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Review article

Analytical methods in sphingolipidomics: Quantitative and profiling approaches in food analysis

Núria Canela, Pol Herrero, Sílvia Mariné, Pedro Nadal, Maria Rosa Ras, Miguel Ángel Rodríguez, Lluís Arola*

Centre for Omic Sciences, Universitat Rovira i Virgili (COS-URV), Spain

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ABSTRACT

In recent years, sphingolipidomics has emerged as an interesting omic science that encompasses the study of the full sphingolipidome characterization, content, structure and activity in cells, tissues or organisms. Like other omics, it has the potential to impact biomarker discovery, drug development and systems biology knowledge. Concretely, dietary food sphingolipids have gained considerable importance due to their extensively reported bioactivity. Because of the complexity of this lipid family and their diversity among foods, powerful analytical methodologies are needed for their study. The analytical tools developed in the past have been improved with the enormous advances made in recent years in mass spectrometry (MS) and chromatography, which allow the convenient and sensitive identification and quantitation of sphingolipid classes and form the basis of current sphingolipidomics methodologies. In addition, novel hyphenated nuclear magnetic resonance (NMR) strategies, new ionization strategies, and MS imaging are outlined as promising technologies to shape the future of sphingolipid analyses. This review traces the analytical methods of sphingolipidomics in food analysis concerning sample extraction, chromatographic separation, the identification and quantification of sphingolipids by MS and their structural elucidation by NMR.

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Abbreviations: APCI, atmospheric pressure chemical ionization; APPI, atmospheric pressure photoionization; Cer, ceramide; DESI, desorption electrospray ionization; DHCer, dihydroceramide; DHSM, dihydrosphingomyelin; ESI, electrospray ionization; ELSD, evaporative light scattering detector; FTICR, Fourier transform ion cyclotron resonance; GalCer, galactosylceramide; GC, gas chromatography; GlcCer, glucosylceramide; GSLs, glycosphingolipids; HPLC, high performance liquid chromatography; HPTLC, high performance thin-layer chromatography; HSCCC, high-speed counter-current chromatography; IM-MS, ion mobility mass spectrometry; LacCer, lactosylceramide; LIF, laser-induced fluorescence; LC, liquid chromatography; LFA, long chain fatty acid; MS, mass spectrometry; MSI, mass spectrometry imaging; MALDI, matrix-assisted laser desorption ionization; NPLC, normal-phase liquid chromatography; PC, phosphatidylcholine; phosphoSPL, phosphosphingolipid; phytoCer, phytoceramide; phytoSPH, phytosphingosine; PLE, pressurized liquid extraction; QTRAP, quadrupole-ion trap mass spectrometer; qTOF, quadrupole-time of flight mass spectrometer; RPLC, reversed-phase liquid chromatography; SPL, sphingolipid; SPH, sphingosine; S1P, sphingosine-1-phosphate; SM, sphingomyelin; SPE, solid phase extraction; TLC, thin-layer chromatography; UHPLC, ultra-high performance liquid chromatography; UV, ultraviolet.

* Corresponding author.
E-mail address: lluis.arola@urv.cat (L. Arola).

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1. Introduction

Sphingolipids (SPLs) are a ubiquitous class of lipids that are found within all living organisms as important structural membrane constituents. In addition, they have significant biological functions as intracellular messengers that modulate cell growth, differentiation, apoptosis and the immune system [1–7]. The metabolic pathways of SPLs form complex networks of reactions that involve many enzymes and intermediate metabolites in the biosynthesis and degradation of individual SPLs [2–4,8–11]. There are currently over 600 known different SPL molecular species that have been identified to occur in nature, described in the Lipid Bank database (http://lipidbank.jp/index.html), but there may be thousands of SPLs yet to be discovered, as suggested by the Lipid Maps database (http://www.lipidmaps.org), which comprises more than 4000 structures and annotations of biologically relevant SPLs.

Different quantities of SPLs are present in a wide variety of foodstuffs. Although there is no evidence that dietary SPLs are essential for growth and development, the products derived from their digestion have been shown to be bioactive molecules that regulate the cell cycle, apoptosis, and inflammation among other functions [12–27].

In recent decades, research has focused on a comprehensive characterization of the individual species of this complex family of lipids, which has derived the study of sphingolipidomics, a new playing area of investigation that encompasses the identification, quantification and structure determination of all SPLs as well as the elucidation of their roles and metabolic interconnections.

