735 (2):130–4. doi: 10.1016/j.bbalip.2005.05.004.

Lambert, J. M., A. K. Anderson, and L. A. Cowart. 2018. Sphingolipids in adipose tissue: What's tipping the scale? *Advances in Biological Regulation* 70:19–30. doi: 10.1016/j.jbior.2018.10.002.

Le Barz, M., M. M. Boulet, C. Calzada, D. Cheillan, and M. C. Michalski. 2020. Alterations of endogenous sphingolipid metabolism in cardiometabolic diseases: Towards novel therapeutic approaches. *Biochimie* 169:133–43. doi: 10.1016/j.biochi.2019.10.003.

Liu, J. J., A. Nilsson, and R. D. Duan. 2000. Effects of phospholipids on sphingomyelin hydrolysis induced by intestinal alkaline sphingomyelinase: An *in vitro* study. *The Journal of Nutritional Biochemistry* 11 (4):192–7. doi: 10.1016/S0955-2863(00)00064-4.

Liu, X. F., J. Xu, Y. Xue, Z. Gao, Z. J. Li, K. L. Leng, J. F. Wang, C. H. Xue, and Y. M. Wang. 2015. Sea cucumber cerebrosides and long-chain bases from *Acaudina molpadioides* protect against high fat diet-induced metabolic disorders in mice. *Food & Function* 6 (11):3428–36. doi: 10.1039/C5FO00602C.

Lone, M. A., T. Santos, I. Alecu, L. C. Silva, and T. Hornemann. 2019. 1-deoxysphingolipids. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1864 (4):512–21. doi: 10.1016/j.bbalip.2018.12.013.

Lynch, D. V., and T. M. Dunn. 2004. An introduction to plant sphingolipids and a review of recent advances in understanding their metabolism and function. *New Phytologist* 161 (3):677–702. doi: 10.1111/j.1469-8137.2004.00992.x.

Maceyka, M., and S. Spiegel. 2014. Sphingolipid metabolites in inflammatory disease. *Nature* 510 (7503):58–67. doi: 10.1038/nature13475.

Macheleidt, O., H. W. Kaiser, and K. Sandhoff. 2002. Deficiency of epidermal protein-bound omega-hydroxyceramides in atopic dermatitis. *Journal of Investigative Dermatology* 119 (1):166–73. doi: 10.1046/j.1523-1747.2002.01833.x.

Manev, H., M. Favaron, S. Vicini, A. Guidotti, and E. Costa. 1990. Glutamate-induced neuronal death in primary cultures of cerebellar granule cells: Protection by synthetic derivatives of endogenous sphingolipids. *The Journal of Pharmacology and Experimental Therapeutics* 252 (1):419–27. doi: 10.1002/jps.2600790121.

Manne, V., P. Handa, and K. V. Kowdley. 2018. Pathophysiology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *Clinics in Liver Disease* 22 (1):23–37. doi: 10.1016/j.cld.2017.08.007.

Marasas, W. F. O., R. T. Riley, K. A. Hendricks, V. L. Stevens, T. W. Sadler, J. Gelineau-van Waes, S. A. Missmer, J. Cabrera, O. Torres, W. C. A. Gelderblom, et al. 2004. Fumonisins disrupt sphingolipid metabolism, folate transport, and neural tube development in embryo culture and *in vivo*: A potential risk factor for human neural tube defects among populations consuming fumonisin-contaminated maize. *The Journal of Nutrition* 134 (4):711–6. doi: 10.1093/jn/134.4.711.

Matloubian, M., C. G. Lo, G. Cinamon, M. J. Lesneski, Y. Xu, V. Brinkmann, M. L. Allende, R. L. Proia, and J. G. Cyster. 2004. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature* 427 (6972):355–60. doi: 10.1038/nature02284.

Matsumoto, M., N. Umemoto, H. Sugiura, and M. Uehara. 1999. Difference in ceramide composition between "dry" and "normal" skin in patients with atopic dermatitis. *Acta Dermato-Venereologica* 79 (3):246–7. doi: 10.1080/000155599750011183.

McJarrow, P., N. Schnell, J. Jumpsen, and T. Clandinin. 2009. Influence of dietary gangliosides on neonatal brain development. *Nutrition Reviews* 67 (8):451–63. doi: 10.1111/j.1753-4887.2009.00211.x.

McKay, C. S., and M. G. Finn. 2014. Click chemistry in complex mixtures: Bioorthogonal bioconjugation. *Chemistry & Biology* 21 (9):1075–101. doi: 10.1016/j.chembiol.2014.09.002.

Merrill, A. H., Jr., and M. C. Sullards. 2017. Opinion article on lipidomics: Inherent challenges of lipidomic analysis of sphingolipids. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1862 (8):774–6. doi: 10.1016/j.bbalip.2017.01.009.

Merrill, A. H. Jr. 2011. Sphingolipid and glycosphingolipid metabolic pathways in the era of sphingolipidomics. *Chemical Reviews* 111 (10):6387–422. doi: 10.1021/cr2002917.

Miyake, Y., Y. Kozutsumi, S. Nakamura, T. Fujita, and T. Kawasaki. 1995. Serine palmitoyltransferase is the primary target of a sphingosine-like immunosuppressant, ISP-1/myriocin. *Biochemical and*

Biophysical Research Communications 211 (2):396–403. doi: 10.1006/bbrc.1995.1827.

Mocchetti, I. 2005. Exogenous gangliosides, neuronal plasticity and repair, and the neurotrophins. *Cellular and Molecular Life Sciences* 62 (19-20):2283–94. doi: 10.1007/s00018-005-5188-y.

Morad, S. A., and M. C. Cabot. 2013. Ceramide-orchestrated signalling in cancer cells. *Nature Reviews Cancer* 13 (1):51–65. doi: 10.1038/nrc3398.

Morifuji, M., M. Kitade, C. Oba, T. Fukasawa, K. Kawahata, T. Yamaji, Y. Manabe, and T. Sugawara. 2017. Milk fermented by lactic acid bacteria enhances the absorption of dietary sphingomyelin in rats. *Lipids* 52 (5):423–31. doi: 10.1007/s11745-017-4247-0.

