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Review Article

Sphingolipids in spinal cord injury

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Abstract: Spinal cord injury (SCI) is a debilitating condition that affects millions of individuals worldwide. Despite progress over the last few decades, the molecular mechanisms of secondary SCI that continue to occur days and weeks after the original trauma remain poorly understood. As a result, current therapies for SCI are only marginally effective. Sphingolipids, a diverse class of bioactive lipids, have been shown to regulate SCI repair and key secondary injury processes such as apoptosis, ischemia and inflammation. This review will discuss the numerous roles of sphingolipids and highlight the potential of sphingolipid-targeted therapies for SCI.

Keywords: Spinal cord injury, sphingolipid metabolism, ceramide, S1P, apoptosis, inflammation

Introduction

Spinal cord injury (SCI) is a devastating medical emergency that results from severe physical trauma to the spine. Damage to the spinal cord and surrounding cells begins immediately, and subsequent damage continues to occur days and even weeks later [1]. Accordingly, these two processes can be classified as either primary injury-cell death due to the original trauma-or secondary injury-cell death due to inflammation, ischemia, activation of apoptosis pathways or other complex biological responses such as edema, excitotoxicity, free radical production or axon demyelination [2, 3]. An unfortunate consequence of these secondary processes is that they often perpetuate each other in a vicious cycle such that the traumatic injury is compounded and expanded beyond the initial lesion area. Due to the lack of effective therapies, the prognosis for patients with SCI is poor, and these individuals often live with significant physical, emotional, and financial burdens.

Of the secondary SCI mechanisms, inflammation is a major contributor to cell death and loss of neuronal function [4, 5]. The inflammatory response in SCI is marked by the release of inflammatory cytokines in or near the SCI site which then induce the activation and migration of immune cells toward the lesion area [6]. The role of inflammation in SCI has long been debated, but the general consensus is that there are both harmful and beneficial aspects to inflammatory responses after SCI. Inflammation is a key process in the clearance of cytotoxic cell debris, but sustained activation of inflammatory responses ultimately leads to tissue damage and cell death [2, 3]. While the primary SCI is largely intractable, secondary mediators of injury such as inflammation present several targets that can be exploited for SCI treatment [7-10].

Named after the mythical Sphinx [11], sphingolipids are a class of bioactive lipids made up of long-chain sphingoid bases. The sphingolipids sphingosine, sphingosine-1-phosphate (S1P), ceramide and ceramide-1-phosphate (C1P) were thought to be merely structural components of cellular membranes, although in recent years they have come to be more fully appreciated for their roles in a variety of processes such as signal transduction [12], cell growth [13] and apoptosis [14]. In addition, ceramide is an essential precursor in the synthesis of complex sphingolipids such as sphingomyelin, cerebrosides, sulfatides, globosides and gangliosides. The number of bioactive molecules resulting from sphingolipid metabolism is quite staggering, and so is the number of biological processes mediated by these molecules: cell migration

