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Review

Sphingosine 1-phosphate and sphingosine kinases in health and disease: Recent advances

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ABSTRACT

Sphingosine kinases (isoforms SK1 and SK2) catalyse the formation of a bioactive lipid, sphingosine 1-phosphate (S1P). S1P is a well-established ligand of a family of five S1P-specific G protein coupled receptors but also has intracellular signalling roles. There is substantial evidence to support a role for sphingosine kinases and S1P in health and disease. This review summarises recent advances in the area in relation to receptor-mediated signalling by S1P and novel intracellular targets of this lipid. New evidence for a role of each sphingosine kinase isoform in cancer, the cardiovascular system, central nervous system, inflammation and diabetes is discussed. There is continued research to develop isoform selective SK inhibitors, summarised here. Analysis of the crystal structure of SK1 with the SK1-selective inhibitor, PF-543, is used to identify residues that could be exploited to improve selectivity in SK inhibitor development for future therapeutic application.

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1. Introduction

Sphingosine 1-phosphate (S1P) is a pleiotropic lipid that has a wide variety of physiological and pathophysiological roles [1–3]. It is one of a multitude of sphingolipids and glycosphingolipids that are readily synthesised and/or inter-converted in a spatial and temporal manner in response to environmental change and stimuli [4,5]. These, in turn, are integrated with the wider cellular metabolic network [6]. S1P is synthesised by two distinct isoforms of sphingosine kinase (SK1 and SK2) and elicits cellular responses through well-established receptor-mediated mechanisms and by affecting a number of intracellular target proteins. In general, the effects of S1P (proliferation, migration, cell

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survival *etc.*) are largely opposed to those of ceramide (apoptosis, senescence, growth arrest *etc.*) and the concept of the 'sphingolipid rheostat' was proposed, whereby the inter-conversion of ceramide, *via* sphingosine, to intracellular S1P contributes to cellular fate [7,8]. However, it is now apparent that the situation is far more complex and a more advanced model incorporates the autocrine and paracrine effects of S1P (acting *via* its receptors), amplification loops whereby S1P activates pathways that enhance its own formation and signalling as well as the intracellular effects of S1P, mediated by its target proteins [4,9]. Furthermore, it is recognised that ceramides of differing acyl chain and sphingoid base composition may have distinct roles [10] and act independently of S1P in a membrane- and target-specific manner. For example, ceramide-enriched microdomains affect mitochondrial function [11] whereas ceramide-activated target molecules include protein phosphatases (PP1, PP2A and PP2C), protein kinase Cζ and AKT [12]. Moreover, ceramides with different fatty acid chain length can exert opposing cellular effects in a given cell type (*e.g.* C16 ceramide promotes proliferation whereas C18 ceramide mediates cell death) [13]. Recent advances in lipidomics and cell surface analysis of lipids is likely to progress our understanding here [14,15] but will need to be coupled with the development of biosensors for S1P and for specific molecular species of ceramide. Importantly, other sphingolipids (such as dihydroceramides) and sphingolipid derivatives (such as *trans*-2-hexadecenal, a breakdown product of the irreversible cleavage of S1P by S1P lyase [16]) that were previously believed to be biologically inactive are also now proposed signalling molecules, which require further investigation [17,18] (Fig. 1). However, the focus of this article is on some of the more recent advances in relation to S1P and, particularly, the function of SK1 and SK2 in health and disease.

2. Sphingosine kinases

S1P is produced by the ATP-dependent phosphorylation of sphingosine, catalysed by SK1 and SK2. Recent comprehensive reviews on these enzymes are available [19,20]. Therefore, only key features are included here. The two enzymes exhibit partial redundancy since $Sk1^{-/-}$ or $Sk2^{-/-}$ mice are phenotypically normal whereas elimination of both genes is embryonic lethal due to neurological and vascular defects [21]. SK1 and SK2 contain five conserved domains (C1–C5), with the catalytic domain formed within C1–C3 and the ATP binding domain located in the C2 region [22]. These well characterised enzymes, which differ in their biochemical properties, sub-cellular distribution and physiological roles, are regulated in a spatial and temporal manner by post-translational modification and interaction with specific proteins and lipids (for review see [4]). For example, while both enzymes can be phosphorylated by extracellular signal-regulated kinases (ERK-1/2) in response to agonists [23,24], the activation of SK1 is more pronounced and coupled with its translocation, in a calcium and integrin-binding protein 1 (CIB1)-dependent manner [25], from the cytoplasm to the plasma membrane (where S1P could be available for export). In contrast, SK2, which can localise to the endoplasmic reticulum or is associated with mitochondria [26], also contains both nuclear localisation and nuclear export sequences and shuttles in and out of the nucleus, being exported upon phosphorylation by protein kinase D [27]. S1P generated in the nucleus has the potential to regulate gene expression (see Section 4 Intracellular targets of S1P and novel roles of sphingosine kinases).

