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Review

Sphingolipids and expression regulation of genes in cancer

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ABSTRACT

Sphingolipids including glycosphingolipids have myriad effects on cell functions and affect cancer in aspects of tumorigenesis, metastasis and tumor response to treatments. Bioactive ones like ceramide, sphingosine 1-phosphate and globotriaosylceramide initiate and process cellular signaling to alter cell behaviors immediately responding to oncogenic stress or treatment challenges. Recent studies pinpoint that sphingolipid-mediated gene expression has long and profound impacts on cancer cells, and these play crucial roles in tumor progression and in treatment outcome. More than 10 sphingolipids and glycosphingolipids selectively mediate expressions of approximately 50 genes including c-myc, p21, c-fos, telomerase reverse transcriptase, caspase-9, Bcl-x, cyclooxygenase-2, matrix metalloproteinases, integrins, Oct-4, glucosylceramide synthase and multidrug-resistant gene 1. By diverse functions of these genes, sphingolipids enduringly affect cellular processes of mitosis, apoptosis, migration, stemness of cancer stem cells and cellular resistance to therapies. Mechanistic studies indicate that sphingolipids regulate particular gene expression by modulating phosphorylation and acetylation of proteins that serve as transcription factors (β-catenin, Sp1), repressor of transcription (histone H3), and regulators (SRp30a) in RNA splicing. Disclosing molecular mechanisms by which sphingolipids selectively regulate particular gene expression, instead of other relevant ones, requires understanding of the exact roles of individual lipid instead of a group, the signaling pathways that are implicated in and interaction with proteins or other lipids in details. These studies not only expand our knowledge of sphingolipids, but can also suggest novel targets for cancer treatments.

Contents

Abbreviations: C1P, ceramide 1-phosphate; CAPP, ceramide-activated protein phosphatase; CerK, ceramide kinase; CerS, ceramide synthase; CERT, ceramide transfer protein; COX-2, cyclooxygenase-2; CPPase, ceramide phosphate phosphatase; CSC, cancer stem cell; ES, embryo stem cell; FAPP2, four-phosphate adaptor protein 2; Gb3, globotriaosylceramide; Gb5, globopentosylceramide; GCase, glucosylceramide β-glucosidase; GCS, glucosylceramide synthase; GEM, GSL-enriched microdomain; GSL, glycosphingolipid; HDAC, histone deacetylase; hTERT, human telomerase reverse transcriptase; MAPK, mitogen-activated protein kinase; MDR1, multidrug resistance gene 1; MMP, matrix metalloproteinase; MSGb5, monosialyl globopentosylceramide; PKC, protein kinase C; S1P, sphingosine 1-phosphate; SMase, sphingomyelinase; siRNA, small interfering RNA; SphK, sphingosine kinase; SPPase, sphingosine phosphate phosphatase; SSEA, stage specific embryonic antigen; TNF-α, tumor necrosis factor α; uPA, urokinase plasminogen activator.

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1. Introduction

Sphingolipids are a class of lipids derived from the aliphatic amino alcohol sphingosine and are present mainly in eukaryote membranes [1,2]. All sphingolipids consist of sphingoid base (phytoceramide or sphinganine) linked to a fatty acid, and ceramide is the simplest one in structure (Fig. 1). Diverse sphingolipids result from different hydrophobic sphingoid bases combined with fatty acids; both vary in chain length and degrees of saturation and hydroxylation. Complex sphingolipids possess additional hydrophilic regions, such as phosphate, phosphorylcholine and sugar moieties, attached to sphingoid base in the R position (Fig. 1) [3,4]. Glucose or galactose replaces "H" in the R position, attached to the 1-hydroxy group of ceramide, and generates the simple glycosphingolipid, glucosylceramide by UDP-glucose:ceramide glucosyltransferase (UGCG; glucosylceramide synthase, GCS) or galactosylceramide by UDP-galacose:ceramide galacosyltransferase (CGT; galactosylceramide synthase), respectively. From these, more complex glycosphingolipids, such as lactosylceramide, globotriaosylceramide (Gb3) and monosialoganglioside GM3, can be synthesized by incorporation of additional glycose subunits in the Golgi [1,5] (Fig. 2). Biosynthesis of sphingolipids is intertwined and regulated by two different enzymes, respectively. Ceramide is in the centre of metabolism, and is predominantly synthesized by the *de novo* pathway from serine and palmitoyl-CoA in the endoplasmic reticulum (ER) and in the ER-associated membrane. Ceramide can be produced from sphingomyelin breakdown catalyzed by sphingomylinases (SMase) in the inner leaflet of plasma membrane (neutral SMase) or in the outer leaflet of lysosome membrane (acid SMase) [1,6]. The generic "ceramide" is a family of more than 50 distinct molecular species that are synthesized by 6 ceramide synthases (CerS1–6 or longevity assurance genes, LASS1–6) that catalyze dihydro-sphingosine acylation in the *de novo* biosynthetic pathway [7,8]. CerS1–6 selectively utilize variant acyl-CoA (CerS1, C_{18}; CerS2, C_{22-24}; CerS3, C_{16-26}; CerS5, C_{18}/C_{20}; CerS5, C_{16}; CerS6, C_{14-16}) to produce different ceramides. However, C_{18}-ceramide is the major one. Ceramide can be metabolized to diverse derivatives like glucosylceramide, ceramide 1-phosphate, 1-O-acylceramide and sphingosine by respective kinases and synthases [9,10] (Fig. 2).