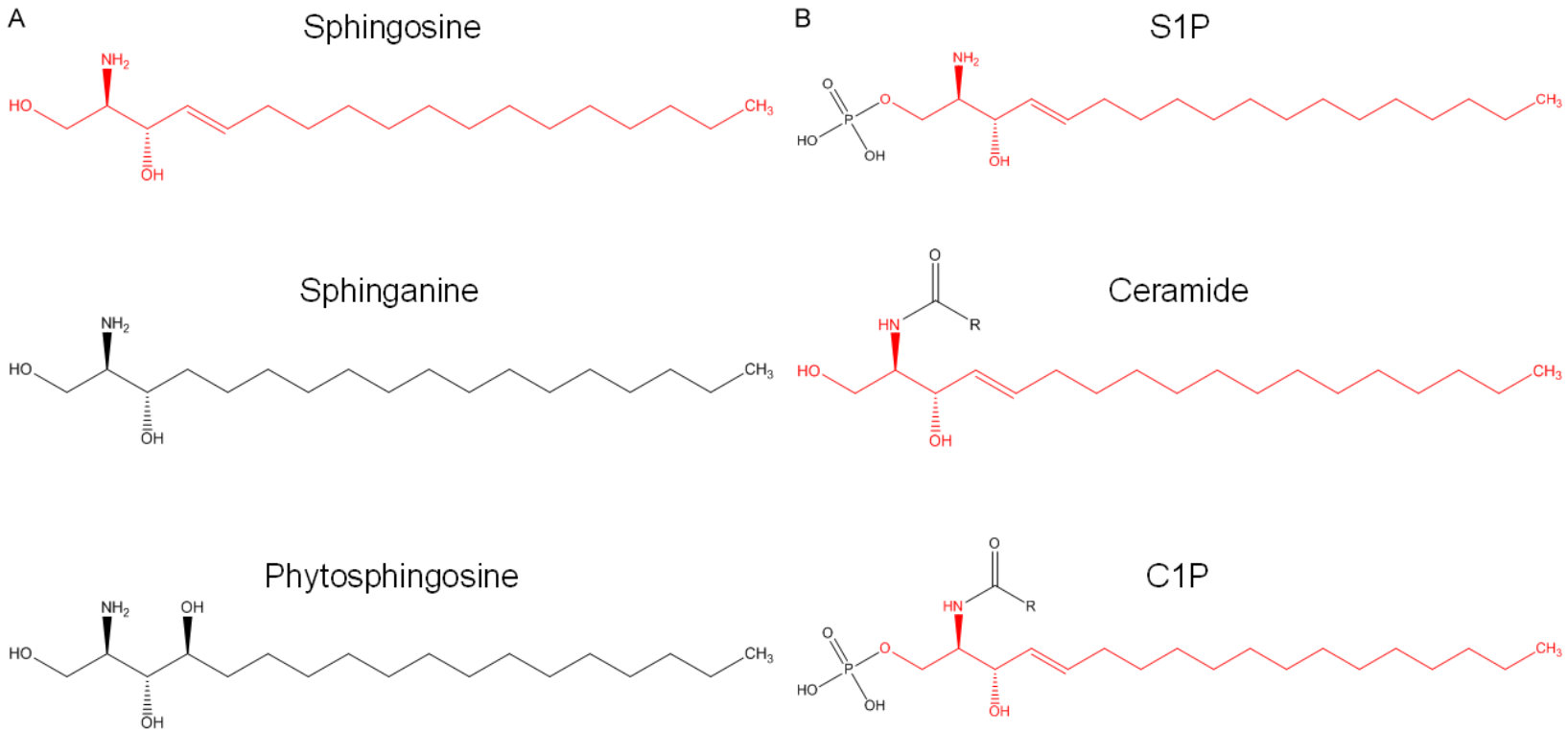

Figure 1. Structure of sphingoid bases and simple sphingolipids. A. The sphingoid bases sphingosine, sphinganine and phytosphingosine are long-chain acyclic aliphatic compounds. B. Sphingosine, shown in red, is the base for the other three simple sphingolipids: S1P, ceramide and C1P. Note the variable chain length of ceramide which adds to the complexity of sphingolipid metabolism.