Morifuji, M., S. Higashi, C. Oba, S. Ichikawa, K. Kawahata, T. Yamaji, H. Itoh, Y. Manabe, and T. Sugawara. 2015. Milk phospholipids enhance lymphatic absorption of dietary sphingomyelin in lymph-cannulated rats. *Lipids* 50 (10):987–96. doi: 10.1007/s11745-015-4054-4.

Murakami, I., S. Mitsutake, N. Kobayashi, J. Matsuda, A. Suzuki, T. Shigyo, and Y. Igarashi. 2013. Improved high-fat diet-induced glucose intolerance by an oral administration of phytosphingosine. *Bioscience Biotechnology and Biochemistry* 77 (1):194–7. doi: 10.1271/bbb.120644.

Murphy, R. C., and A. H. Merrill. Jr. 2011. Lipidomics and imaging mass spectrometry. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1811 (11):635–6. doi: 10.1016/j.bbalip.2011.09.003.

Mutoh, T., A. Tokuda, T. Miyadai, M. Hamaguchi, and N. Fujiki. 1995. Ganglioside gm1 binds to the trk protein and regulates receptor function. *Proceedings of the National Academy of Sciences of Sciences* 92 (11):5087–91. doi: 10.1073/pnas.92.11.5087.

Newton, J., S. Lima, M. Maceyka, and S. Spiegel. 2015. Revisiting the sphingolipid rheostat: Evolving concepts in cancer therapy. *Experimental Cell Research* 333 (2):195–200. doi: 10.1016/j.yexcr.2015.02.025.

Nicolas, G., T. E. Nadira, Y. Nouara, and F. Jacques. 2005. Apical uptake and transepithelial transport of sphingosine monomers through intact human intestinal epithelial cells: Physicochemical and molecular modeling studies. *Archives of Biochemistry & Biophysics* 440 (1):91–100. doi: 10.1016/j.abb.2005.06.001.

Nieuwenhuizen, W. F., I. Duivenvoorden, P. J. Voshol, P. C. N. Rensen, W. V. Duyvenvoorde, J. A. Romijn, J. J. Emeis, and L. M. Havekes. 2007. Dietary sphingolipids lower plasma cholesterol and triacylglycerol and prevent liver steatosis. *European Journal of Lipid Science and Technology* 109 (10):994–7. doi: 10.1002/ejlt.200600250.

Nikolova-Karakashian, M. 2018. Sphingolipids at the crossroads of NAFLD and senescence. *Advances in Cancer Research*, 140:155–90. doi: 10.1016/bs.acr.2018.05.002.

Nilsson, A., and R. D. Duan. 2006. Absorption and lipoprotein transport of sphingomyelin. *Journal of Lipid Research* 47 (1):154–71. doi: 10.1194/jlr.M500357-JLR200.

Nilsson, A. 1969. Metabolism of cerebroside in the intestinal tract of the rat. *Biochimica et Biophysica Acta* (Bba) - Lipids and Lipid Metabolism 187 (1):113–21. doi: 10.1016/0005-2760(69)90138-6.

Nilsson, A. 1968. Metabolism of sphingomyelin in the intestinal tract of the rat. *Biochimica et Biophysica Acta (BBA)/Lipids and Lipid Metabolism* 187 (1):113–21. doi. 10.1016/0005-2760(69)90138-6.

Norris, G. H., and C. N. Blesso. 2017a. Dietary sphingolipids: Potential for management of dyslipidemia and nonalcoholic fatty liver disease. *Nutrition Reviews* 75 (4):274–85. doi: 10.1093/nutrit/nux004.

Norris, G. H., and C. N. Blesso. 2017b. Dietary and endogenous sphingolipid metabolism in chronic inflammation. *Nutrients* 9 (11):1180. doi: 10.3390/nu9111180.

Norris, G. H., C. Jiang, J. Ryan, C. M. Porter, and C. N. Blesso. 2016. Milk sphingomyelin improves lipid metabolism and alters gut microbiota in high fat diet-fed mice. *The Journal of Nutritional Biochemistry* 30 (38):93–101. doi: 10.1016/j.jnutbio.2015.12.003.

Norris, G. H., C. M. Porter, C. Jiang, C. L. Millar, and C. N. Blesso. 2017. Dietary sphingomyelin attenuates hepatic steatosis and adipose tissue inflammation in high-fat-diet-induced obese mice. *The Journal of Nutritional Biochemistry* 40:36–43. doi: 10.1016/j.jnutbio.2016.09.017.

Nyberg, L., A. Nilsson, P. Lundgren, and R. D. Duan. 1997. Localization and capacity of sphingomyelin digestion in the rat intestinal tract. *The Journal of Nutritional Biochemistry* 8 (3):112–8. doi: 10.1016/S0955-2863(97)00010-7.

Oba, C., M. Morifuji, S. Ichikawa, K. Ito, K. Kawahata, T. Yamaji, Y. Asami, H. Itou, and T. Sugawara. 2015. Dietary milk sphingomyelin prevents disruption of skin barrier function in hairless mice after UV-B irradiation. *PloS One* 10 (8):e0136377. doi: 10.1371/journal.pone.0136377.

Ofek, I., D. L. Hasty, and N. Sharon. 2003. Anti-adhesion therapy of bacterial diseases: Prospects and problems. *FEMS Immunology & Medical Microbiology* 38 (3):181–91. doi: 10.1016/S0928-8244(03)00228-1.

Ogretmen, B. 2018. Sphingolipid metabolism in cancer signalling and therapy. *Nature Reviews Cancer* 18 (1):33–50. doi: 10.1038/nrc.2017.96.

Olsen, A. S. B., and N. J. Faergeman. 2017. Sphingolipids: Membrane microdomains in brain development, function and neurological diseases. *Open Biology* 7 (5):170069. doi: 10.1098/rsob.170069.

Otto, T. C., and M. D. Lane. 2005. Adipose development: From stem cell to adipocyte. *Critical Reviews in Biochemistry and Molecular Biology* 40 (4):229–42. doi: 10.1080/10409230591008189.

