Sphingolipid Metabolism and Signaling Minireview Series*

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William L. Smith‡‡ and Alfred H. Merrill, Jr.†

From the ‡Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, Michigan 48824 and *School of Biology, Georgia Institute of Technology, Atlanta, Georgia 30332-0290

Sphingolipids are a diverse family of phospholipids and glycolipids built upon “sphingoid base” backbones such as (2S,3R,4E)-2-aminoocadec-4-ene-1,3-diol (sphingosine) shown in Fig. 1. The name “sphingosin” was chosen by Thudichum in “commemoration of the many enigmas which it has presented to the inquirer” (1), and many enigmas (including fundamental questions about how and why these compounds are made) persisted for the century following this classic 1884 publication. This minireview series provides an overview of the current understanding of sphingolipid biosynthesis, intracellular transport and turnover, with particular reference to the roles of the lipid backbones in cell regulation and signaling. Although the series does not attempt to address the biochemistry of all of the complex sphingolipids, which number in the thousands of compounds varying in headgroup, backbone sphingoid base, and fatty acid, the minireview by Kolter et al. on combinatorial ganglioside synthesis illustrates how changes in enzymes at key branch points profoundly influence the product profile and biologic functions.

In the first minireview of the series, Alfred H. Merrill, Jr. provides a synopsis of sphingoid base and ceramide biosynthesis in eukaryotic systems, highlighting the structural diversity of the lipid backbones and the importance of controlling their amounts. De novo biosynthesis of the sphingoid bases is essential because dietary sphingolipids are mostly catabolized; however, careful control of the de novo pathway is critical because many of its intermediates are highly bioactive. Enzymes of the biosynthetic pathway are all membrane-bound and have intriguing features. Serine palmitoyltransferase, the first enzyme of the pathway, is a pyridoxal 5’-phosphate-dependent decarboxylase comprised of two subunits, one of which has been shown to be defective in human sensory neuropathies. (Dihydro)ceramide synthase catalyzes the formation of an amide linkage between a long chain (typically saturated) fatty acid and the amino group of the sphingoid bases and is the target of a family of mycotoxins (fumonisins) that cause a wide spectrum of disease symptoms (neurotoxicity, hepatotoxicity, and nephrotoxicity, pulmonary edema, cancers of liver, kidney, and esophagus, birth defects, and possibly other disorders). And finally, dihydrceramide desaturase and hydroxylase, which introduce the 4-trans double bond (to produce sphingosine) and the C-4 hydroxyl of phytosphingosines, respectively. The desaturase reaction is critical because it converts an essentially innocuous precursor (dihydrceramide) into a highly bioactive product (ceramide and downstream species such as sphingosine and their derivatives). The minireview by Merrill also comments on the widespread use of inhibitors to define the actions of sphingolipids and the possible complications that may arise from the use of these inhibitors.

Yusuf A. Hannun and Lina M. Obeid provide a current prospectus on the metabolism and function of ceramide, a central player in sphingolipid metabolism that is the immediate precursor of sphingomyelins and glycosphingolipids as well as the bioactive products sphingosine and sphingosine 1-phosphate. Hannun and Obeid argue that ceramide is a mediator/regulator both of stress responses downstream of cytokines and other agonists and of physical stresses. Presumably, these actions occur through certain protein phosphatases and kinases that are activated by ceramide. The authors also describe the production of ceramide by sphingomyelin turnover via different types of sphingomyelinases as well as the consequences of generating ceramide at different subcellular sites; for example, targeting neutral sphingomyelinase to mitochondria (but apparently not to other organelles) induces apoptosis.

Sarah Spiegel and Sheldon Milstien discuss the novel lipid mediator sphingosine 1-phosphate emphasizing biochemical aspects of its biosynthesis and mechanisms of action. This compound is formed from sphingosine through the action of two different but specific kinases. Sphingosine 1-phosphate appears to be both an intracellular mediator and an extracellular agonist for a family of G protein-linked receptors that were originally named “edg” (endothelium-derived growth) receptors. Other families of edg receptors utilize the closely related lipid mediator lysophosphatidic acid. Disruption of the edg-1 receptor, which is specific for sphingosine 1-phosphate and has recently been renamed the SIP1 receptor, prevents maturation of the vasculature and leads to embryonic hemorrhage and intrauterine death. The intracellular receptor(s) for sphingosine 1-phosphate have not been characterized, but they appear to influence calcium signaling, cell proliferation, and survival.