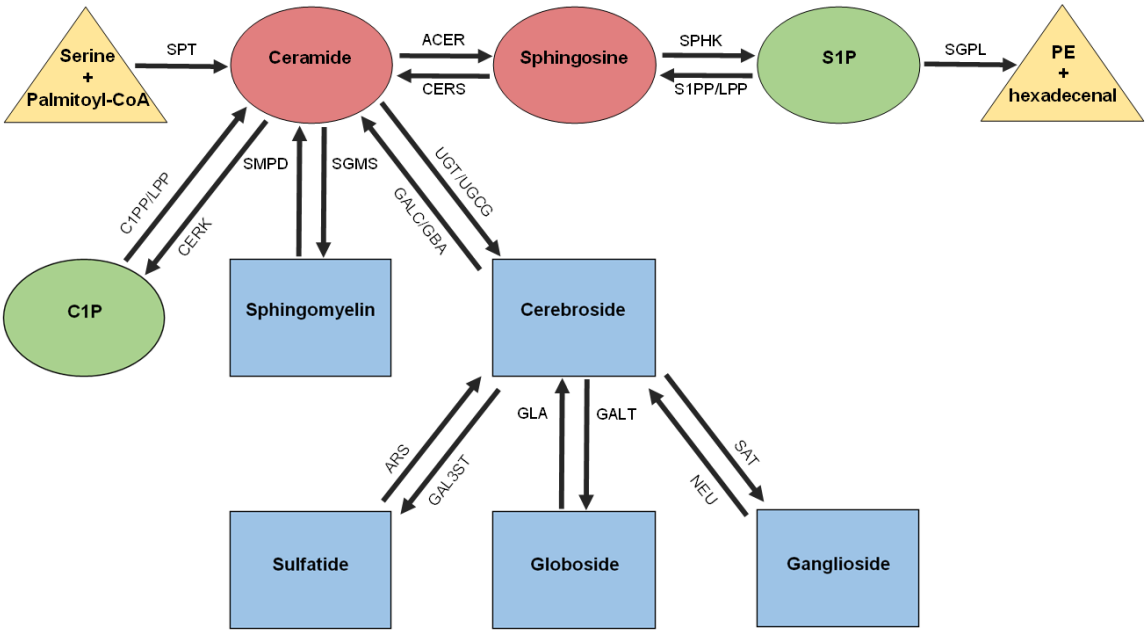

Figure 2. Sphingolipid Metabolism. Once ceramide is synthesized *de novo* from serine and palmitoyl-CoA, it can undergo one of several reversible reactions. Ceramide can be phosphorylated by CERK to form C1P. Ceramide is a precursor to the complex sphingolipids including sphingomyelin, cerebrosides, sulfatides, globosides and gangliosides. Breakdown of sphingolipids proceeds via hydrolysis of ceramide to sphingosine, phosphorylation by SPHK to form S1P, and lysis to PE and hexadecenal. Per the "sphingolipid rheostat" model, C1P and S1P (green) have pro-survival effects, whereas ceramide and sphingosine (red) have pro-apoptotic effects. Abbreviations: SPT = Serine Palmitoyltransferase, S1P = Sphingosine-1-phosphate, C1P = Ceramide-1-phosphate, ACER = Acid/Alkaline Ceramidase, CERS = Ceramide Synthase, SPHK = Sphingosine Kinase, S1PP = S1P Phosphatase, LPP = Lipid Phosphate Phosphatase, SGPL = S1P Lyase, PE = Phosphoethanolamine, C1PP = C1P Phosphatase, CERK = Ceramide Kinase, SMPD = Sphingomyelin Phosphodiesterase, SGMS = Sphingomyelin Synthase, GALC = Galactosylceramidase, GBA = Glucosidase Beta Acid, UGT = UDP Glycosyltransferase, UGCG = UDP-Glucose Ceramide Glucosyltransferase, ARS = Arylsulfatase, GAL3ST = Galactose-3-O-Sulfotransferase, GLA = Galactosidase, GALT = Galactosyltransferase, NEU = Sialidase, SAT = Sialyltransferase.

and proliferation [15, 16], differentiation [17], stress response [18], neuronal plasticity [19], angiogenesis [20] and immune function [21], among many others. This review is by no means exhaustive but rather endeavors to discuss the role of sphingolipid signaling in SCI processes and underscores the potential of sphingolipid metabolism as a therapeutic target for SCI.

Overview of sphingolipid metabolism

Simple sphingolipids

A discussion of sphingolipid metabolism should naturally begin with *de novo* synthesis of simple sphingolipids and sphingoid bases, the building blocks of sphingolipids (**Figure 1**). Sphingoid bases are generally described as long-chain acyclic aliphatic compounds and are synthesized *de novo* by serine palmitoyltransferase (SPT) from palmitoyl-CoA and serine or via ceramide catabolism [22]. The most common sphingoid bases are sphingosine, sphinganine and phytosphingosine. Of these, sphingosine is often regarded as the most biologically relevant sphingoid base in mammals, since sphingosine and its phosphorylated form (S1P) are implicated in a variety of physiological and pathological processes [23]. In addition, sphingosine is reversibly convertible with another highly relevant sphingolipid: ceramide. Sphingolipid metabolism involves a series of such reversible reactions, with anabolic and catabolic processes working in parallel to regulate cellular levels of the various sphingolipids (**Figure 2**). A particularly important example of this involves the balance between kinases and phosphatases in this pathway. Sphingosine kinase (SPHK) and ceramide kinase (CERK) catalyze the phosphorylation of sphingosine and ceramide, respectively, while S1P phosphatase and C1P phosphatase-in addition to other lipid phosphate phosphatases (LPPs)-catalyze the dephosphorylation of S1P and C1P. Maintaining the appro-

priate balance of these sphingolipids is vital to cell survival, as an excess of one or the other can have disastrous consequences. This relationship is often referred to as the "sphingolipid rheostat" model. First proposed in 1996 [24], the sphingolipid rheostat model posits that the levels of S1P and ceramide are key determinants of cell fate, with S1P promoting cell survival and ceramide promoting cell death [25].

Complex sphingolipids

Complex sphingolipids such as phosphosphingolipids and glycosphingolipids (GSLs) are predominantly structural components of plasma membranes [22], and their synthesis requires ceramide (**Figure 3**). Of note, mammals have six genes dedicated to the synthesis of ceramide and are appropriately named ceramide synthases (CerS). Ceramide is unique among sphingolipids in the sheer number of genes dedicated to its synthesis, suggesting that ceramides and the CerS serve vital functions. Through the action of sphingomyelin synthase (SMS), phosphocholine is added to ceramide to form sphingomyelin. Conversely, sphingomyelinases (SMases) catalyze the reverse reaction, generating ceramide. Sphingomyelin is a complex phosphosphingolipid and a major component of both myelin sheath and cell plasma membrane. In humans, the sphingomyelin content of CNS and PNS myelin is 7.9% and 17.7%, respectively (**Table 1**). Plasma membrane sphingomyelin content normally falls between 10-20% in humans and is highly variable by cell type, with Schwann cells, the PNS myelin-producing cells, reaching as high as 30% [27].

