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Synthesis and degradation pathways, functions, and pathology of ceramides and epidermal acylceramides

Akio Kihara

Laboratory of Biochemistry, Faculty of Pharmaceutical Sciences, Hokkaido University, Kita 12-jo, Nishi 6-choume, Kita-ku, Sapporo 060-0812, Japan

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ABSTRACT

Ceramide (Cer) is a structural backbone of sphingolipids and is composed of a long-chain base and a fatty acid. Existence of a variety of Cer species, which differ in chain-length, hydroxylation status, and/or double bond number of either of their hydrophobic chains, has been reported. Ceramide is produced by Cer synthases. Mammals have six Cer synthases (CERS1–6), each of which exhibits characteristic substrate specificity toward acyl-CoAs with different chain-lengths. Knockout mice for each Cer synthase show corresponding, isozyme-specific phenotypes, revealing the functional differences of Cers with different chain-lengths. Cer diversity is especially prominent in epidermis. Changes in Cer levels, composition, and chain-lengths are associated with atopic dermatitis. Acylceramide (acyl-Cer) specifically exists in epidermis and plays an essential role in skin permeability barrier formation. Accordingly, defects in acyl-Cer synthesis cause the cutaneous disorder ichthyosis with accompanying severe skin barrier defects. Although the molecular mechanism by which acyl-Cer is generated was long unclear, most genes involved in its synthesis have been identified recently. In Cer degradation pathways, the long-chain base moiety of Cer is converted to acyl-CoA, which is then incorporated mainly into glycerophospholipids. This pathway generates the lipid mediator sphingosine 1-phosphate. This review will focus on recent advances in our understanding of the synthesis and degradation pathways, physiological functions, and pathology of Cers/acyl-Cers.

Contents

Abbreviations: ABC, ATP-binding cassette; acyl-Cer, acylceramide; ACS, acyl-CoA synthetase; ACSBG, acyl-CoA synthetase bubblegum; ACSF, acyl-CoA synthetase family; ACSL, acyl-CoA synthetase long-chain; ACSM, acyl-CoA synthetase medium-chain; ACSS, acyl-CoA synthetase short-chain; ACSVL, acyl-CoA synthetase very long-chain; ALDH, aldehyde dehydrogenase; ARCI, autosomal recessive congenital ichthyosis; BAT, brown adipose tissue; CE, cornified envelope; Cer, ceramide; Cer (Sph), ceramide containing sphingosine; CHO, aldehyde; CLE, corneocyte lipid envelope; COOH, carboxylic acid; dihydro-Cer, dihydroceramide; dihydro-Sph, dihydrosphingosine; dihydro-S1P, dihydrosphingosine 1-phosphate; ER, endoplasmic reticulum; FA, fatty acid; FAS, fatty acid synthase; GalCer, galactosylceramide; GlcCer, glucosylceramide; KDS, 3-ketodihydrosphingosine; KO, knockout; LacCer, lactosylceramide; LC, long-chain; LCB, long-chain base; LCBP, long-chain base 1-phosphate; LCFA, long-chain fatty acid; MC, medium-chain; 2-OH, 2-hydroxy; ω-OH, ω-hydroxy; 6-OH Sph, 6-hydroxysphingosine; PC, phosphatidylcholine; phyto-Cer, phytoceramide; phyto-Sph, phytosphingosine; phyto-S1P, phytosphingosine 1-phosphate; PUFA, polyunsaturated fatty acid; SLS, Sjögren-Larsson syndrome; SM, sphingomyelin; Sph, sphingosine; S1P, sphingosine 1-phosphate; SPT, serine palmitoyltransferase; STGD3, Stargardt disease type 3; tC16:1-CHO, *trans*-2-hexadecenal; tC16:1-COOH, *trans*-2-hexadecenoic acid; tC16:1-CoA, *trans*-2-hexadecenoyl-CoA; ULC, ultra-long-chain; ULCFA, ultra-long-chain fatty acid; VLC, very-long-chain; VLCFA, very-long-chain fatty acid; X-ALD, X-linked adrenoleukodystrophy.

E-mail address: kihara@pharm.hokudai.ac.jp.

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1. Introduction

Ceramide (Cer) is a hydrophobic backbone of sphingolipids. Sphingolipids exist in all eukaryotes, but not in prokaryotes, except for a limited number of bacteria species such as *Sphingomonas* [1]. Cer contains two hydrophobic chains, a long-chain base (LCB) and a fatty acid (FA), which are connected via an amide bond (Fig. 1A). Addition of a polar head group at the C1 hydroxyl group of the LCB portion of Cer endows the resulting sphingolipid with amphipathic properties. Characteristic *in vivo* head group types differ among organisms [2–5]. In mammals, it is either phosphocholine [in sphingomyelin (SM)] or sugar chains (in glycosphingolipids) [5,6] (Fig. 1A). Hundreds of glycosphingolipids differing in sugar classes and/or their linking modes exist. The sugar residues found in mammalian sphingolipids are glucose, galactose, *N*-acetylglucosamine, *N*-acetylgalactosamine, fucose, and sialic acid [5,7,8] (Fig. 1B). The simplest glycosphingolipids are glucosylceramide (GlcCer) and galactosylceramide (GalCer), which respectively contain a glucose or galactose residue linked to Cer via β-linkage (Fig. 1C). GlcCer and GalCer are collectively referred as cerebroside or mono-hexosylceramide. Sulfatide is a sulfated derivative of GalCer (Fig. 1B and C). Gangliosides refer to glycosphingolipids containing sialic acid(s). Other derivatives of GalCer include the ganglioside GM4 and the gala-series of glycosphingolipids (Fig. 1C). Addition of a galactose residue to GlcCer produces lactosylceramide (LacCer), which is a precursor of SM4, a sulfated derivative of LacCer, and numerous glycosphingolipid series (the ganglio-series, asialoganglio-series, isoganglio-series, globo-series, isoglobo-series, muco-series, lacto-series, and neolacto-series) (Fig. 1C).

Intracellular sphingolipids constitute ~10% of total lipids in mammals [9], although their levels vary among tissues. Sphingolipids are enriched in the plasma membrane, especially in the outer leaflet [10]. Sphingolipids account for 20–30% of total plasma membrane lipids [9]. SM is the most abundant sphingolipid species in mammals; SM levels are higher than even the sum of all glycosphingolipid levels in most tissues. In erythrocytes, in which the only cellular membrane is the plasma membrane, SM and glycosphingolipids account for 18% and 10% of total lipids, respectively [11].

Levels of glycerophospholipids, another lipid class constituting membranes, are much higher than those of sphingolipids [9]. Therefore, only glycerophospholipids may be sufficient to build biological membranes, as is the case for prokaryotes. Rather, the importance of sphingolipids may lie in their conferring specialized functions and/or properties to the membranes. During the course of evolution, eukaryotes produced a variety of cell types differing in functions: creation of a multiplicity of sphingolipids with individualized functions was likely necessary to fulfill this wide range of roles. Loss of sphingolipids by mutations in sphingolipid biosynthetic genes is lethal in all organisms examined to date [12–15], indicating that sphingolipids indeed possess specialized functions and cannot be substituted by glycerophospholipids.

Sphingolipids are involved in a variety of physiological functions including skin barrier formation, myelin maintenance, immunity, blood vessel stabilization, recognition of bacteria, bacterial toxins, and viruses, insulin resistance, spermatogenesis, and auditory sense formation [5,7, 16–22]. They fulfill these roles through modulating cellular events such as lipid microdomain formation, apoptosis, organelle and