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Review

Unraveling the role of the Target of Rapamycin signaling in sphingolipid metabolism

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ABSTRACT

Sphingolipids are important bioactive molecules that regulate basic aspects of cellular metabolism and physiology, including cell growth, adhesion, migration, senescence, apoptosis, endocytosis, and autophagy in yeast and higher eukaryotes. Since they have the ability to modulate the activation of several proteins and signaling pathways, variations in the relative levels of different sphingolipid species result in important changes in overall cellular functions and fate.

Sphingolipid metabolism and their route of synthesis are highly conserved from yeast to mammalian cells. Studies using the budding yeast *Saccharomyces cerevisiae* have served in many ways to foster our understanding of sphingolipid dynamics and their role in the regulation of cellular processes. In the past decade, studies in *S. cerevisiae* have unraveled a functional association between the Target of Rapamycin (TOR) pathway and sphingolipids, showing that both TOR Complex 1 (TORC1) and TOR Complex 2 (TORC2) branches control temporal and spatial aspects of sphingolipid metabolism in response to physiological and environmental cues. In this review, we report recent findings in this emerging and exciting link between the TOR pathway and sphingolipids and implications in human health and disease.

Contents

Abbreviations: AbA, Aureobasidin A; ABC, ATP-binding cassette; AMPK, AMP-activated protein kinase; ATG, Autophagy-related; ATP, Adenosine triphosphate; C1P, Ceramide-1-phosphate; CERS, Ceramide synthase; CK2, Casein kinase II; CLS, Chronological lifespan; CMA, Chaperone-mediated autophagy; COX, Cytochrome *c* oxidase; CWI, Cell wall integrity; DHS, Dihydrosphingosine; eIF2, Eukaryotic initiator factor 2; ER, Endoplasmic reticulum; ERK, Extracellular signal–regulated kinase; FAPP, Fas receptor-associated death domain; FKBP12, FK506-binding protein; GEF, Guanine exchange factor; GTP, Guanosine triphosphate; HEAT, Huntingtin Elongation factor 3 regulatory subunit A of PP2A TOR1; HOG, High osmolarity glycerol; HM, Hydrophobic motif; IGF-1, Insulin-like growth factor-1; IPC, Inositolphosphorylceramide; JNK, c-Jun NH_2-terminal kinase; LCB, Long-chain sphingoid base; LC3B, Microtubule-associated protein 1 light chain 3B; MAPK, Mitogen-activated protein kinase; MIPC, Mannosyl-inositol phosphorylceramide; $M(IP)_2C$, Mannosyl-diinositol phosphorylceramide; NCR, Nitrogen-catabolic repression; NPC, Niemann-Pick type C; PAK1, p21-activated kinase 1; PDGF, Platelet-derived growth factor; PDK1, 3-phosphoinositide-dependent kinase; PDS, Post-diauxic shift; PH, Pleckstrin homology; PHS, Phytosphingosine; PI3K, Phosphatidylinositol 3-kinase; PIP2, Phosphatidylinositol 4-5-biphosphate; PKA, Protein kinase A; PKC, Protein kinase C; PLC, Phospholipase C; PP1, Protein phosphatase 1; PP2A, Protein phosphatase 2A; RiBi, Ribosome biogenesis; RNA Pol, RNA polymerase; ROS, Reactive oxygen species; RTG, Retrograde; S1P, Sphingosine-1-phosphate; S1PR, Sphingosine-1-phosphate receptor; S6K, S6 kinase; SDK1, Sphingosine-dependent kinase 1; SGK, Serum- and glucocorticoid-induced protein kinase; SK, Sphingosine kinase; SMase, Sphingomyelinase; Sph, Sphingosine; SPT, Serine palmitoyltransferase; TFEB, Transcription factor EB; TNF-α, Tumor necrosis factor α; TOR, Target of Rapamycin; TORC1, TOR Complex 1; TORC2, TOR Complex 2; *Ts*, Temperature sensitive; UPR, Unfolded protein response; UV, Ultraviolet; 4E-BP1, Eukaryotic translation initiation factor 4E binding protein 1.