GSLs are formed by the addition of varying carbohydrate groups to ceramide. Cerebrosides, sulfatides, globosides and gangliosides constitute the four main classes of GSLs, and they have both overlapping and non-overlapping functions within cells [28]. Cerebrosides, as their name suggests, were first isolated from the brain [11], and are the most abundant class of GSLs found in nervous tissue. Cerebrosides consist of ceramide with an added glucose or galactose, yielding glucocerebroside (also known as glucosylceramide) and galactocerebroside (also known as galactosylceramide), respectively. The reverse reaction generates ceramide via the action of cerebrosidases. The diversity of ceramides coupled with the diversity of glycan modifications yields a remarkable number of permutations for this class of lipids [28]. Cerebrosides can be sulfated (sulfatides), glycosylated (globosides) or sialyated (gangliosides) to generate bioactive GSLs with roles in numerous biological processes. The plasma membrane concentration of GSLs is relatively low and ranges by cell type under 10%, while the GSL content of CNS and PNS myelin in humans is much higher, at 27.5% and 22.1%, respectively (**Table 1**).

Despite the vast complexity of sphingolipid metabolism, all sphingolipids share a common synthesis and breakdown pathway through ceramide (**Figure 2**). Ceramide can be irreversibly synthesized *de novo* from serine and palmitoyl-CoA, or it can be generated by SMases, cerebrosidases, LPPs or CerS in the ceramide salvage pathway. Likewise, the common sphingolipid breakdown pathway involves catabolism to ceramide, conversion to sphingosine, phosphorylation to S1P and irreversible degradation by S1P lyase to form phosphoethanolamine and hexadecenal.

Sphingolipids and SCI

While the biochemical changes involved in SCI are not completely understood, recent studies suggest that sphingolipids may play a prominent role [29-31]. The simple sphingolipids ceramide, C1P, sphingosine and S1P have been shown to mediate several aspects of SCI pathogenesis. Nearly three decades ago, researchers demonstrated that exogenous ceramide promotes survival or death of spinal motor neurons by regulating apoptosis in a dose-dependent manner [32]. This key role of ceramide was further elucidated in subsequent work which showed that inhibition of ceramide biosynthesis via CerS and SMase inhibitors significantly improved motor function and reduced the amount of tissue injury, neutrophil infiltration, apoptosis and cytokine production in a mouse model of SCI [33]. C1P has also been implicated in spinal neuronal death via the activation of cytosolic phospholipase A2 (cPLA2)-a key enzyme in the production of various inflammatory lipid mediators. Further, genetic deletion of cPLA2 or pharmacological inhibition at just 30 minutes post-injury substantially reversed these effects in mice, improving motor function and reducing tissue damage after SCI [30, 34]. Several studies in rodent models have shown that administration of FTY720, a sphin-

