Cellular Signalling 28 (2016) 1349–1363

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Recent advances in the development of sphingosine kinase inhibitors

Melissa R. Pitman [a], Maurizio Costabile [a,b], Stuart M. Pitson [a,*]

[a] Centre for Cancer Biology, University of South Australia and SA Pathology, Frome Road, Adelaide, SA 5000, Australia
[b] School of Pharmacy and Medical Sciences, Division of Health Sciences, University of South Australia, Adelaide, SA 5001, Australia

ARTICLE INFO

Article history:
Received 4 May 2016
Received in revised form 9 June 2016
Accepted 9 June 2016
Available online 11 June 2016

Keywords:
Sphingosine kinase 1
Sphingosine kinase 2
Sphingosine
Sphingosine-1-phosphate
Ceramide

ABSTRACT

Sphingosine kinase (SK) 1 and 2 are lipid kinases that catalyse the formation of sphingosine 1-phosphate (S1P), a potent signalling molecule with a wide array of cellular effects. SK1 and 2 have been shown to be up-regulated in tumours and their genetic ablation or inhibition has been shown to slow tumour growth as well as sensitise cancer cells to chemotherapeutics. The SKs have been extensively studied, with a plethora of inhibitors developed that target the sphingosine-binding pocket of the enzyme, some with nanomolar affinities. Recently, inhibitors targeting the ATP pocket of SK have also been described. Here we discuss the development of these new small molecule SK inhibitors, summarise the recent discovery of off-targets effects of many current SK inhibitors, and provide an overview of the usefulness of these inhibitors as *in vitro* tools and therapeutic agents.

Contents

Abbreviations: AML, acute myeloid leukaemia; CERK, ceramide kinase; Des1, dihydroceramide desaturase; EGF, epidermal growth factor; ER, endoplasmic reticulum; GPCRs, G protein-coupled receptors; LPP, lipid phosphate phosphatase; SPP, sphingosine phosphate phosphatase SK; sphingosine kinase, S1P phosphatase; S1P, sphingosine 1-phosphate.

* Corresponding author.
E-mail address: stuart.pitson@unisa.edu.au (S.M. Pitson).

http://dx.doi.org/10.1016/j.cellsig.2016.06.007
0898-6568/

1. Introduction

Sphingolipids such as ceramide, sphingosine and sphingosine 1-phosphate (S1P) (Fig. 1), are important cell signalling molecules regulating a plethora of important cellular processes [1]. S1P functions through both its binding to a family of five S1P-specific G protein-coupled receptors (GPCRs; named $S1P_{1-5}$) [2], as well as modulating the actions of a number of intracellular proteins [3–6]. S1P, *via* its GPCRs, coordinates immune cell trafficking and vascular integrity, and appears to combine with its intracellular targets to elicit pro-proliferative, pro-survival signalling [7]. Many ceramide species, however, have opposing roles to S1P and promote apoptosis through multiple mechanisms, including altering intracellular membrane dynamics and modulation of protein phosphatase (PP1, PP2A, PP2C) and protein kinase activities (reviewed in [8]). In some contexts, sphingosine can also promote pro-apoptotic signalling *via* binding and facilitating inhibition of the pro-survival 14-3-3 proteins [9,10]. This cellular sphingolipid rheostat, regulated by a network of dynamic metabolic pathways (Fig. 1) [1,11], controls the levels of pro-survival S1P and pro-apoptotic ceramides, the balance of which can be a major determinant of cell fate.

As the only enzymes with the ability to phosphorylate sphingosine to produce S1P, the sphingosine kinases (SKs) are key players in the regulation of the cellular rheostat. There are two mammalian SKs; SK1 and SK2 which both utilize sphingosine to generate S1P. SK2, however, displays a broader substrate specificity, and can phosphorylate phytosphingosine and a number of artificial substrates that are not substrates for SK1 [12]. While the SKs appear to share some common roles in the cell, they also have different functions which appear governed in-part by differing subcellular localisation. For example, SK1 resides predominantly in the cytoplasm and is translocated to the plasma membrane upon cell stimulation [13], while SK2 is primarily associated with various cellular organelles [12], including the endoplasmic reticulum (ER) [14] and mitochondria [15] where it can regulate apoptosis [14], and the nucleus where it has a demonstrated role in epigenetic regulation [16].

Elevated cellular SK1 and S1P can enhance cell survival, proliferation and migration, [17], promote angiogenesis [18] and contribute to altered cancer cell metabolism [19]. Thus, SK and S1P contribute to many of the hallmarks of cancer [20], and perhaps for this reason, cancer cells often appear to develop a "non-oncogene addiction" to SK1 [21,22].