Sphingolipids are important biological molecules and highly associated with several diseases including cancer. Besides providing structural integrity in cell membranes, sphingolipids play crucial roles in signal transduction and gene regulation. Through these, sphingolipids actively modulate various aspects of cells including apoptosis, proliferation, endocytosis, transport, migration, senescence, and inflammation [1]. These sphingolipid-modulated processes, in turn are crucial in tumorigenesis, cancer progression, and efficacies of cancer therapies [11–14]. The balance between different types of sphingolipids can make cells undergo

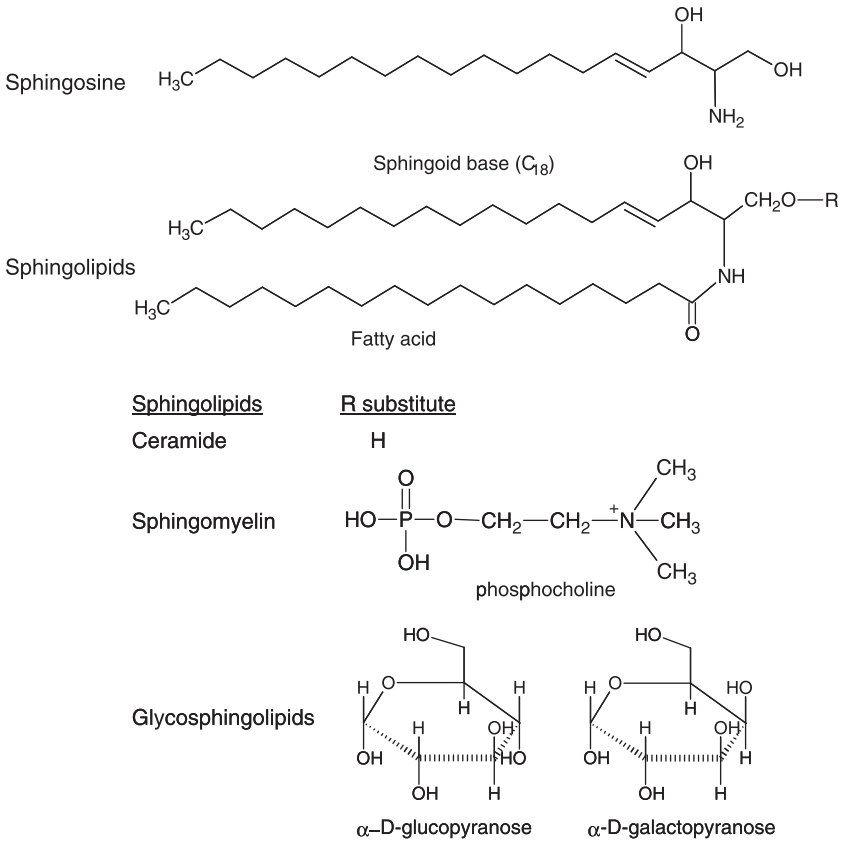

Fig. 1. Basic structures and classification of sphingolipids. In mammals, the prevalent sphingoid base is sphingosine which has a chain length of 18 carbon atoms and *E*-double bond between C_4 and C_5.