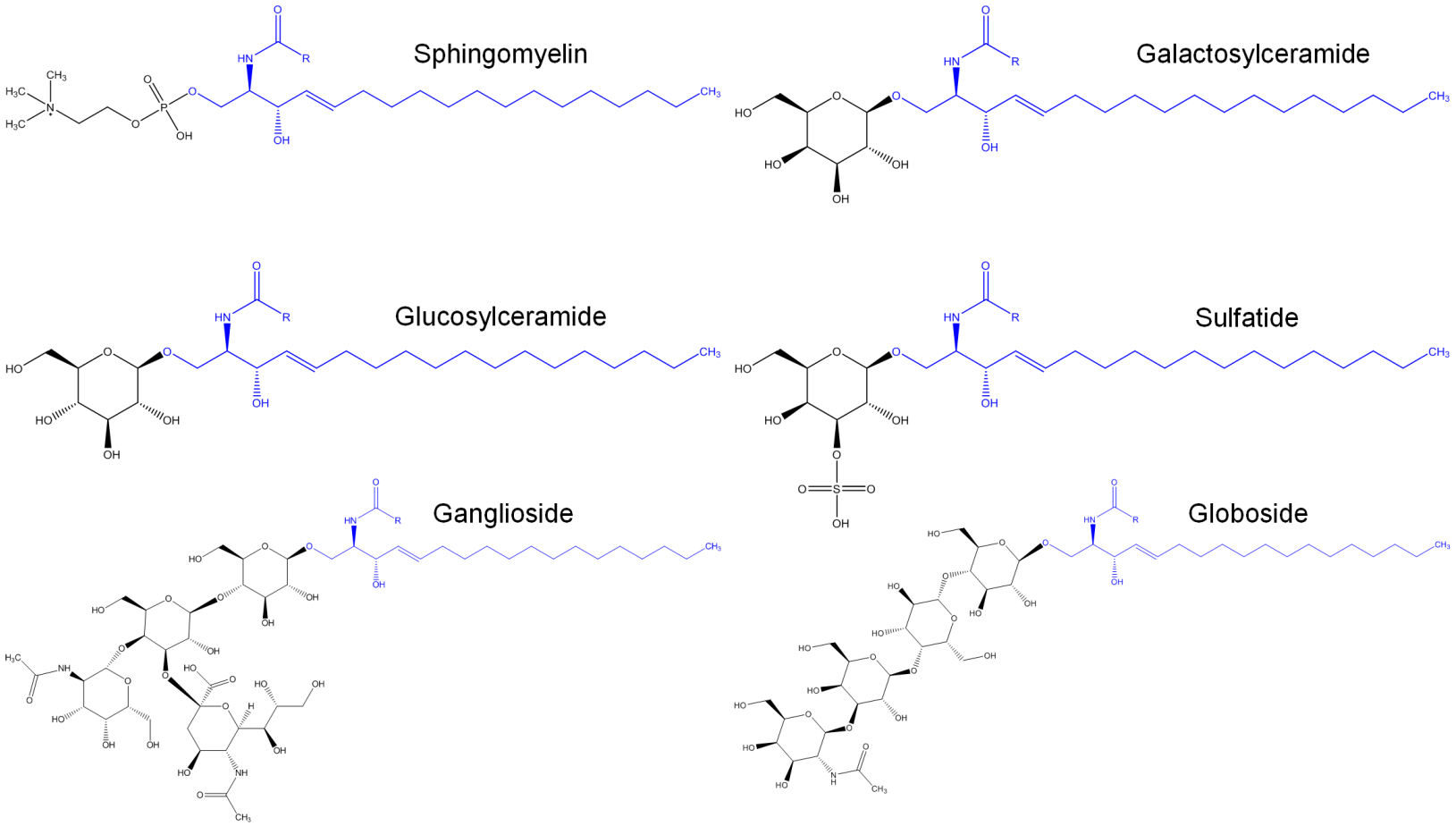

Figure 3. Structure of complex sphingolipids. Phosphosphingolipids and glycosphingolipids are synthesized via modifications to ceramide, shown in blue. Addition of phosphocholine to ceramide yields sphingomyelin. Addition of glucose or galactose to ceramide yields the cerebrosides glucosylceramide and galactosylceramide, respectively. These cerebrosides can be further glycosylated (globoside), sulfated (sulfatide) or sialyated (ganglioside).

Table 1. Myelin composition [26]

Component	Human CNS Myelin	Rat CNS Myelin	Human PNS Myelin	Rat PNS Myelin
Protein	30.0	29.5	28.7	-
Lipid	70.0	70.5	71.3	-
Cholesterol	27.7	27.3	23.0	27.2
Total Galactolipid	27.5	31.5	22.1	21.5
Cerebroside	22.7	23.7	-	15.8
Sulfatide	3.8	7.1	-	5.7
Sphingomyelin	7.9	3.2	17.7	7.0

gosine analog, promotes functional recovery after SCI [35-37] and reduces trauma-induced neuropathic pain via spinal S1P receptors (S1PRs) [38]. S1P was found to be elevated at the SCI site and enhanced the viability, migration and differentiation of neural progenitor cells [39]. This increased S1P at the injury site is posited to act as a chemoattractant for microglia and macrophages that is intended to be protective but inevitably becomes destructive.

The complex sphingolipids sphingomyelin and GM1 ganglioside are linked to SCI as well. A recent study used shiverer (myelin deficient) mice to assess axon regeneration following SCI. While *in vitro* shiverer neurons displayed neurite outgrowth comparable to wildtype neurons, *in vivo* shiverer fibers had an increased regenerative capacity. In this SCI model, myelin lipids-specifically cholesterol and sphingomyelin-were highly inhibitory for neurite outgrowth, and treatment with 2-hydroxypropyl-β-cyclodextrin, a drug that reduces the levels of these lipids, increased regeneration of wildtype axons following SCI [31]. GM1 ganglioside has been studied for decades (albeit with some debate [40]) as a therapeutic for SCI and is reported to have anti-neurotoxic, anti-inflammatory and neuroprotective effects that result in limited neurological improvement [41-44]. Nevertheless, this drug is not available for widespread clinical use.

In addition to these direct effects, simple and complex sphingolipids are well known mediators of secondary SCI mechanisms, namely apoptosis, ischemia and inflammation. What follows is a discussion of sphingolipids in each of these processes.

