Introduction: Enigmas of Sphingolipids

1

Johnny Stiban

Abstract

Sphingolipid biology has enjoyed a remarkable rise to fame over the last two decades. Various molecules from this lipid family have been implicated in a variety of cellular functions in health and disease. Ceramides, which constitute the hub of sphingolipid metabolism, are apoptogenic molecules that have many proposed mechanisms of actions. Enigmas revolving around this area of research are slowly being cleared with the advent of better laboratory techniques and data analyses. In this chapter, a general introduction of the topics presented in this book is undertaken highlighting the main ideas of each chapter.

Keywords

Ceramide · Ceramide 1-phosphate · Ceramide channels · Ceramide microdomains · CerS · Disease biomarkers · Inflammation · Ocular health · Sphingolipids

When Thudichum coined the term "sphingolipids" near the end of the nineteenth century, the mysterious Sphinx of the Greek mythology was referenced (Thudichum 1962). Indeed, back then, and for many years to come, sphingolipids were so enigmatic that limited functions were assigned to them. They were merely considered structural components of membranes that complement the glycerophospholipid bilayer. Not until the late 1970s and early 1980s of the twentieth century did researchers start to assign some biological roles to a subset of glycosphingolipids, gangliosides (Aloj et al. 1979; Tsuji et al. 1983; Yavin et al. 1981). Structurally, sphingolipids are diverse; nevertheless they all contain the amino alcohol sphingoid backbone. Either sphingosine or dihydrosphingosine (sphinganine) constitute the base, which is N-acylated to form ceramides or dihydroceramides, respectively. The hydroxyl group on C-1 of the base can be further modified to generate ceramide 1-phosphate, globosides, gangliosides and sphingomyelins (Fahy et al. 2005). Various members of the sphingolipid family possess strong biologic functions in the cell. Ceramide, the parent molecule of sphingolipids, has been shown to induce a plethora of cellular functions. The bioactivity of this group of biomolecules has been implicated in cellular growth, metabolism, senescence, and death (Hannun et al. 1993). Ceramide 1-phosphate and sphingosine 1-phosphate also have important functions in the cell and extracellularly. Sphingosine 1-phosphate has G protein coupled receptors (GPCRs) on the surface of target cells and is a mitogenic substance (Lee et al. 1998).

J. Stiban (✉)
Department of Biology and Biochemistry, Faculty of Science, Birzeit University, Ramallah, Palestine
e-mail: jstiban@birzeit.edu

J. Stiban (ed.), *Bioactive Ceramides in Health and Disease*, Advances in Experimental Medicine and Biology 1159, https://doi.org/10.1007/978-3-030-21162-2_1

In the first part of this book, we focus on the parent sphingolipid, ceramide, and its phosphorylated derivative, ceramide 1-phosphate and discuss their biological activities. Bioactive ceramides function as second messengers (Hannun 1996), protein modulators (Becker et al. 2005) and channel formers (Colombini 2013; Siskind and Colombini 2000). Ceramide 1-phosphate, on the other hand, was shown to be involved in the regulation of adipogenesis (Ordonez et al. 2018), the control of immunological response (Gomez-Munoz et al. 2016) and migration of mesenchymal stem cells to the sites of injury (Yu et al. 2019).

These molecules are discussed in the following chapters and are the main topic of this specialized book. World experts in the field of ceramide and sphingolipid biochemistry and biology have been assembled to discuss specific facets of bioactive ceramide biology. In the final chapters of this book, a global picture of bioactive sphingolipids in health and disease is presented in a concise, yet thorough manner.

In the second chapter of this book, a survey of similar evolutionary origins between mitochondrial lipids, especially ceramides, and the membranes of bacteria is undertaken. The processes of mitochondrial and bacterial apoptosis are discussed in relation to sphingolipid content and utilization. The mechanistic details of ceramide- induced permeabilization of mitochondrial outer membranes to initiate intrinsic apoptosis is discussed in Chap. 3, in which the discoverer of the ceramide channel, Marco Colombini, reviews the accumulating data on these surprising biological structures and presents new exciting findings. In Chap. 4, Anthony H. Futerman and colleagues excellently describe the enzymology of the mammalian ceramide synthase enzyme family and review the evidence that link the structure and function of the various ceramide synthase proteins. The most recent literature on the topic is presented in this chapter along with new figures and analysis. In the following chapter, Charles Chalfant, a world expert in ceramide 1-phosphate biology, outlines and discusses the various roles this molecule plays in inflammation, cellular proliferation, and wound healing. Interesting new findings and enigmatic functions are assigned to ceramide 1-phosphate.