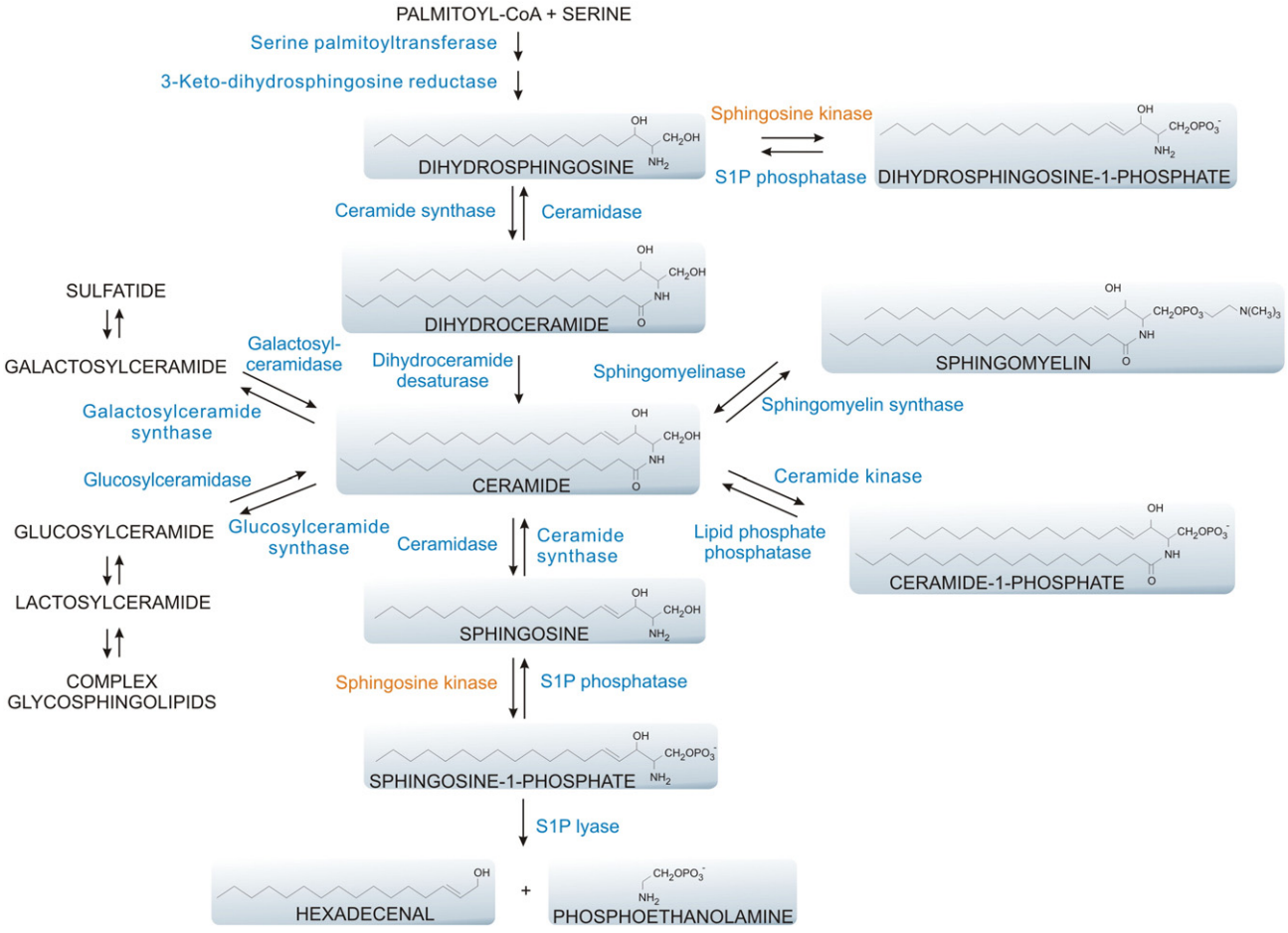

Fig. 1. Sphingolipid biosynthesis and degradation pathways. Sphingolipid structures and key metabolic enzymes responsible for the formation and degradation are displayed. All enzymes are labelled in blue with sphingosine kinase labelled in orange. C18 (dihydro)ceramide is used as a representative image, however N-acylation of dihydrosphingosine by ceramide synthase enzymes results in a range of dihydroceramide species, dependent on the fatty acyl CoA employed.