Apoptosis and cell survival

Apoptosis of neurons and oligodendrocytes (the CNS myelin-producing cells) in the injured spinal cord can be observed within a few hours of the traumatic event [45, 46]. As time goes on, expansion of the lesion area and Wallerian degeneration take effect, exacerbating the deleterious effects of the initial injury [47, 48]. According to the sphingolipid rheostat model, the dynamic balance between ceramide and S1P largely determines cellular fates [24]. More broadly, a mass of evidence suggests that sphingosine and C1P can be included in this model as promoters of apoptosis and cell survival, respectively. Whether directly or indirectly, a variety of cellular events alter the levels of ceramide and sphingosine to promote apoptosis, just as a variety of events alter the levels of S1P and C1P to promote cell survival [49, 50]. Complex sphingolipids such as sphingomyelin [51] and gangliosides [52, 53] have also been linked to apoptosis in diverse cell types.

Ceramide and sphingosine: Sphingosine and the FTY720 analog have been shown to induce apoptosis in a variety of cell types [54-57], and ceramide-induced apoptosis has been an intensely studied phenomena since its discovery in the early 1990s [14, 58, 59]. Numerous apoptotic stimuli can activate acid SMase and neutral SMase to generate ceramide [60, 61], while SMS can suppress ceramide-induced apoptosis [62]. CerS and SPT are also activated during apoptosis in response to various stimuli [63-65]. Of note, recent work has shown that ceramides are capable of forming protein-permeable mitochondrial outer membrane channels, and that this process is inhibited *in vitro* and *in vivo* by B-cell lymphoma (Bcl) extra-large [66, 67]. This finding has meaningful implications for our understanding of the regulation of apoptosis by ceramide and provides intriguing new insights into the process of apoptosis.

S1P and C1P: S1P promotes cell survival and proliferation in a myriad of ways, either via the action of S1P transporters [68], S1PRs [69] or LPPs [70]. S1P stimulates a number of secondary messengers including nitric oxide synthase, phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK) and protein kinase B and suppresses c-Jun N-terminal kinase and Bcl-2 associated X protein to enhance survival [71-73]. Likewise, C1P functions through PI3K, protein kinase B, protein kinase C, c-Jun N-terminal kinase, MAPK, nitric oxide synthase and mechanistic target of rapamycin

signaling to promote cell survival [74-78] and is a demonstrated mitogen [79]. C1P-mediated inhibition of acid SMase and SPT has been implicated in regulating survival as well [80, 81]. CERK is a regulator of cell growth and survival [82], though, intriguingly, there is conflicting evidence on the role of SPHK in apoptosis. SPHK activation has been known to inhibit apoptosis for decades [83] and has been linked to cell survival [84-86]. However, SPHK overexpression has also been shown to suppress growth and enhance apoptosis [87, 88]. In addition, inhibition of SPHKs has paradoxically been shown to both promote [89, 90] and inhibit apoptosis [91]. While these contradictory roles are largely attributed to divergent functions of the isoenzymes SPHK1 and SPHK2 [92], this explanation is insufficient to describe the full range of observed phenomena. Consequently, crosstalk between these pathways or yet unknown functions of these kinases may play a role in regulating apoptosis/cell survival.

Ischemia

Loss of blood flow in SCI is a major contributor to SCI pathogenesis [2, 3] and has several connections to sphingolipid signaling and metabolism. Indeed, the balance of ceramide and S1P seems play a significant role in angiogenesis, with ceramide acting as an inhibitor [93, 94] and S1P (and thus SPHK) acting as an activator for this process [95-98]. Ischemic events can lead to increased production of ceramide via SMase upregulation or UDP-glucose ceramide glucosyltransferase and SMS downregulation [99-102], and neutral SMase inhibition prevents neuron death caused by ischemic stress [103]. Unexpectedly, exogenous ceramide has also been found to inhibit apoptosis and reduce the infarct size in focal cerebral ischemia via Bcl-2 upregulation [104]. This dual role of ceramide may be a result of crosstalk between pro-apoptotic and anti-apoptotic pathways or dose-dependency, that is, varying concentrations of ceramide may have differential effects. S1P, FTY720 and SPHKs exhibit protective effects during ischemic events [105-109]. S1P promotes functional recovery in the infarcted brain by enhancing neural progenitor cell migration. In line with this, the concentration of S1P in the brain was increased after ischemia, and inhibition of S1PRs enhanced S1P-mediated neural progenitor cell migration toward the injury site [110]. This is analogous to the chemoattractant effect of S1P in SCI [39] and may represent a generalized mechanism for S1P in CNS injuries.

