Special Section on Therapeutic Implications for Sphingolipids in Health and Disease—Perspective

Perspective: Therapeutic Implications for Sphingolipids in Health and Disease

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ABSTRACT

Long thought to be structural components of cell membranes, sphingolipids (SLs) have emerged as bioactive molecules whose metabolism is tightly regulated. These bioactive lipids and their metabolic enzymes have been implicated in numerous disease states, including lysosomal storage disorders, multiple sclerosis, inflammation, and cancer as well as metabolic syndrome and obesity. In addition, the indications for many of these lipids to potentially serve as biomarkers for disease continue to emerge with increasing metabolomic and lipidomic studies. The implications of these studies have, in turn, led to the examination of SL enzymes and their bioactive lipids as potential therapeutic targets and as markers for therapeutic efficacy.

SIGNIFICANCE STATEMENT

Many sphingolipids (SLs) and their metabolizing enzymes have been implicated in disease. This perspective highlights the potential for SLs to serve as therapeutic targets and diagnostic markers and discusses the implications for the studies and reviews highlighted in this Special Section on Therapeutic Implications for Sphingolipids in Health and Disease.

Despite being considered as structural molecules for over 100 years, the sphingolipid (SL) family of lipids have emerged over the last two decades as bioactive molecules with distinct and important biologic functions (Hannun and Obeid, 2008, 2018). Disruptions in SL metabolism have been implicated in numerous diseases, including autoimmune disorders, insulin resistance, inflammatory bowel disease, and neurologic disorders, whereas mutations in SL enzymes have been associated with various developmental disorders, such as Niemann-Pick, Gaucher, Farber, and Tay-Sachs among others. This has led to substantial efforts aimed at understanding these bioactive molecules and their metabolic enzymes as therapeutic targets (Shaw et al., 2018). This issue of Molecular Pharmacology hosts a Special Section on Therapeutic Implications for Sphingolipids in Health and Disease. In this issue, there are five articles focusing on topics pertaining to SL metabolism in disease as well as potential roles for SLs as therapeutic targets, in therapeutic responses, and as biomarkers of disease.

In recent years, there has been a growing potential for sphingolipids as biomarkers. Indeed, the Mayo Clinic has begun analysis of three specific plasma ceramide species as a measure for cardiovascular disease. Here, the article by Perez-Paramo et al. (2024) sets out to determine if sphingolipids serve as potential biomarkers for disease activity in multiple sclerosis (MS). Autoimmune responses result in neurologic deficits due to demyelination and axonal damage in the central nervous system (Shaw et al., 2018). Typically, this initially occurs and remits (relapsing MS; RMS) and eventually advances to primary-progressive MS (PPMS). Sphingolipids have long been implicated in MS, with four current therapeutics approved that specifically target sphingosine-1-phosphate receptors (S1PRs). Additional studies have examined the prognostic effects of glycosphingolipids in cerebrospinal fluid (Novakova et al., 2023), and SL levels have been shown to be altered in plasma from MS patients (Solmaz et al., 2022). However, these studies have mixed results, and the effects of MS therapeutics that do not target S1PRs on sphingolipid levels are poorly understood. In their manuscript, the authors define a high-throughput liquid chromatography tandem mass spectrometry method to analyze sphingolipid species in cerebrospinal fluid and demonstrated elevated SL levels in both RMS and PPMS.

ABBREVIATIONS: CerS, ceramide synthase; ER, endoplasmic reticulum; MS, multiple sclerosis; PPMS, primary-progressive MS; RMS, relapsing MS; SL, sphingolipid; SMase D, sphingomyelinase D; UPR, unfolded protein response.
patients as compared with healthy controls. Furthermore, SL levels were decreased after 1 year of ocrelizumab treatment in RMS but not PPMS patients (Perez-Paramo et al., 2024). Their results suggest that sphingolipids may serve as biomarkers for disease activity in patients with RMS.

As ceramide is the central hub of the SL network, it is perhaps unsurprising that altered ceramide levels have been implicated in many diseases. However, the multiplicity of ceramide-generating pathways, and which pathways are involved in which condition, can be a confounding factor in identifying appropriate targets of interest. In the second manuscript, Richardson et al. (2024) examined the expression of ceramide synthases (CerS)—key ceramide-generating enzymes—in specific tissues and their contributions to downstream SL metabolism. Of note, several studies have examined tissue-specific SL levels (Muralidharan et al., 2021) as well as correlating the expression of CerS with specific N-acyl chain ceramides (Laviad et al., 2012). However, the contribution of specific CerS in specific tissues to N-acyl chain sphingolipid composition has not been previously described. In this article, the authors determined that expression of specific CerS correlated not only with levels of ceramide species but also with levels of complex sphingolipids (Richardson et al., 2024). This suggests that when studying biologies associated with specific CerS isoforms, it is important to look beyond the immediate downstream product and to consider further metabolites. Furthermore, the results of this study also suggest that particular CerS isoforms may serve as specific therapeutic targets or diagnostic markers based on disease states and tissues of origin.