Moving into the biophysics of structured ceramide microdomains in membranes, Silva and colleagues expertly discuss, in details, the varying roles of sphingolipid structured domains in health and disease in Chap. 6. The biophysical nature of ceramide microdomains and their proposed biochemical functions are detailed in this chapter.

Moreover, in the last two chapters, the roles of sphingolipids in diseases, especially in ocular health are discussed. In Chap. 7, the group of Samar Hammad outlines the remarkable prevalence of sphingolipids as biomarkers of disease in general noting different metabolic routes that are encountered in diseased states. New sets of data are presented in this chapter and the authors present them in an elaborate manner. Finally, in Chap. 8, the specific effects of sphingolipids in the various diseases of the eye are presented by Mandal and coworkers.

In summary, whereas sphingolipid research has surged in the last two decades, questions remain and intensify with more knowledge of the subject. This book is intended to illuminate the field of bioactive sphingolipids with new information for both the novice and expert reader. As editor of this book, I extend my sincere gratitude to all authors who contributed chapters and the reviewers for the time spent to write and to edit and critique the work diligently and accurately.

References

Aloj SM, Lee G, Consiglio E, Formisano S, Minton AP, Kohn LD (1979) Dansylated thyrotropin as a probe of hormone-receptor interactions. J Biol Chem 254(18):9030–9039

Becker KP, Kitatani K, Idkowiak-Baldys J, Bielawski J, Hannun YA (2005) Selective inhibition of juxtanuclear translocation of protein kinase C betaII by a negative feedback mechanism involving ceramide formed from the salvage pathway. J Biol Chem 280(4):2606–2612. https://doi.org/10.1074/jbc.M409066200

Colombini M (2013) Membrane channels formed by ceramide. Handb Exp Pharmacol 215:109–126. https://doi.org/10.1007/978-3-7091-1368-4_6

Fahy E, Subramaniam S, Brown HA, Glass CK, Merrill AH Jr, Murphy RC et al (2005) A comprehensive clas-

sification system for lipids. J Lipid Res 46(5):839–861. https://doi.org/10.1194/jlr.E400004-JLR200

Gomez-Munoz A, Presa N, Gomez-Larrauri A, Rivera IG, Trueba M, Ordonez M (2016) Control of inflammatory responses by ceramide, sphingosine 1-phosphate and ceramide 1-phosphate. Prog Lipid Res 61:51–62. https://doi.org/10.1016/j.plipres.2015.09.002

Hannun YA (1996) Functions of ceramide in coordinating cellular responses to stress. Science 274(5294):1855–1859

Hannun YA, Obeid LM, Wolff RA (1993) The novel second messenger ceramide: identification, mechanism of action, and cellular activity. Adv Lipid Res 25:43–64

Lee MJ, Van Brocklyn JR, Thangada S, Liu CH, Hand AR, Menzeleev R et al (1998) Sphingosine-1-phosphate as a ligand for the G protein-coupled receptor EDG-1. Science 279(5356):1552–1555

Ordonez M, Presa N, Dominguez-Herrera A, Trueba M, Gomez-Munoz A (2018) Regulation of adipogenesis by ceramide 1-phosphate. Exp Cell Res 372(2):150–157. https://doi.org/10.1016/j.yexcr.2018.09.021

Siskind LJ, Colombini M (2000) The lipids C2- and C16-ceramide form large stable channels. Implications for apoptosis. J Biol Chem 275(49):38640–38644. https://doi.org/10.1074/jbc.C000587200

Thudichum JLW (1962) A treatise on the chemical constitution of the brain. Archon Books, North Haven

Tsuji S, Arita M, Nagai Y (1983) GQ1b, a bioactive ganglioside that exhibits novel nerve growth factor (NGF)-like activities in the two neuroblastoma cell lines. J Biochem 94(1):303–306

Yavin E, Yavin Z, Habig WH, Hardegree MC, Kohn LD (1981) Tetanus toxin association with developing neuronal cell cultures. Kinetic parameters and evidence for ganglioside-mediated internalization. J Biol Chem 256(13):7014–7022

Yu J, Kim HM, Kim KP, Son Y, Kim MS, Park KS (2019) Ceramide kinase regulates the migration of bone marrow-derived mesenchymal stem cells. Biochem Biophys Res Commun 508(2):361–367. https://doi.org/10.1016/j.bbrc.2018.11.154