Endothelial cells: It is well established that endothelial cells (ECs) and vascular endothelial growth factor (VEGF) regulate the process of angiogenesis in numerous ways [111, 112], and this holds true in SCI as well [113-115]. There is mounting evidence that sphingolipids can interact with ECs and VEGF to regulate angiogenesis and vasculogenesis [116, 117]. S1P has long been implicated in EC function, and has been shown to stimulate EC migration [118, 119], increase barrier integrity [120-122] and enhance EC differentiation [123], proliferation [124], survival [125], adhesion [126] and VEGF expression [127]. Similarly, SPHKs have diverse functions in these processes [128-132]. Akin to their roles in apoptosis, ceramide and S1P regulate EC function in an antagonistic fashion, as ceramide has been shown to decrease barrier integrity and induce senescence in ECs [133, 134]. Cerebrosides and gangliosides have proangiogenic functions via VEGF [135-137], although ganglioside GM3 is able to suppress these effects, suggesting a more complex and nuanced relationship [138]. It is important to note that sphingolipids have not been shown to directly affect barrier integrity in a SCI model. Nonetheless, these results underscore the distinct possibility that sphingolipids contribute to SCI pathology by altering vascular permeability.

Inflammation

Inflammation in the injured spinal cord is a highly pathological process that begins shortly after the primary injury event. Despite, or perhaps owing to the diversity of inflammatory responses in SCI, immunotherapy has enjoyed only modest success in patients with SCI [7-10]. Cytokines and eicosanoids play central roles in the activation, differentiation, function and migration of immune cells, and sphingolipids are able to regulate these inflammatory mediators in diverse and complex ways to promote or inhibit inflammation. The function of sphingolipids in regulating immune cells has been the topic of numerous research papers and literature reviews in recent years [139-144].

Cytokines and eicosanoids: SCI pathogenesis is highly associated with cytokine dysregulation [2, 3], and SCI can induce the expression of cytokines in a matter of hours [145]. Sphingo-

lipids are critical mediators of cytokine signaling [146, 147], though their effects are complex and often cell-type specific. S1P has been shown to enhance expression of IFN-γ and IL-2 [148], IL-27 [149], IL-17 [150] and IL-8 [151] and reduces expression of IL-12 and IL-23 [149]. Inhibition of SPHK1 reduces IL-17, TNF-α and IL-1β production in activated microglia [144, 150], and SPHK1 interacts with the TNFα receptor via scaffolding protein TRAF2 [152]. SPHK2 associates with IL-12 receptors to modulate IL-12 signaling [153]. Exogenous C1P decreases secretion of TNF-α, IL-6, IL-8 and IL-1β in peripheral blood mononuclear cells [154]. C1P and S1P stimulate the production of prostaglandin E2 [155] at least in part by activating cPLA2 [156, 157]. Sphingolipid phosphatases play a role, as TNFα induced transcription of IL-1β was significantly reduced by S1P phosphatase siRNAs [158], and LPP regulates NF-κB activation and IL-8 secretion [159]. Neutral SMase activity induces the production of TNFα, IL-1β and IL-6 in astrocytes [160]. Sulfatide increases and cerebroside decreases the production of cytokines IL-1β, IL-6, IL-8, TNF-α and CCL3 [161].

Macrophages: A number of studies have shown that the inflammatory response in SCI is mediated by the activation and invasion of bone marrow derived-macrophages at the site of injury [162-166], and these macrophages can assume either a pro-inflammatory or anti-inflammatory phenotype. Exposure of macrophages to myelin debris, as in SCI, has been shown to promote a pro-inflammatory phenotype [167, 168]. Myelin has a characteristically high sphingolipid content (**Table 1**), though it remains to be seen whether its effect on macrophages can be attributed to sphingolipids specifically. S1P in particular has diverse roles in mediating macrophage function and phenotype. Intracellular S1P, generated via SPHK, induces a pro-inflammatory macrophage phenotype, while extracellular S1P binding to S1PRs induces an anti-inflammatory phenotype, inhibiting NF-κB activation and the production of pro-inflammatory cytokines while promoting the production of anti-inflammatory molecules [169]. Macrophages are protected from apoptosis via S1P-mediated inhibition of SMase [170], upregulation of anti-apoptotic Bcl-2 and Bcl extra-large [171] or activation of PI3K/MAPK/Ca^{2+} signaling [172]. S1P can act as a chemoattractant for monocyte and macrophage trafficking [173-175] and alter cytokine production in human macrophages [171, 176]. Conversely, the sphingosine analog FTY720 reduces macrophage infiltration *in vivo* [177-179]. SPHK1 mediates a variety of inflammatory responses in macrophages such as migration, NF-κB activation and secretion of cytokines [180, 181], and inhibition of SPHK sensitizes macrophages to lipopolysaccharide-induced cell death [182, 183]. C1P also stimulates macrophage NF-κB activation and chemokine CCL2 release to promote cell migration [184].