Recent studies have begun to investigate the potential of sphingolipid enzymes as druggable targets in nonmammalian systems, such as Cryptococcus neoformans (Mor et al., 2016). In a similar fashion, the research article by Lachmayr and Merrill (2024) examines the activity of an understudied phospholipase D, or sphingomyelinase D (SMase D), that generates the novel sphingolipid 1,3-cyclic phosphate (Cer1,3P). This SMase D activity occurs in the venom of the brown recluse spider (Loxosceles reclusa) and several other Sicariid spiders and directly leads to tissue necrosis after envenomation (Tambourgi et al., 1998). The differences in structure and activities of these nonmammalian isoforms make them attractive therapeutic targets as there is potential for selective inhibitors. This is further heightened in this case as there are currently no treatments for injuries following the bites of these spiders. This original article and mini-review describes two simple methods for the detection of SMase D activity using fluorescent sphingomyelin (Lachmayr and Merrill, 2024). The simplicity of the methods outlined will hopefully serve as a platform for developing new therapeutic approaches for targeting the activity of SMase D/phospholipase D.

Sphingolipids are generated de novo in the endoplasmic reticulum (ER). Dysregulation of this process can both be modulated by and directly modulate ER stress or the unfolded protein response (UPR). The UPR is typically initiated by excess unfolded proteins but can also be activated by lipid bilayer stress (Kitai et al., 2013) and is mediated by three main ER stress proteins: activating transcription factor 6 (ATF6), pancreatic ER kinase-like ER kinase (PERK), and inositol requiring enzyme 1x (IRE1x) [reviewed in Wang et al. (2009)]. Activation of ER stress pathways regulate ER-stress response genes, halt global protein translation, and lead to apoptosis (Harding et al., 1999, 2003; Ye et al., 2000; Arshad et al., 2013). Of note, activation of ER stress pathways, mediated at least in part by sphingolipids, has also been linked to immunogenic cell death (Kar et al., 2023), a key biologic process that elicits antitumor immune responses and can prime tumor cells for immunotherapies. This review provides a brief discussion of the roles of sphingolipids in the UPR, specifically focusing on the mechanism(s) by which sphingolipids modulate the ER stress and the critical roles of sphingolipids in immunogenic cell death associated with ER stress (Hengst et al., 2024). Importantly, this review serves to emphasize that, when it comes to modulating sphingolipids to induce cell death, it is important to look beyond apoptosis as the final endpoint.

Lipid metabolism and remodeling requires the coordinated activities of numerous enzymes, including fatty acyl elongases, desaturases, lipases, and acyltransferases, with recent discoveries defining both novel sphingolipids, and new pathways of sphingolipid metabolism have broadened the scope of potential druggable targets. In this vein, the recent emergence of the novel sphingolipid 1-O-acylceramide, which can be generated from ceramide by the enzyme diacylglycerol acyltransferase enzyme (DGAT2) (Senkal et al., 2017), is of particular interest as a putative ceramide acyltransferase (CAT) enzyme. This novel enzymatic activity and family of sphingolipids may have significant therapeutic implications in diseases such as cancer or metabolic syndromes. The review in this special section by Hernandez-Corbacho and Canals (2024) examines the potential for DGAT2 and other lipid acyltransferases as therapeutic targets as well as the current status of such inhibitors in clinical trials.

In the nearly 40 years since the discovery of the signaling functions of sphingolipids, the community has made great strides in identifying the diversity of lipid species and is beginning to define and understand their cellular functions. However, in a growing era of translational research, it is imperative that we continue to push forward into understanding the physiologic and pathologic impacts of sphingolipids. This Special Section on Therapeutic Implications for Sphingolipids in Health and Disease serves to highlight some of the significance of sphingolipids and their metabolism in health and disease. However, we firmly believe that this is just the tip of the iceberg, and there is an untapped potential of these enzymes (and lipids) as therapeutic and diagnostic targets. As technical capabilities and studies into sphingolipid signaling and metabolism become more sophisticated, we both look forward to the promise that the next 40 years holds.

Data Availability
This article contains no datasets generated or analyzed during the current study.

Authorship Contributions
Wrote or contributed to the writing of the manuscript: Clarke, Snider.

References

