In the last two decades sphingolipids (SLs) have emerged as bioactive lipids with significant roles in various diseases. This issue of Molecular Pharmacology hosts a Special Section on Therapeutic Implications for Sphingolipids in Health and Disease featuring original articles and systematic reviews focusing on the roles of SLs as therapeutic targets in health and disease and as potential biomarkers for disease.

The issue begins with a brief perspective on the current status of sphingolipids as therapeutic targets and biomarkers in health and disease (Clarke and Snider, 2024). The first manuscript utilizes liquid chromatography tandem mass spectrometry to develop a quantitative high-throughput assay to define SLs as potential biomarkers for multiple sclerosis. The authors examined cerebrospinal fluid from patients with relapsing multiple sclerosis and primary-progressive multiple sclerosis and determined a 14 SL signature that was higher in patients with MS than healthy controls. This method and SL signature may also enable future studies into additional central nervous system disorders (Perez-Paramo et al., 2024). The second original research article evaluates sphingolipids and the expression of the different ceramide-generating enzymes, with a specific focus on ceramide synthases (CerS) in various tissues in C57BL/6J mice (Richardson et al., 2024). CerS expression in specific tissues correlated with the predicted ceramide species chain lengths but not always the chain lengths of the complex sphingolipids. As many of the CerS and specific ceramide species have been implicated in disease, these studies suggest the potential for CerS as therapeutic targets and the use of sphingolipid species as diagnostics in specific tissues. The third manuscript provides a mini-review on the activity of sphingomyelinase D, found in the venom of the brown recluse spider and the generation of ceramide 1,3-cyclic phosphate. This manuscript also details a simple thin layer chromatography method to detect sphingomyelinase D activity. This assay for detection of sphingomyelinase D activity will be useful for studies examining therapeutic interventions for spider bites (Lachmayr and Merrill, 2024).

The final two manuscripts of this Special Section systematically review the potential for SLs and their generating enzymes as therapeutic targets and modulators of cellular responses. The first review provides a brief discussion of the intersection between SL metabolism and the unfolded protein response. The primary focus of the review details the mechanism(s) by which SLs regulate endoplasmic reticulum stress response pathways and the roles for these bioactive SLs in immunogenic cell death associated with the endoplasmic reticulum stress (Hengst et al., 2024). The final review focuses on the family of fatty acyltransferases that function in the generation of glycerolipids and sphingolipids. These enzymes are intriguing targets in many disease states including metabolic syndrome and cancer. The review also highlights the potential for diacylglycerol acyltransferase 2 as a ceramide acyltransferase in the generation of 1-O-acylceramide. This review further highlights the current status of drug development in lipid acyltransferases (Hernandez-Corbacho and Canals, 2024).

In summary, this Special Section on Therapeutic Implications for Sphingolipids in Health and Disease highlights the importance of these bioactive lipids and their metabolic enzymes as therapeutic targets and as potential biomarkers for disease status.
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References