This review aims to summarize milestone publications in the field of sphingolipidomics in food, focusing on the analytical techniques used for the identification, structure elucidation, and quantification of SPLs, as well as describing the connections of diet, SPL structure and SPL function. Particular attention will be dedicated to sample preparation and extraction, chromatographic separation, the identification and quantification of SPL species by mass spectrometry (MS) and structural elucidation by nuclear magnetic resonance (NMR) techniques.

1.1. Structure, classification and nomenclature

SPLs are amphipathic molecules consisting mainly of a polar head group and two nonpolar tails, the sphingoid base and a long-chain fatty acid. The general structure of the SPL species is detailed in Fig. 1. The core of an SPL is an organic aliphatic amino alcohol, termed a sphingoid base. The number of C-atoms from this amino alcohol varies from 12 to 22, with C18 compounds being the most common. Sphingoid bases are abbreviated similarly to fatty acids; the chain length and number of double bonds are denoted in the same manner, with the prefix "d" or "t" to designate di- and trihydroxylation, respectively. Mammalian organisms contain mainly sphingosine (SPH) (trans-4-sphingenine, d18:1D4), sphinganine (dihydrosphingosine, d18:0) and phytosphingosine (phytoSPH) (t18:0, 4-hydroxysphinganine), while plants and yeast contain principally sphinganine, phytoSPH, cis and trans isomers of 8-sphingenine (d18:1D8), 4,8-sphingadienine (d18:2D4,D8), and 4-hydroxy-8-sphingenine (t18:1D8) [28,29].

Ceramide (Cer) is the resulting molecule when a sphingoid base is acylated at the 2-amino position and linked via an amide bond to a long-chain fatty acid (C16–C24). Thus, N-acyl-SPH gives Cer, N-acyl-sphinganine gives dihydroceramide (DHCer), and 4-hydroxylated DHCer produces phytoceramide (phytoCer). Other positions have also been described to be hydroxylated or desaturated [28]. Additionally, different fatty acids can be bonded to the sphingoid base (e.g., a nonhydroxy fatty acid, α-hydroxy fatty acid or esterified ω-hydroxy fatty acid), resulting in different Cer subclasses [30]. Covalent linkage of the 1-hydroxyl group of a Cer to a phosphate or carbohydrate moiety generates the highly complex phosphosphingolipids (phosphoSPLs) and glycosphingolipids (GSLs), respectively. Moreover, GSLs are subdivided into cerebrosides, sulfatides, globosides and gangliosides, depending on the nature of the carbohydrate structure [9,31,32].

PhosphoSPLs, also known as sphingomyelins, result from an ester linkage between the primary hydroxyl group of Cer and a phosphocholine or phosphoethanolamine yielding sphingomyelin (SM), an abundant membrane lipid, or Cer phosphoethanolamine, respectively. Other phosphoSPLs have also been described, such as the inositol phosphorylCer derived from phytoCer in yeast [33], or the lyso forms of phosphoSPLs that include the sphingoid base without the amide linked to a long-chain fatty acid.

The most structurally diverse SPLs are GSLs, which are Cers with a wide variety of carbohydrate moieties linked to the 1-hydroxyl position through a β-glycosidic bond. There are over 10,000 potential GSL structures. The simplest neutral GSLs are cerebrosides, with a glucose, glucosylceramide (GlcCer), or galactose, galactosylceramide (GalCer) sugar moiety. GlcCer is found predominantly in neuronal cell membranes, and further additions of sulfate groups to cerebrosides give the acidic GSLs, sulfatides. GlcCer followed by the addition of galactose forms lactosylceramide (LacCer) (Galβ1-4Glcβ1Cer), which serves as the central structure of globosides, a more complex family of SPLs with oligosaccharide moiety. In addition, the sequence and position of sugar linkages in globosides further differentiates the molecules into globo-, isoglobo-, lacto-, neolacto-, and ganglioside series. One of the most differentiated series are gangliosides, acidic GLSs with at least three sugars, one of them sialic acid, also called N-acetylneuraminic acid (Neu5Ac) [34].

1.2. SPL activity

SPLs have been primarily classified as essential membrane components. However, their large structural heterogeneity reveals a high functional complexity, and it has been widely confirmed that SPLs and metabolic intermediates play important key roles in membrane integrity, cell adhesion and recognition, proliferation, apoptosis, differentiation, migration, cellular signal transduction, inflammation and immunity activity in many mammalian cells [1–7].

The function of SPLs depends on their acyl chain length and degree of saturation, as well as the nature of the head group substitution. The balance between levels of individual SPLs is critical in cellular functionality. For instance, SPH and sphingosine-1-phosphate (S1P) are interconverted by kinases and phosphatases.

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