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Review

Sphingosine kinases, sphingosine 1-phosphate, apoptosis and diseases

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Abstract

Sphingolipids are ubiquitous components of cell membranes and their metabolites ceramide (Cer), sphingosine (Sph), and sphingosine-1-phosphate (S1P) have important physiological functions, including regulation of cell growth and survival. Cer and Sph are associated with growth arrest and apoptosis. Many stress stimuli increase levels of Cer and Sph, whereas suppression of apoptosis is associated with increased intracellular levels of S1P. In addition, extracellular/secreted S1P regulates cellular processes by binding to five specific G protein coupled-receptors (GPCRs). S1P is generated by phosphorylation of Sph catalyzed by two isoforms of sphingosine kinases (SphK), type 1 and type 2, which are critical regulators of the “sphingolipid rheostat”, producing pro-survival S1P and decreasing levels of pro-apoptotic Sph. Since sphingolipid metabolism is often dysregulated in many diseases, targeting SphKs is potentially clinically relevant. Here we review the growing recent literature on the regulation and the roles of SphKs and S1P in apoptosis and diseases.

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Keywords: Sphingosine kinase; Sphingosine-1-phosphate; Apoptosis; Cancer; Allergy; Asthma; Development

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1. Synthesis and metabolism of sphingolipids

De novo synthesis of sphingolipids is initiated at the cytoplasmic face of the endoplasmic reticulum (ER) by the condensation of serine and palmitate to produce 3-keto-sphinganine catalyzed by serine palmitoyl transferase (Fig. 1) [1]. In two rapid enzymatic reactions, 3-keto-sphinganine is reduced to sphinganine (dihydro-sphingosine, DHS) by 3-keto-sphinganine reductase in a NADH-dependent reaction. DHS is then N-acylated by dihydroceramide synthase using various fatty acyl CoAs to form dihydroceramide (DHCer) which is converted to Cer by a desaturase. The insertion of the trans 4,5-double bond into Cer by the desaturase is an important reaction because Cer, but not DHCer, mediates apoptosis [2]. Cer (and DHCer) is translocated from the ER to the Golgi apparatus in a non-vesicular transport manner by CERT [3], a cytoplasmic protein with a phosphatidylinositol-4-phosphate-binding domain and a putative catalytic domain for lipid transfer. Once in the Golgi, Cer and DHCer can be used to form sphingomyelin (SM) and dihydrosphingomyelin (DH-SM), respectively, by sphingomyelin synthase on the lumenal side of the Golgi, or to glucosylceramide (GlcCer) and dihydroglucosylceramide (DH-GlcCer) on the cytosolic surface of the Golgi [4]. After translocation into the Golgi lumen, GlcCers are further converted to lactosylceramides and more complex glycosphingolipids [5]. The sphingoid base sphingosine (Sph) is not produced de novo and is only formed from Cer by ceramidase-catalyzed hydrolysis. Sph can also arise during degradation of plasma membrane glycosphingolipids and SM in the endocytic recycling pathway.

Sph and DHS can be phosphorylated by SphKs to form S1P and dihydro-S1P, which are both substrates for specific S1P phosphatases that reside in the ER. Yeast SphKs, the products of two genes, LCB4 and LCB5, are required for the efficient utilization of exogenously added sphingoid bases [6]. LCB4 is principally required for this process and is found on the cytoplasmic face of internal membranes, including the ER, Golgi and probably endosomes [7]. There are also two mammalian isoforms, SphK1 and SphK2, that differ in sequence, catalytic properties, localization, and in their functions [8]. SphK1 has pro-survival functions and is mainly a cytosolic protein, whereas SphK2 is a putative BH3-only protein, inhibits cell growth and enhances apoptosis [9]. Recent results from our lab demonstrated that SphK1 decreases and SphK2 increases ceramide levels in HEK 293 cells.

From a mechanistic point of view, our results support the notion that SphK2, similar to yeast LCB4 [10], might play a role in the sphingosine salvage pathway of mammalian cells, acting in concert with S1P phosphatase (SPP-1) to convert S1P back to sphingosine and then to ceramide in the ER. Ceramide generated in the ER has been linked to increased Ca^{2+} release, leading to apoptosis. Moreover, cytosolic S1P formed by SphK1 inhibits *de novo* ceramide biosynthesis as a cellular sensing mechanism to minimize unneeded biosynthesis of ceramide [8]. S1P can also be further degraded by S1P lyase (SPL), an integral ER membrane protein facing the cytoplasm [11], which yields the cleavage products, hexadecenal and ethanolamine phosphate, the major exit route of metabolism of sphingolipids (Fig. 1).

2. The sphingosine kinase family

SphKs are an evolutionary conserved lipid kinase family that contains five conserved domains. SphK1 was originally purified to homogeneity from rat kidney as a 49-kDa protein. Based on tryptic peptides, murine SphK1 was then cloned [12]. Two isoforms, termed SphK1α and SphK1β, with 42.2 and 43.2 kDa predicted molecular mass were identified which only differed in a few amino acids at their N-termini, suggesting that they were derived by alternative splicing. SphK1 has a broad tissue distribution, with higher levels in brain, heart, lung and spleen. It has no trans-membrane domains, rather it has three calcium/calmodulin-binding consensus sequences and several potential protein kinase phosphorylation sites [12]. Indeed, the lack of a hydrophobic domain or an identifiable signal peptide is consistent with its predominant cytosolic localization [12]. SphK1 displays specificity for the natural trans isomer of D-*erythro*-sphingosine. Several SphK inhibitors have been discovered including threo-dihydrosphingosine (DHS), *N*,*N*-dimethylsphingosine (DMS) [13], fungal-derived inhibitors [14], and 2-(*p*-hydroxyanilino)-4-(*p*-chlorophenyl) thiazole [15], which have been widely used to implicate SphK and S1P formation in many biological processes. Yet, most of these results must be interpreted with caution as all of the known inhibitors block both SphK1 and SphK2.

Based on homology to SphK1, a second isoform, SphK2, was cloned and characterized from mouse and human [16]. SphK2 shares five conserved domains with SphK1 (about 80% similarity and 50% identity) but has an additional 200 amino acids, making it a predicted 68 kDa protein. SphKs have a conserved ATP-binding motif ($SGDGX_{(17-21)}K(R)$) found in diacylglycerol kinases [16] that has some similarity to the highly conserved glycine-rich loop involved in binding ATP in the catalytic site of many protein kinases [17]. Unlike SphK1, SphK2 has a somewhat lower substrate specificity and also can phosphorylate FTY720, an immunosuppressive drug currently in Phase 3 clinical trials for kidney transplantation and multiple sclerosis treatment [18–20]. Although SphK2 has four

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