Patry, R. T., M. Stahl, M. E. Perez-Munoz, H. Nothaft, C. Q. Wenzel, J. C. Sacher, C. Coros, J. Walter, B. A. Vallance, and C. M. Szymanski. 2019. Bacterial AB5 toxins inhibit the growth of gut bacteria by targeting ganglioside-like glycoconjugates. *Nature Communications* 10 (1):1390. doi: 10.1038/s41467-019-09362-z.

Park, T. S., R. L. Panek, S. B. Mueller, J. C. Hanselman, W. S. Rosebury, A. W. Robertson, E. K. Kindt, R. Homan, S. K. Karathanasis, and M. D. Rekhter. 2004. Inhibition of sphingomyelin synthesis reduces atherogenesis in apolipoprotein E-knockout mice. *Circulation* 110 (22):3465–71. doi: 10.1161/01.CIR.0000148370.60535.22.

Pham, P. H., T. L. Duffy, A. L. Dmytrash, V. W. Lien, A. B. Thomson, and M. T. Clandinin. 2011. Estimate of dietary ganglioside intake in a group of healthy edmontonians based on selected foods. *Journal of Food Composition and Analysis* 24 (7):1032–7. doi: 10.1016/j.jfca.2011.01.011.

Piccinini, M., F. Scandroglio, S. Prioni, B. Buccinnà, N. Loberto, M. Aureli, V. Chigorno, E. Lupino, G. DeMarco, A. Lomartire, et al. 2010. Deregulated sphingolipid metabolism and membrane organization in neurodegenerative disorders. *Molecular Neurobiology* 41 (2-3):314–40. doi: 10.1007/s12035-009-8096-6.

Polo, A., G. Kirschner, A. Guidotti, E. J. M. Costa, and C. Neuropathology. 1994. Brain content of glycosphingolipids after oral administration of monosialogangliosides GM1 and LIGA20 to rats. *Molecular and Chemical Neuropathology* 21 (1):41–53. doi: 10.1007/BF03160083.

Possemiers, S., J. V. Camp, S. Bolca, and W. Verstraete. 2005. Characterization of the bactericidal effect of dietary sphingosine and its activity under intestinal conditions. *International Journal of Food Microbiology* 105 (1):59–70. doi: 10.1016/j.ijfoodmicro.2005.05.007.

Poti, F., S. Costa, V. Bergonzini, M. Galletti, E. Pignatti, C. Weber, M. Simoni, and J. R. Nofer. 2012. Effect of sphingosine 1-phosphate (S1P) receptor agonists FTY720 and CYM5442 on atherosclerosis development in ldl receptor deficient (LDL-$R^{-/-}$) mice. *Vascular Pharmacology* 57 (1):56–64. doi: 10.1016/j.vph.2012.03.003.

Pralhada, R. R., N. Vaidyanathan, M. Rengasamy, O. A. Mammen, N. Somaiya, and M. R. Jagannath. 2013. Sphingolipid metabolic pathway: An overview of major roles played in human diseases. *Journal of Lipids* 2013 (14):178910. doi: 10.1155/2013/178910.

Prentice, B. M., N. J. Hart, N. Phillips, R. Haliyur, A. Judd, R. Armandala, J. M. Spraggins, C. L. Lowe, K. L. Boyd, R. W. Stein, et al. 2019. Imaging mass spectrometry enables molecular profiling of mouse and human pancreatic tissue. *Diabetologia* 62 (6):1036–47. doi: 10.1007/s00125-019-4855-8.

Qiao, G. F., Z. F. Cheng, R. Huo, X. H. Sui, Y. J. Lu, and B. Y. Li. 2008. GM1 ganglioside contributes to retain the neuronal conduction and neuronal excitability in visceral and baroreceptor afferents. *Journal of Neurochemistry* 106 (4):1637–45. doi: 10.1111/j.1471-4159.2008.05515.x.

Ramprasath, V. R., P. J. H. Jones, D. D. Buckley, L. A. Woollett, and J. E. Heubi. 2013. Effect of dietary sphingomyelin on absorption and

fractional synthetic rate of cholesterol and serum lipid profile in humans. *Lipids in Health and Disease* 12 (1):125. doi: 10.1186/1476-511X-12-125.

Reis, M. G., N. C. Roy, E. N. Bermingham, L. Ryan, R. Bibiloni, W. Young, L. Krause, B. Berger, M. North, K. Stelwagen, et al. 2013. Impact of dietary dairy polar lipids on lipid metabolism of mice fed a high-fat diet. *Journal of Agricultural and Food Chemistry* 61 (11): 2729–38. doi: 10.1021/jf303795b.

Rekhter, M., and S. Karathanasis. 2006. Sphingolipids in atherosclerosis: A metabolic underpinning of vascular disease. *Future Lipidology* 1 (5):605–14. doi: 10.2217/17460875.1.5.605.

Riley, R. T., K. A. Voss, M. Speer, V. L. Stevens, and W. J. Gelineau-van. 2006. Fumonisin inhibition of ceramide synthase: A possible risk factor for human neural tube defects. In *Sphingolipid biology*, eds. Y. Hirabayashi, Y. Igarashi and A. H. Merrill Jr. Tokyo: Springer.

Riley, R. T., and A. H. Merrill. Jr. 2019. Ceramide synthase inhibition by fumonisins: A perfect storm of perturbed sphingolipid metabolism, signaling, and disease. *Journal of Lipid Research* 60 (7):1183–9. doi: 10.1194/jlr.S093815.

Rivera, J., R. L. Proia, and A. Olivera. 2008. The alliance of sphingosine-1-phosphate and its receptors in immunity. *Nature Reviews Immunology* 8 (10):753–63. doi: 10.1038/nri2400.

Rombaut, R., D. Koen, and C. John Van. 2007. Phospho- and sphingolipid content of selected dairy products as determined by HPLC coupled to an evaporative light scattering detector (HPLD-ELSD). *Journal of Food Composition and Analysis* 20 (3):308–12. doi: 10.1016/j.jfca.2006.01.010.