Glia: CNS inflammation, e.g. from a SCI, induces the migration and activation of microglia and astrocytes [2, 3]. These glial populations initially have constructive effects in response to injury, but prolonged activation contributes to further inflammation and tissue damage [185]. Astrogliosis is a common feature of CNS inflammation and is characterized by astrocyte proliferation and increased glial fibrillary acidic protein expression. Uncontrolled astrogliosis results in the formation of a glial scar surrounding the injury site which inhibits neural regeneration and functional recovery after SCI [186]. Studies in the 1980s and 1990s provided early evidence of sphingolipid-mediated glial activation by demonstrating that gangliosides stimulate glial cell proliferation and differentiation [187-189], and other known activators of glia include ceramide [160, 190-192] and sulfatide [193]. FTY720 has been shown to have diverse effects on glia: reducing reactive astrogliosis [29], altering calcium homoeostasis [194], inhibiting vesicle mobility and secretion [195], decreasing NO production [144, 196], promoting migration [197], downregulating pro-inflammatory cytokines production [144, 198] and upregulating production of brain-derived neurotrophic factor and glial cell-derived neurotrophic factor [198]. Together, these results highlight a neuroprotective role for FTY720 through regulation of glial function.

Clinical applications

Components of the sphingolipid metabolic pathway have been targeted in various clinical trials, although only GM1 ganglioside has specifically been tested in patients with SCI [41-44]. As seen throughout this review, animal studies have uncovered a wealth of information regarding SCI pathology and treatment app-

roaches. Ceramide biosynthesis inhibitors and FTY720 have been shown to attenuate nervous system insults in various rodent models [33, 36, 38, 103, 109, 177, 199], thus targeting the sphingolipid rheostat in future SCI studies is warranted and could mitigate tissue damage, alleviate pain and promote functional recovery in patients.

Despite early promise, GM1 ganglioside therapy development languished for decades due to criticisms of experimental design or failure to achieve defined endpoints in clinical trials [43, 44]. In recent years, however, new studies using GM1 ganglioside alone or with methylprednisolone-another controversial treatment for SCI [200]-have yielded positive results [41, 42].

FTY720, also known as fingolimod or Gilenya®, is the first oral drug approved by the FDA to treat relapsing multiple sclerosis [201, 202]. Since multiple sclerosis is a demyelinating disease that affects spinal neurons, these findings can be extended toward SCI therapies. For this reason, in addition to all of the previously described actions of FTY720, fingolimod may be a promising therapeutic for SCI.

Problematic methods for quantifying sphingolipids have impeded the development of sphingolipid biomarkers for human diseases, although recent progress has been made through advances in genomics and proteomics. Researchers are actively evaluating the utility of sphingolipid biomarkers in a variety of diseases such as cancer, diabetes, liver disease, acute brain injury and Alzheimer's disease [203-211]. Even so, predictive and prognostic biomarkers for SCI remain to be discovered.

Conclusion and outlook

The diversity of sphingolipids and the complexity of their metabolism are reflected in the diverse and complex ways by which they affect cell physiology and pathophysiology. Far beyond the well-known functions of ceramide and S1P in the sphingolipid rheostat model, simple and complex sphingolipids regulate the processes of apoptosis, cell survival, ischemia, angiogenesis, inflammation and SCI repair. Despite the wealth of evidence that suggests sphingolipids are involved in the pathogenic processes of SCI, there is a paucity of clinical research in this field. Can we quantify sphingolipid dysregulation to develop useful predictive and prognostic biomarkers for SCI? Can we improve SCI outcomes by using our knowledge of sphingolipid metabolism to shift the balance toward pro-survival S1P and away from apoptotic ceramide? SCI is a tragic and disabling condition with no existing cure, and current therapies have only a modest effect. Tackling these important questions may prove to be a critical step forward in treating SCI and improving the lives of millions of people around the world.

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Disclosure of conflict of interest

None.

Abbreviations

Bcl, B-cell lymphoma; C1P, ceramide-1-phosphate; CERK, ceramide kinase; CerS, ceramide synthase; cPLA2, cytosolic phospholipase A2; EC, endothelial cell; GSL, glycosphingolipid; LPP, lipid phosphate phosphatase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; S1P, sphingosine-1-phosphate; S1PR, S1P receptor; SCI, spinal cord injury; SMase, sphingomyelinase; SMS, sphingomyelin synthase; SPHK, sphingosine kinase; SPT, serine palmitoyltransferase; VEGF, vascular endothelial growth factor.

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