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1. Introduction

The cell membrane is regarded as a defined bilayer of phospholipids and other lipids that regulate the flux of metabolites between the external environment and the intracellular content [1]. The physicochemical nature of membrane lipids is the crucial basis for the lipid assembly into structural and functional membranes [2,3]. In particular, this physical organization allows the membrane to function as a permeability barrier and limits the occurrence of chemical reactions for the purposes of maintenance of cellular metabolism and biochemical energetic efficiency to a particular cellular microenvironment, leading to chemical compartmentalization [1,3]. The conjugation of lipids with proteins into supramolecular complexes with distinct properties and functionality within the membrane is known to be paramount for many biological processes, namely, cellular membrane biosynthesis, cell homeostasis, and regulation of membrane biophysics (fluidity, thickness, lipid phase) in response to environmental and physiological cues [4]. In addition to structural and adhesive roles in the cell, lipids function as bioactive second messenger molecules with the ability to transduce signals from a variety of stimuli through the activation/inactivation of cell signaling pathways which in turn control basic aspects of cellular metabolism and physiology, namely, cell growth, proliferation, inflammation, migration, and even cell fate [5–8].

A class of lipids that has come to the foreground of research area in the past decades is sphingolipids. They are important structural components of cell membranes [9,10] found in essentially all animals, plants, and fungi, as well as some prokaryotic organisms belonging to genera *Sphingomonas*, *Sphingobacterium*, and *Bacteroides* [11]. Sphingolipids are mostly found on the outer leaflet of the plasma membrane in lipid domains [8] or in conjugation with proteins (combinations of glycosphingolipids, cholesterol, and protein receptors organized in glycolipoprotein microdomains termed lipid rafts) [12,13], although they are also present at membranes of different organelles at variable ratio. Furthermore, they are major constituents of lipoproteins [14].

The potential of sphingolipids as bioactive lipids was firstly recognized when Hannun et al. [15] and Okazaki et al. [16] showed that sphingosine (Sph) inhibits protein kinase C (PKC) in human platelets and vitamin D3 promotes sphingomyelin hydrolysis to generate ceramide, which then induces differentiation in HL-60 cells, respectively. Currently, Sph, ceramide, and sphingosine-1-phosphate (S1P) are considered core metabolites in sphingolipid metabolism because they regulate a vast number of cellular processes including cell growth, adhesion, migration, senescence, inflammation, apoptosis, endocytosis, and autophagy, from yeast to higher eukaryotes [9,17–19]. Since they have the ability to modulate a variety of effectors and receptors, changes in the relative levels of bioactive sphingolipids have major effects on cellular functions and fate [8].

More recently, a crosstalk between sphingolipid metabolism and the Target of Rapamycin (TOR) signaling pathway has been unraveled. Most studies have been performed using the budding yeast *Saccharomyces cerevisiae* as a biological model system. In yeast, TOR signaling is dictated by two phosphatidylinositol 3-kinase (PI3K)-like Ser/Thr kinases encoded by the *TOR1* and *TOR2* genes, which form two distinct protein complexes with specific subunit compositions [20–23]. The TOR Complex 1 (TORC1) is a nutrient and rapamycin-sensitive pathway that regulates ribosome biogenesis and translation, nutrient sensing and acquisition, autophagy and temporal aspects of cell growth and proliferation [20,23,24]. In addition, TORC1 regulates sphingolipid metabolism by inhibiting the synthesis of complex sphingolipids [25]. The TOR Complex 2 (TORC2) branch, on the other hand, is involved in cell cycle regulation and cytoskeleton dynamics [26] and it was recently implicated in the modulation of the *de novo* sphingolipid biosynthetic pathway in a TORC1-independent manner [27,28].

This review describes and integrates recent advances in understanding the interplay between sphingolipid metabolism and TOR signaling, its role in the regulation of cellular physiology and metabolism, and its potential in therapeutics. Previous reviews should be consulted for topics that are not extensively described here and for more detailed coverage of areas only briefly mentioned in this review [8,29–32].

2. Sphingolipids structure and metabolism

From a structural point of view, sphingolipids have an amphipathic nature and are composed by a long-chain sphingoid base (LCB) (Sph in mammals and phytosphingosine (PHS) and dihydrosphingosine (DHS) in yeast), with the 2-amino group amide-linked to a fatty acid, thereby forming the core unit (ceramide) to which polar head groups are added to form different types of sphingolipids. The nature of the fatty acid (carbon length, degree of unsaturation, and hydroxylation) along with other modifications of the LCBs and the polar head group define the vast family of sphingolipids [8,33].