Rösner, H. 1998. Significance of gangliosides in neuronal differentiation of neuroblastoma cells and neurite growth in tissue culture. *Annals of the New York Academy of Sciences* 845 (1):200–14. doi: 10.1111/j.1749-6632.1998.tb09672.x.

Ross, J. S., S. B. Russo, G. C. Chavis, and L. A. Cowart. 2014. Sphingolipid regulators of cellular dysfunction in type 2 diabetes mellitus: A systems overview. *Clinical Lipidology* 9 (5):553–69. doi: 10.2217/clp.14.37.

Rueda, R., J. Maldonado, E. Narbona, and A. Gil. 1998. Neonatal dietary gangliosides. *Early Human Development* 53:S135–S47. doi: 10.1016/S0378-3782(98)00071-1.

Russo, D., F. Della Ragione, R. Rizzo, E. Sugiyama, F. Scalabrì, K. Hori, S. Capasso, L. Sticco, S. Fioriniello, R. De Gregorio, et al. 2018. Glycosphingolipid metabolic reprogramming drives neural differentiation. *The EMBO Journal* 37 (7):e97674. doi: 10.15252/embj.201797674.

Saito, M., A. Guidotti, M. J. Berg, and N. Marks. 1998. The semisynthetic glycosphingolipid LIGA20 potently protects neurons against apoptosis. *Annals of the New York Academy of Sciences* 845 (1 SPHINGOLIPIDS):253–62. doi: 10.1111/j.1749-6632.1998.tb09678.x.

Sandhoff, R., and K. Sandhoff. 2018. Emerging concepts of ganglioside metabolism. *FEBS Letters* 592 (23):3835–64. doi: 10.1002/1873-3468.13114.

Sandhoff, R., H. Schulze, and K. Sandhoff. 2018. Ganglioside metabolism in health and disease. *Progress in Molecular Biology and Translational Science* 156:1–62. doi: 10.1016/bs.pmbts.2018.01.002.

Sang, K. N., and I. K. Sung. 2004. Milk sphingomyelin is more effective than egg sphingomyelin in inhibiting intestinal absorption of cholesterol and fat in rats. *Journal of Nutrition* 134 (10):2611–6. doi: 10.1093/jn/134.10.2611.

Schmelz, E. M., H. Zhou, and P. C. Roberts. 2015. Dietary sphingolipids in colon cancer prevention. In *Bioactive sphingolipids in cancer biology and therapy*, eds. Y. A. Hannun, C. Luberto, C. Mao, L. M. Obeid, 161–88. Cham: Springer International Publishing.

Schmelz, E. M., M. C. Sullards, D. L. Dillehay, and A. H. Merrill. Jr. 2000. Colonic cell proliferation and aberrant crypt foci formation are inhibited by dairy glycosphingolipids in 1, 2-dimethylhydrazine-treated CF1 mice. *The Journal of Nutrition* 130 (3):522–7. doi: 10.1093/jn/130.3.522.

Schmelz, E. M., K. J. Crall, R. Larocque, D. L. Dillehay, and A. H. Merrill. Jr. 1994. Uptake and metabolism of sphingolipids in isolated intestinal loops of mice. *The Journal of Nutrition* 124 (5):702–12. doi: 10.1093/jn/124.5.702.

Schnabl, K. L., M. Larcelet, A. B. R. Thomson, and M. T. Clandinin. 2009. Uptake and fate of ganglioside GD3 in human intestinal Caco-2 cells. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 297 (1):G52–59. doi: 10.1152/ajpgi.90599.2008.

Senik, S. V., E. R. Kotlova, N. V. Psurtseva, A. V. Novikov, V. A. Khanin, A. L. Shavarda, J. M. Savoie, M. Foulongneoriol, M. Largeteau, and G. Barroso. 2011. Effect of exogenous sphingolipids on growth and metabolism in surface cultures of basidial fungi. In International Conference on Mushroom Biology & Mushroom Products.

Seren, M. S., A. Lazzaro, C. L. Yang, R. Canella, M. Bassan, R. Zanoni, and H. Manev. 1994. Orally administered glycolipid derivative LIGA20 reduces infarct volume and behavioral impairment after focal cerebral ischemia. *Journal of Pharmacology and E. Therapeutics* 268 (1):460–5. doi: 10.1002/jps.2600830129.

Serra, M., and J. D. Saba. 2010. Sphingosine 1-phosphate lyase, a key regulator of sphingosine 1-phosphate signaling and function. *Advances in Enzyme Regulation* 50 (1):349–62. doi: 10.1016/j.advenzreg.2009.10.024.

Shaner, R. L., J. C. Allegood, H. Park, E. Wang, S. Kelly, C. A. Haynes, M. C. Sullards, and A. H. Merrill. Jr. 2009. Quantitative analysis of sphingolipids for lipidomics using triple quadrupole and quadrupole linear ion trap mass spectrometers. *Journal of Lipid Research* 50 (8): 1692–707. doi: 10.1194/jlr.D800051-JLR200.

Shimada, E., K. Aida, T. Sugawara, and T. Hirata. 2011. Inhibitory effect of topical maize glucosylceramide on skin photoaging in UVA-irradiated hairless mice. *Journal of Oleo Science* 60 (6):321–5. doi: 10.5650/jos.60.321.

Shimizu, H., F. Okajima, T. Kimura, K. Ohtani, T. Tsuchiya, H. Takahashi, A. Kuwabara, H. Tomura, K. Sato, and M. J. E. J. Mori. 2000. Sphingosine 1-phosphate stimulates insulin secretion in HIT-T 15 cells and mouse islets. *Endocrine Journal* 47 (3):261–9. doi: 10.1507/endocrj.47.261.

Smirnova, G. P. 2003. Structure of gangliosides from gonads of the starfish *Evasterias retifera*. *Russian Chemical Bulletin* 52 (10):2270–5. doi: 10.1023/B:RUCB.0000011890.59554.d2.