Both enzymes are expressed as multiple spliced variant forms, although the functional significance of this is yet to be fully established. In general, studies of SK employ the shortest isoforms (SK1a, NM_001142601, 384 amino acids and SK2a, AF245447, 654 amino acids) and it should be borne in mind that these might not necessarily be the most physiologically relevant forms in a particular cell system studied. Interestingly, the 36 amino acid N-terminally extended SK2b isoform has higher catalytic activity, using FTY720 and sphingosine as substrates, compared with the SK2a isoform, indicating that the N terminus may contribute to a conformation with improved catalytic activity [28]. Moreover, SK1b (which contains an additional N-terminal 86 amino-acids) is more resistant to removal from cells *via* the proteasome (compared with SK1a). For example, the treatment of androgen-sensitive LNCaP cells with a catalytic inhibitor of SK1, SKi (SKI-II, 2-(*p*-hydroxyanilino)-4-(*p*-chlorophenyl)thiazole) [29], induced the proteasomal degradation of SK1a and SK1b, accompanied by a reduction in S1P and an increase in sphingosine and C22:0 and C24:0

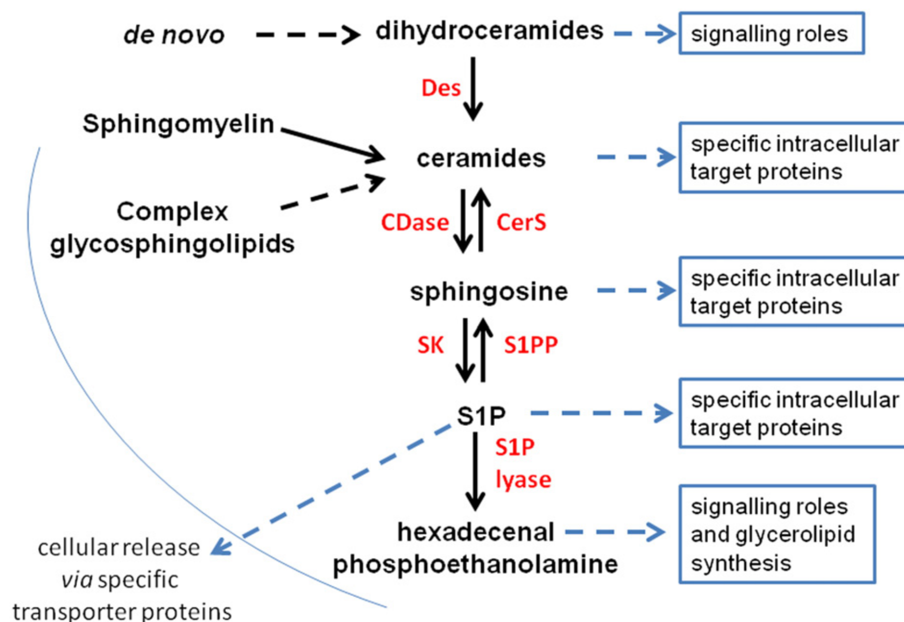

Fig. 1. Sphingolipid metabolic pathways. Ceramides can be derived from *de novo* synthesis, *via* dihydroceramides, or from hydrolysis of sphingomyelin or breakdown of glycosphingolipids. Ceramide, sphingosine and S1P are interconverted and S1P irreversibly cleaved to hexadecenal and phosphoethanolamine. The biological activities (blue dotted arrows) of the various sphingolipids are summarised. Enzymes, which occur as multiple isoforms, are shown in red (Des, dihydroceramide desaturase; CDase, ceramidase; CerS, ceramide synthase; SK, sphingosine kinase; S1PP, S1P phosphatase) and have specific subcellular localisations (not shown).

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