BJP British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2012.01898.x
www.brjpharmacol.org

COMMENTARY

Sphingosine kinase: a key to solving the 'French Paradox'?

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Keywords
resveratrol; sphingosine kinase; ceramide; sphingosine-1-phosphate; cancer

Received
26 January 2012
Accepted
8 February 2012

A host of beneficial effects have been attributed to the red wine polyphenol, resveratrol. Foremost, among these are its anti-cancer properties. Yet, the mechanism by which resveratrol achieves these effects are unknown. In this issueof the *BJP*, Lim *et al*. report that resveratrol and its higher order oligomers inhibit sphingosine kinase 1 (SphK1). SphK1 is a key regulator of sphingolipid metabolism and alterations of this key metabolic pathway have been linked to many hyperproliferative diseases. This study identifies a target for the action of resveratrol and its higher order oligomers and opens the door to evaluation of SphK1 as a target for chemo-prevention of cancer.

LINKED ARTICLE
This article is a commentary on Lim *et al.*, pp. 1605–1616 of this issue. To view this paper visit http://dx.doi.org/10.1111/j.1476-5381.2012.01862.x

Abbreviations
DAGK, diacylglycerol kinase; EGCG, epigallocatechin gallate; S1P, sphingosine-1-phosphate; SphK1, sphingosine kinase 1; SphK2, sphingosine kinase 2

Red wine polyphenols, such as resveratrol, gained notoriety in the 1990s when they were posited as an explanation to the 'French Paradox'. Subsequent studies revealed a host of positive effects including cardio-protective, lifespan prolonging and anti-cancer roles. Initially, these effects were attributed to the antioxidant properties of the polyphenols, but soon it was realized that other mechanisms must be responsible for the anti-cancer effects (Baur *et al*., 2006). In this issue of the *British Journal of Pharmacology*, Lim *et al*. (2012) describe a novel role for resveratrol and its higher order oligomers in inhibition of sphingosine kinase 1 (SphK1).

SphK1 is an oncogenic lipid kinase that generates pro-mitogenic sphingosine-1-phosphate (S1P) from the substrate D-erythro-sphingosine (Sph). Sphingosine itself is generated by the de-acylation of ceramide a well-documented pro-apoptotic sphingolipid (Ponnusamy *et al*., 2010). S1P is a potent first and second messenger molecule that has both intracellular and extracellular actions primarily through activation of pro-mitogenic and pro-survival signalling cascades (MAP kinase and PI3 kinase cascades respectively; Pyne and Pyne, 2011). Likewise, ceramide is a potent inducer of apoptotic signalling and is generated in response to many chemotherapeutic agents. Thus, SphK1, like its isoenzyme SphK2, is precariously perched at the balance point between pro-growth and pro-death signalling in the cell. The balance of ceramide and S1P has been termed the 'sphingolipid rheostat' and alteration of this balance is a key determinant of cellular fate. Perturbation of the 'sphingolipid rheostat', favouring the production of S1P at the expense of ceramide, is a core feature of many hyperproliferative diseases including cancer and inflammatory diseases.

Recent studies have added additional layers of complexity to the 'sphingolipid rheostat' concept. The demonstration that ceramide species of different acyl chain lengths have distinct and opposing roles in regulation of apoptotic signalling has initiated a dogmatic shift in the sphingolipid field (Hartmann *et al*., 2012). Similarly, a better understanding of the metabolic breakdown of S1P has demonstrated that S1P levels are not static (Loh *et al*., 2011). Thus, we can no longer consider only the steady-state levels of ceramide and S1P when evaluating sphingolipid metabolic enzyme inhibitors. Together, these studies highlight the complexity and interconnectedness of the sphingolipid metabolites and reinforce the idea that the sphingolipid metabolic pathway is a rich source of new therapeutic targets.

Because of its unique role in the cell, SphK1 has been recognized, for years, as a potential target for the development of anti-cancer and anti-inflammatory strategies and this

has been borne out in numerous studies (Pyne *et al.*, 2011). Numerous inhibitors of SphK have been identified including substrate analogues (i.e. dimethylsphingosine) and small molecule inhibitors. Recent advances have seen the identification of isotype specific inhibitors and inhibition of either SphK1 or SphK2 seems to have the potential for future therapeutic development.

Studies such as those of Lim *et al.* (2012) have several important outcomes. First and foremost, they identify a novel target for the actions of resveratrol and its higher order oligomers. The observation that resveratrol dimers are more potent than resveratrol itself is intriguing. Given that these authors have also recently identified SphK as a minimal dimer, it is tempting to speculate that the larger resveratrol oligomers are binding to multiple SphK molecules simultaneously. Identification of the residues of SphK required for resveratrol binding could therefore serve as a way to gain important knowledge about the oligomeric structure of SphK. Further studies of the oligomerization of SphK1 and whether it can hetero-oligomerize with SphK2 could prove useful in explaining the intracellular localization of both SphK isoenzymes.

Secondly, considering the role of SphK in regulation of the 'sphingolipid rheostat' and the correlation between SphK activity, S1P production and hyperproliferative diseases, identifying resveratrol as an inhibitor of SphK opens the door to drug development. Chemical libraries are flush with polyphenol compounds that may be potential SphK inhibitors. Treating balanocarpol and ampelopsin A as 'hits' might allow for the development of interesting new 'lead' compounds that are potent and specific inhibitors of SphK. SphK1 is a validated target for many cancers, and any new 'lead' has the potential for success.

Lastly, the connection between the anti-cancer effects of resveratrol or its oligomers and inhibition of SphK1, paves the way to evaluating SphK inhibition as a chemo-preventative strategy to prevent the development of cancer. Indeed, resveratrol is not alone in its inhibition of SphK1. The green tea polyphenol, epigallocatechin gallate (EGCG) has been shown to inhibit SphK1 activity in cells, albeit indirectly. Nevertheless, that these natural compounds with purported anti-cancer activities, have been linked to SphK1 suggests that their effects are, least partially, mediated through modulation of the 'sphingolipid rheostat'. Thus, evaluation of chemo-preventative studies of natural compounds such as resveratrol and EGCG should include measurements of sphingolipid metabolites to determine whether these compounds are capable of tipping the scales against the development of cancer. Similarly, the chemo-preventative effect of currently available SphK inhibitors should be investigated. Given the preponderance of mouse models for carcinogen induced tumour formation, these types of studies are feasible.

On the other hand, the major barrier to the advancement of SphK inhibitors from the 'bench' to the 'bedside' has been the lack of structural information for the SphKs. SphKs are very distantly related to other lipid kinases like diacylglycerol kinase (DAGK) and studies have identified several residues required for sphingosine and ATP binding and plasma membrane binding, but overall, very little is known about the domain architecture of SphK1. Recently, Kennedy *et al.*, have had some success with rational drug design employing a limited homology model of SphK1 based on DAGK, so this approach may offer some hope (Kennedy *et al.*, 2011). However, the lack of X-ray crystallographic studies have severely hampered the development of more potent SphK inhibitors and these studies should be a priority for the future.

Conflicts of interest

The authors of this manuscript have no conflicts of interest to declare.

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