Smirnova, G. P. 1990. Cheminform abstract: Gangliosides from the starfish evasterias echinosoma: Identification of a disialoganglioside containing 8-o-methyl-N-acetylneuraminic acid and N-formylgalactosamine. *Russian Chemical Bulletin* 49 (1):159–64. doi: 10.1007/BF02499084.

Snel, M., M. A. Sleddering, H. Pijl, W. F. Nieuwenhuizen, M. Frolich, L. M. Havekes, J. A. Romijn, and I. M. Jazet. 2010. The effect of dietary phytosphingosine on cholesterol levels and insulin sensitivity in subjects with the metabolic syndrome. *European Journal of Clinical Nutrition* 64 (4):419–23. doi: 10.1038/ejcn.2009.154.

Snider, A. J., B. X. Wu, R. W. Jenkins, J. A. Sticca, T. Kawamori, Y. A. Hannun, and L. M. Obeid. 2012. Loss of neutral ceramidase increases inflammation in a mouse model of inflammatory bowel disease. *Prostaglandins & Other Lipid Mediators* 99 (3-4):124–30. doi: 10.1016/j.prostaglandins.2012.08.003.

Snider, A. J., T. Kawamori, S. G. Bradshaw, K. A. Orr, G. S. Gilkeson, Y. A. Hannun, and L. M. Obeid. 2009. A role for sphingosine kinase 1 in dextran sulfate sodium-induced colitis. *The FASEB Journal* 23 (1):143–52. doi: 10.1096/fj.08-118109.

Song, Y., P. X. Cong, L. Lu, Y. M. Wang, Q. J. Tang, H. Zhang, J. Xu, and C. H. Xue. 2017. Effects of dietary glucocerebrosides from sea cucumber on the brain sphingolipid profiles of mouse models of Alzheimer's disease. *Food & Function* 8 (3):1271–81. doi: 10.1039/C6FO01659F.

Soreghan, B., S. N. Thomas, and A. J. Yang. 2003. Aberrant sphingomyelin/ceramide metabolic-induced neuronal endosomal/lysosomal dysfunction: Potential pathological consequences in age-related neurodegeneration. *Advanced Drug Delivery Reviews* 55 (11):1515–24. doi: 10.1016/j.addr.2003.07.007.

Sperling, P., and E. Heinz. 2003. Plant sphingolipids: Structural diversity, biosynthesis, first genes and functions. *Biochimica et Biophysica Acta (Bba) - Molecular and Cell Biology of Lipids* 1632 (1-3):1–15. doi: 10.1016/S1388-1981(03)00033-7.

Sprong, R. C., M. F. E. Hulstein, and R. van der Meer. 2002. Bovine milk fat components inhibit food-borne pathogens. *International Dairy Journal* 12 (2-3):209–15. doi: 10.1016/S0958-6946(01)00139-X.

Strader, C. R., C. J. Pearce, and N. H. Oberlies. 2011. Fingolimod (FTY720): A recently approved multiple sclerosis drug based on a fungal secondary metabolite. *Journal of Natural Products* 74 (4): 900–7. doi: 10.1021/np2000528.

Sugawara, T., and M. Teruo. 1999. Separation and determination of glycolipids from edible plant sources by high-performance liquid chromatography and evaporative light-scattering detection. *Lipids* 34 (11):1231–7. doi: 10.1007/s11745-999-0476-3.

Sugawara, T., M. Kinoshita, M. Ohnishi, and T. Miyazawa. 2002. Apoptosis induction by wheat-flour sphingoid bases in DLD-1 human colon cancer cells. *Bioscience, Biotechnology and Biochemistry* 66 (10):2228–31. doi: 10.1271/bbb.66.2228.

Sugawara, T., M. Kinoshita, M. Ohnishi, J. Nagata, and M. Saito. 2003. Digestion of maize sphingolipids in rats and uptake of sphingadienine by Caco-2 cells. *The Journal of Nutrition* 133 (9):2777–82. doi: 10.1093/jn/133.9.2777.

Sugawara, T., K. Aida, J. J. Duan, and T. Hirata. 2010. Analysis of glucosylceramides from various sources by liquid chromatography-ion trap mass spectrometry. *Journal of Oleo Science* 59 (7):387–94. doi: 10.5650/jos.59.387.

Sugawara, T., N. Zaima, A. Yamamoto, S. Sakai, R. Noguchi, and T. Hirata. 2006. Isolation of sphingoid bases of sea cucumber cerebrosides and their cytotoxicity against human colon cancer cells. *Bioscience, Biotechnology and Biochemistry* 70 (12):2906–12. doi: 10.1271/bbb.60318.

Sugawara, T., K. Aida, J. J. Duan, N. Tomonaga, Y. Manabe, and T. Hirata. 2019. Analysis of chemical structures of glucosylceramides from rice and other foodstuffs. *Journal of Nutritional Science and Vitaminology* 65 (Supplement):S228–S230. doi: 10.3177/jnsv.65.S228.

Sugawara, T., T. Tsuduki, S. Yano, M. Hirose, J. J. Duan, K. Aida, I. Ikeda, and T. Hirata. 2010. Intestinal absorption of dietary maize glucosylceramide in lymphatic duct cannulated rats. *Journal of Lipid Research* 51 (7):1761–9. doi: 10.1194/jlr.M002204.

Suh, M., M. Belosevic, and M. T. Clandinin. 2004. Dietary lipids containing gangliosides reduce *Giardia muris* infection *in vivo* and survival of *Giardia lamblia* trophozoites *in vitro*. *Parasitology* 128 (6): 595–602. doi: 10.1017/S0031182004005128.

Summers, S. A., and D. H. Nelson. 2005. A role for sphingolipids in producing the common features of type 2 diabetes, metabolic syndrome X, and Cushing's syndrome. *Diabetes* 54 (3):591–602. doi: 10.2337/diabetes.54.3.591.

Symolon, H., A. Bushnev, Q. Peng, H. Ramaraju, S. G. Mays, J. C. Allegood, S. T. Pruett, M. C. Sullards, D. L. Dillehay, D. C. Liotta, et al. 2011. Enigmol: A novel sphingolipid analogue with anticancer activity against cancer cell lines and in vivo models for intestinal and prostate cancer. *Molecular Cancer Therapeutics* 10 (4):648–57. doi: 10.1158/1535-7163.MCT-10-0754.