Under most circumstances, the prevalent sphingolipids of cells are the complex sphingolipids: phosphosphingolipids such as sphingomyelins and glycosphingolipids such as ganglioside G33 shown in Fig. 1. Complex sphingolipids are found in all eukaryotes and some prokaryotes and viruses, mainly as components of the plasma membrane and related organelles (endosomes, lysosomes, Golgi membranes, etc.). The amounts vary considerably but can be quite high (e.g. about 30% of the total lipid of plasma membranes). Furthermore, the percentages in particular regions of the membrane can be considerably higher because sphingolipids are asymmetrically distributed (mainly on the exoplasmic leaflet), and some categories of sphingolipids such as sphingomyelin, ceramide, and glucosylceramide (sometimes in combination with cholesterol) spontaneously aggregate to form liquid ordered microdomains termed “rafts,” “caveolae,” and “detergent-resistant membranes” as discussed in an earlier minireview by Brown and London (2). These sphingolipid-rich microdomains are believed to be important in clustering proteins involved in cell signaling; for example, glycoprophosphatidylinositol-anchored proteins congregate in the exoplasmic region of lipid rafts while myristoylated and palmitoylated G proteins can protrude into the cytoplasmic side of rafts. An update on lipid rafts is presented in a minireview by Gerrit van Meer and Quirine Lismam, although these authors concentrate primarily on the specificity of sphingolipid transport, beginning with the point that the major sites of sphingolipid biosynthesis are the endoplasmic reticulum and Golgi membranes whereas most of the major sphingolipids end up on the exoplasmic layer of the plasma membrane (and in analogous membrane compartments such as endosomes). Thus, trans-membrane movement is necessary as part of

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‡ To whom correspondence should be addressed: 513 Biochemistry Bldg., Dept. of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI 48824. Tel.: 517-353-1604; Fax: 517-353-9334; E-mail: smithw@pilot.msu.edu.
sphingolipid biosynthesis and presumably also for the generation of ceramide acting as a second messenger from complex sphingolipid turnover. van Meer and Lisman describe the topology of the enzymes and substrates involved in sphingolipid biosynthesis and the energy-dependent and -independent translocators important in directing the distribution of sphingolipids in cells.

The last minireview of the series by Thomas Kolter, Richard L. Proia, and Konrad Sandhoff provides a sophisticated look at the biosynthesis of glycosphingolipids focusing on the sialic acid-containing glycolipids called gangliosides. Although there are hundreds of different species of glycosphingolipids, each of which has a different carbohydrate chain, not all of the possible combinations of carbohydrates are used to form the glycosyl portion of these lipids. This is explained in the context of a combinatorial synthesis matrix where certain key enzymes channel intermediates toward families of related product glycosphingolipids. This model is surviving the test of gene knock-out mice, which display changes in sphingolipid content that follow its predictions. Furthermore, these knock-out animals are providing new insight into the roles of glycosphingolipids as information-containing molecules.

These minireviews illustrate the substantial advances that have been made in the understanding of sphingolipid biochemistry, while underscoring that much remains to be learned. As noted by Hakomori in a minireview a little over a decade ago (3), sphingolipids are both "modulators for transmembrane signaling and mediators for cellular interactions." As such, a full understanding of how sphingolipids are involved in cell regulation must take into account that perturbations in sphingolipids of one type may enhance or interfere with the actions of another (e.g. ceramide as a growth inhibitory, pro-apoptotic mediator versus its downstream metabolite sphingosine 1-phosphate, which is mitogenic and inhibits apoptosis). If one must analyze all of the sphingolipids of a cell to understand fully how this family of compounds regulates cell behavior, one could say we have entered the era of sphingolipidomics.

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