Takabe, K., S. W. Paugh, S. Milstien, and S. Spiegel. 2008. Inside-out" signaling of sphingosine-1-phosphate: Therapeutic targets. *Pharmacological Reviews* 60 (2):181–95. doi: 10.1124/pr.107.07113.

Tan, R. X., and J. H. Chen. 2003. The cerebrosides. *Natural Product Reports* 20 (5):509–34. doi: 10.1039/b307243f.

Thudichum, J. L. W. 1884. *A treatise on the chemical constitution of the brain*. London, UK: Bailliere, Tindall, and Cox.

Tian, Y. Y., S. W. Hu, H. Xu, J. F. Wang, C. H. Xue, and Y. M. Wang. 2016. Long-chain bases from *Cucumaria frondosa* inhibit adipogenesis and regulate lipid metabolism in 3T3-L1 adipocytes. *Food Science and Biotechnology* 25 (6):1753–60. doi: 10.1007/s10068-016-0267-4.

Toledo, J. B., M. Arnold, G. Kastenmüller, R. Chang, R. A. Baillie, X. L. Han, M. Thambisetty, J. D. Tenenbaum, K. Suhre, and J. W. Thompson. 2017. Metabolic network failures in Alzheimer's disease: A biochemical road map. *Alzheimer's & Dementia* 13 (9):965–84. doi: 10.1016/j.jalz.2017.01.020.

Tomonaga, N., Y. Manabe, and T. J. L. Sugawara. 2017. Digestion of ceramide 2-aminoethylphosphonate, a sphingolipid from the jumbo flying squid *Dosidicus gigas*, in mice. *Lipids* 52 (4):353–62. doi: 10.1007/s11745-017-4239-0.

Tomonaga, N., T. Tsuduki, Y. Manabe, and T. Sugawara. 2019. Sphingoid bases of dietary ceramide 2-aminoethylphosphonate, a marine sphingolipid, absorb into lymph in rats. *Journal of Lipid Research* 60 (2):333–40. doi: 10.1194/jlr.M085654.

Tsuji, K., S. Mitsutake, J. Ishikawa, Y. Takagi, M. Akiyama, H. Shimizu, T. Tomiyama, and Y. Igarashi. 2006. Dietary glucosylceramide improves skin barrier function in hairless mice. *Journal of Dermatological Science* 44 (2):101–7. doi: 10.1016/j.jdermsci.2006.08.005.

Turpin, S. M., J. G. Ryall, R. Southgate, I. Darby, A. L. Hevener, M. A. Febbraio, B. E. Kemp, G. S. Lynch, and M. J. Watt. 2009. Examination of 'lipotoxicity' in skeletal muscle of high-fat fed and ob/ob mice. *The Journal of Physiology* 587 (7):1593–605. doi: 10.1113/jphysiol.2008.166033.

Uchida, Y., and W. M. Holleran. 2008. Omega-O-acylceramide, a lipid essential for mammalian survival. *Journal of Dermatological Science* 51 (2):77–87. doi: 10.1016/j.jdermsci.2008.01.002.

Ueda, O., M. Hasegawa, and S. Kitamura. 2009. Distribution in skin of ceramide after oral administration to rats. *Drug Metabolism and Pharmacokinetics* 24 (2):180–4. doi: 10.2133/dmpk.24.180.

Ueda, O., T. Uchiyama, and M. Nakashima. 2010. Distribution and metabolism of sphingosine in skin after oral administration to mice. *Drug Metabolism and Pharmacokinetics* 25 (5):456–65. doi: 10.2133/dmpk.DMPK-10-RG-038.

Unger, R. H., G. O. Clark, P. E. Scherer, and L. Orci. 2010. Lipid homeostasis, lipotoxicity and the metabolic syndrome. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids* 1801 (3):209–14. doi: 10.1016/j.bbalip.2009.10.006.

Ussher, J. R., T. R. Koves, V. J. J. Cadete, L. Y. Zhang, J. S. Jaswal, S. J. Swyrd, D. G. Lopaschuk, S. D. Proctor, W. Keung, D. M. Muoio, et al. 2010. Inhibition of de novo ceramide synthesis reverses diet-induced insulin resistance and enhances whole-body oxygen consumption. *Diabetes* 59 (10):2453–64. doi: 10.2337/db09-1293.

Utermohlen, O., J. Herz, M. Schramm, and M. Kronke. 2008. Fusogenicity of membranes: The impact of acid sphingomyelinase on innate immune responses. *Immunobiology* 213 (3-4):307–14. doi: 10.1016/j.imbio.2007.10.016.

Vasireddy, V.,. Y. Uchida, N. Salem, S. Y. Kim, M. N. A. Mandal, G. B. Reddy, R. Bodepudi, N. L. Alderson, J. C. Brown, H. Hama, et al. 2007. Loss of functional ELOVEL4 depletes very long-chain fatty acids (>=C28) and the unique omega-O-acylceramides in skin leading to neonatal death. *Human Molecular Genetics* 16 (5):471–82. doi: 10.1093/hmg/ddl480.

Vesper, H., E. M. Schmelz, M. N. Nikolova-Karakashian, D. L. Dillehay, D. V. Lynch, and A. H. Merrill. Jr. 1999. Sphingolipids in food and the emerging importance of sphingolipids to nutrition. *The Journal of Nutrition* 129 (7):1239–50. doi: 10.1093/jn/129.7.1239.

Vessey, D. A., M. Kelley, J. Zhang, L. Li, R. Tao, and J. S. Karliner. 2007. Dimethylsphingosine and FTY720 inhibit the SK1 form but activate the SK2 form of sphingosine kinase from rat heart. *Journal of Biochemical and Molecular Toxicology* 21 (5):273–9. doi: 10.1002/jbt.20193.

Vieira, K. P., A. R. D. E. S. L. Zollner, C. Malaguti, C. A. Vilella, and R. D. Zollner. 2008. Ganglioside GM1 effects on the expression of nerve growth factor (NGF), Trk-A receptor, proinflammatory cytokines and on autoimmune diabetes onset in non-obese diabetic (NOD) mice. *Cytokine* 42 (1):92–104. doi: 10.1016/j.cyto.2008.01.009.

Walls, S. M., S. J. Attle, G. B. Brulte, M. L. Walls, K. D. Finley, D. A. Chatfield, D. R. Herr, and G. L. Harris. 2013. Identification of sphingolipid metabolites that induce obesity via mis-regulation of appetite, caloric intake and fat storage in drosophila. *PLoS Genetics* 9 (12):e1003970. doi: 10.1371/journal.pgen.1003970.

Wan, J. L., J. Li, S. Bandyopadhyay, S. L. Kelly, Y. Xiang, J. Zhang, A. H. Merrill, Jr., and J. J. Duan. 2019. Analysis of 1-deoxysphingoid bases and their N-acyl metabolites and exploration of their occurrence in some food materials. *Journal of Agricultural and Food Chemistry* 67 (46):12953–61. doi: 10.1021/acs.jafc.9b05708.

Wang, R., Q. S. Chen, Y. Song, Y. Ding, P. X. Cong, J. Xu, and C. H. Xue. 2020. Identification of ceramide 2-aminoethylphosphonate

molecular species from different aquatic products by NPLC/Q-Exactive-MS. *Food Chemistry* 30 (304):125425. doi: 10.1016/j.foodchem.2019.125425.

Wang, X. X., S. Y. Tao, P. X. Cong, Y. M. Wang, J. Xu, and C. H. Xue. 2017. Neuroprotection of *Strongylocentrotus nudus* gangliosides against Alzheimer's disease via regulation of neurite loss and mitochondrial apoptosis. *Journal of Functional Foods* 33:122–33. doi: 10.1016/j.jff.2017.03.030.

Wang, X. S., H. W. Zhang, Y. Song, P. X. Cong, Z. J. Li, J. Xu, and C. H. Xue. 2019. Comparative lipid profile analysis of four fish species by ultraperformance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry. *Journal of Agricultural and Food Chemistry* 67 (33):9423–31. doi: 10.1021/acs.jafc.9b03303.

Wang, X. X., P. X. Cong, Y. J. Liu, S. Y. Tao, Q. S. Chen, J. F. Wang, J. Xu, and C. H. Xue. 2018. Neuritogenic effect of sea cucumber glucocerebrosides on NGF-induced PC12 cells via activation of the TrkA/CREB/BDNF signalling pathway. *Journal of Functional Foods* 46:175–84. doi: 10.1016/j.jff.2018.04.035.

Watanabe, S., T. Tomoki, T. Leo, H. Yuko, S. Makoto, H. Masashi, and M. Kazuo. 2011. The effect of milk polar lipids separated from butter serum on the lipid levels in the liver and the plasma of obese-model mouse (KK-Ay). *Journal of Functional Foods* 3 (4):313–20. doi: 10.1016/j.jff.2011.06.002.

Wehrmuller, K. 2007. Occurrence and biological properties of sphingolipids - A review. *Current Nutrition & Food Science* 3 (2):161–73. doi: 10.2174/157340107780598618.

Wennekes, T., J. B. Richard, G. B. Rolf, A. M. Gijs, O. Herman, and A. Johannes. 2009. Glycosphingolipids—nature, function, and pharmacological modulation. *Angewandte Chemie International Edition* 48 (47):8848–69. doi: 10.1002/anie.200902620.

Wigger, D., E. Gulbins, B. Kleuser, and F. Schumacher. 2019. Monitoring the sphingolipid de novo synthesis by stable-isotope labeling and liquid chromatography-mass spectrometry. *Frontiers in Cell and Developmental Biology* 7:210. doi: 10.3389/fcell.2019.00210.

Wong, L. H., A. Čopič, and T. P. Levine. 2017. Advances on the transfer of lipids by lipid transfer proteins. *Trends in Biochemical Sciences* 42 (7):516–30. doi: 10.1016/j.tibs.2017.05.001.

Wu, F. J., Y. Xue, Q. J. Tang, J. Xu, L. Du, C. H. Xue, T. Koretaro, and Y. M. Wang. 2013. The protective effects of cerebrosides from sea cucumber and starfish on the oxidative damage in PC12 cells. *Journal of Oleo Science* 62 (9):717–27. doi: 10.5650/jos.62.717.

Xia, J. Y., W. L. Holland, C. M. Kusminski, K. Sun, A. X. Sharma, M. J. Pearson, A. J. Sifuentes, J. G. McDonald, R. Gordillo, and P. E. Scherer. 2015. Targeted induction of ceramide degradation leads to improved systemic metabolism and reduced hepatic steatosis. *Cell Metabolism* 22 (2):266–78. doi: 10.1016/j.cmet.2015.06.007.

Xu, H., F. Wang, J. F. Wang, J. Xu, Y. M. Wang, and C. H. Xue. 2015. The WNT/β-catenin pathway is involved in the anti-adipogenic activity of cerebrosides from the sea cucumber *Cucumaria frondosa*. *Food & Function* 6 (7):2396–404. doi: 10.1039/C5FO00273G.

Xu, J., Y. M. Wang, T. Y. Feng, B. Zhang, T. Sugawara, and C. H. Xue. 2011. Isolation and anti-fatty liver activity of a novel cerebroside from the sea cucumber acaudina molpadioides. *Bioscience Biotechnology and Biochemistry* 75 (8):1466–71. doi: 10.1271/bbb.110126.

Xu, J., S. Guo, L. Du, Y. M. Wang, T. Sugawara, T. Hirata, and C. H. Xue. 2013. Isolation of cytotoxic glucoerebrosides and long-chain bases from sea cucumber *Cucumaria frondosa* using high speed counter-current chromatography. *Journal of Oleo Science* 62 (3):133–42. doi: 10.5650/jos.62.133.

Yamada, K., A. Hamada, F. Kisa, T. Miyamoto, and R. Higuchi. 2003. Constituents of Holothuroidea, 13. Structure of neuritogenic active ganglioside molecular species from the sea cucumber *Stichopus chloronotus*. *Chemical & Pharmaceutical Bulletin* 51 (1):46–52. doi: 10.1248/cpb.51.46.

Yamada, K., K. Tanabe, T. Miyamoto, T. Kusumoto, M. Inagaki, and R. Higuchi. 2008. Isolation and structure of a monomethylated ganglioside possessing neuritogenic activity from the ovary of the sea urchin *Diadema setosum*. *Chemical & Pharmaceutical Bulletin* 56 (5):734–7. doi: 10.1248/cpb.56.734.

Yamashita, T., Y.-P. Wu, R. Sandhoff, N. Werth, H. Mizukami, J. M. Ellis, J. L. Dupree, R. Geyer, K. Sandhoff, and R. L. Proia. 2005. Interruption of ganglioside synthesis produces central nervous system degeneration and altered axon-glial interactions. *Proceedings of the National Academy of Sciences of Sciences* 102 (8):2725–30. doi: 10.1073/pnas.0407785102.

Yamauchi, I., M. Uemura, M. Hosokawa, A. Iwashima-Suzuki, M. Shiota, and K. Miyashita. 2016. The dietary effect of milk sphingomyelin on the lipid metabolism of obese/diabetic KK-A(y) mice and wild-type C57BL/6J mice. *Food & Function* 7 (9):3854–67. doi: 10.1039/C6FO00274A.

Yang, H., G. L. Richter, X. Wang, E. Młodzińska, N. Carraro, G. Ma, M. Jenness, C. Dai-yin, W. A. Peer, and A. S. Murphy. 2013. Sterols and sphingolipids differentially function in trafficking of the arabidopsis ABCB19 auxin transporter. *Plant Journal for Cell & Molecular Biology* 74 (1):37–47. doi: 10.1111/tpj.12103.

Yates, A. J., and A. Rampersaud. 1998. Sphingolipids as receptor modulators: An overview. *Annals of the New York Academy of Sciences* 845 (1 SPHINGOLIPIDS):57–71. doi: 10.1111/j.1749-6632.1998.tb09662.x.

Yin, J., K. Miyazaki, R. L. Shaner, A. H. Merrill, Jr., and R. Kannagi. 2010. Altered sphingolipid metabolism induced by tumor hypoxia – New vistas in glycolipid tumor markers. *FEBS Letters* 584 (9):1872–8. doi: 10.1016/j.febslet.2009.11.019.

Yu, R. K., Y. Nakatani, and M. Yanagisawa. 2009. The role of glycosphingolipid metabolism in the developing brain. *Journal of Lipid Research* 50 (Supplement):S440–S45. doi: 10.1194/jlr.R800028-JLR200.

Yunoki, K., T. Ogawa, J. Ono, R. Miyashita, K. Aida, Y. Oda, and M. Ohnishi. 2008. Analysis of sphingolipid classes and their contents in meals. *Bioscience, Biotechnology, and Biochemistry* 72 (1):222–5. doi: 10.1271/bbb.70463.

Yunoki, K., M. Renaguli, M. Kinoshita, H. Matsuyama, S. Mawatari, T. Fujino, Y. Kodama, M. Sugiyama, and M. Ohnishi. 2010. Dietary sphingolipids ameliorate disorders of lipid metabolism in zucker fatty rats. *Journal of Agricultural and Food Chemistry* 58 (11):7030–5. doi: 10.1021/jf100722f.

Zhang, B., C. H. Xue, X. Hu, J. Xu, Z. J. Li, J. F. Wang, T. Yanagita, Y. Xue, and Y. M. Wang. 2012. Dietary sea cucumber cerebroside alleviates orotic acid-induced excess hepatic adipopexis in rats. *Lipids in Health and Disease* 11 (1):48. doi: 10.1186/1476-511X-11-48.

Zhang, L. Y., T. T. Zhang, L. Ding, J. Xu, C. H. Xue, T. Yanagita, Y. G. Chang, and Y. M. Wang. 2018. The protective activities of dietary sea cucumber cerebrosides against atherosclerosis through regulating inflammation and cholesterol metabolism in male mice. *Molecular Nutrition & Food Research* 62 (16):e1800315. doi: ARTN 1800315 doi: 10.1002/mnfr.201800315.

Zhang, L. S., M. Xu, Q. Yang, D. Lou, P. N. Howles, and P. Tso. 2015. ABCG5/G8 deficiency in mice reduces dietary triacylglycerol and cholesterol transport into the lymph. *Lipids* 50 (4):371–79. doi: 10.1007/s11745-015-3995-y.

Zhang, S., R. P. Berntsson, W. H. Tepp, L. Tao, E. A. Johnson, P. Stenmark, and M. Dong. 2017. Structural basis for the unique ganglioside and cell membrane recognition mechanism of botulinum neurotoxin DC. *Nature Communications* 8 (1):1637. doi: 10.1038/s41467-017-01534-z.

Zhang, X. B., and L. K. Frederick. 2004. Review: Glycosphingolipids in health and disease. *Annals of Clinical and Laboratory Science* 34 (1):3–13. http://www.annclinlabsci.org/cgi/content/full/34/1/3.

Zheng, C. Q., H. H. Qu, W. F. Liao, T. Bavaro, M. Terreni, M. Sollogoub, K. Ding, and Y. M. Zhang. 2018. Chemoenzymatically synthesized GM3 analogues as potential therapeutic agents to recover nervous functionality after injury by inducing neurite outgrowth. *European Journal of Medicinal Chemistry* 146:613–20. doi: 10.1016/j.ejmech.2018.01.079.

Zheng, C., H. M. Guan, Y. Liu, Z. H. Li, T. Bavaro, M. Terreni, M. Sollogoub, J. H. Xu, and Y. M. Zhang. 2019. Chemoenzymatically synthesized ganglioside GM3 analogues with inhibitory effects on tumor cell growth and migration. *European Journal of Medicinal Chemistry* 165:107–14. doi: 10.1016/j.ejmech.2019.01.016.