

## Sphingosine Kinases: A Novel Pharmacological Target

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**Abbreviations:** EGF: Epidermal Growth Factor; NGF: Nerve Growth Factor; PDGF: Platelet-Derived Growth Factor; TGF- $\beta$ : Transforming Growth Factor  $\beta$ ; TNF- $\alpha$ : Tumor Necrosis Factor  $\alpha$ ; VEGF: Vascular Endothelial Growth Factor.

Although we know a wealth of information about sphingosine kinases (SphK) as an evolutionary conserved lipid kinase family, but there is paucity in data reporting their differential activity and implication in various diseases. There are two isoforms of sphingosine kinases known as type 1 and type 2 (SphK1 and SphK2; respectively), acting as critical regulators of the “sphingolipid rheostat” [1]. They were derived by alternative splicing and differ in sequence, localization and catalytic properties [2]. The studies provide strong evidence for opposing cellular roles for them where SphK1 has pro-survival and pro-oncogenic functions and is mainly a cytosolic protein, whereas SphK2 is a putative BH3-only protein, inhibits cell growth and enhances apoptosis [3, 4]. Both isoforms generate sphingosine-1-phosphate (S1P) from sphingosine, with SphK2 has ~10-fold lower substrate specificity and has different developmental expression [5, 6]. In most cells the natural balance between S1P generation and degradation results in low basal levels of S1P in the cell. However, when cells are exposed to specific factors and stimuli, S1P levels can increase rapidly and transiently [6, 7]. There are numerous stimuli including agonists of growth factor receptors (including PDGF, VEGF, NGF, and EGF), TGF- $\beta$ , the proinflammatory cytokine TNF- $\alpha$  and cross-linking of immunoglobulin receptors [8]. Intracellularly produced S1P can act in autocrine/paracrine manner to stimulate S1P receptors, designated as S1PR1–5, present at the cell surface (signaling “inside-out”) and initiate downstream diverse array of G protein-mediated signaling pathways. Recently, S1P has been shown to play a vital role in inflammation, immune function and carcinogenesis [9]. The cellular localization of the two isoforms where S1P is produced, appear pivotal in determining their function [2]. The current understanding is that localization of SphK1 activity to the plasma membrane provides pro-survival, pro-proliferative signaling to the cell, while endoplasmic reticulum (ER) localization of SphK2 imparts apoptotic signaling. However, it is still questionable why there is converse preferential direction of ER-generated S1P and plasma membrane-generated S1P away or towards the enzymes responsible for its degradation namely, S1P lyase and S1P phosphatase. Moreover, the effectors of S1P generated at either plasma membrane or ER, controlling these functions remain to be resolved. In an effort to determine such effector a study by Stahelin et al. [10] has suggested that the break-down products (phosphoethanolamine and hexadecenal) of S1P lyase action on S1P may be the true intracellular effectors, and not S1P itself. These accumulating evidences have provided considerable impetus for targeting sphingosine kinase in development of therapies, primarily for cancer, inflammatory and even immune disorders. Another argument arise from the fact that the differential signaling of SphK1 and SphK2 are combined with the known “housekeeping” functions of these enzymes, suggesting that direct inhibitors of total cellular sphingosine kinase activity may not

be the ideal therapeutics. Instead, targeting mechanisms of activation and differential localization of these enzymes that appear to control their signaling functions may provide more specific therapeutic options [7]. Indeed, the current efforts are directed to establish therapeutic inhibitors not only for sphingosine kinases but also to target S1P signaling [11]. It is of utmost importance to verify and validate SphKs/S1P axis as a novel approach in different types of diseases.

### References

1. Hait NC, Oskeritzian CA, Paugh SW, Milstien S, Spiegel S (2006) Sphingosine kinases, sphingosine 1-phosphate, apoptosis and diseases. *Biochim Biophys Acta* 1758: 2016-2026.
2. Maceyka M, Sankala H, Hait NC, Le Stunff H, Liu H, et al. (2005) SphK1 and SphK2, sphingosine kinase isoenzymes with opposing functions in sphingolipid metabolism. *J Biol Chem* 280: 37118-37129.
3. Liu H, Toman RE, Goparaju SK, Maceyka M, Nava VE, et al. (2003) Sphingosine kinase type 2 is a putative BH3-only protein that induces apoptosis. *J Biol Chem* 278: 40330-40336.
4. Fyrst H, Saba JD (2010) An update on sphingosine-1-phosphate and other sphingolipid mediators. *Nat Chem Biol* 6:489-497.
5. Liu H, Sugiura M, Nava VE, Edsall LC, Kono K, et al. (2000) Molecular cloning and functional characterization of a novel mammalian sphingosine kinase type 2 isoform. *J Biol Chem* 275: 19513-19520.
6. Pitson SM, Moretti PA, Zebol JR, Zareie R, Derian CK (2002) The nucleotide-binding site of human sphingosine kinase 1. *J Biol Chem* 277: 49545-49553.
7. Leclercq TM, Pitson SM (2006) Cellular signalling by sphingosine kinase and sphingosine 1-phosphate. *IUBMB Life* 58: 467-72.
8. Spiegel S, Milstien S (2003) Sphingosine-1-phosphate: an enigmatic signalling lipid. *Nat Rev Mol Cell Biol* 4: 397-407.
9. Spiegel S, Milstien S (2011) The outs and the ins of sphingosine-1-phosphate in immunity. *Nat Rev Immunol* 11: 403-415.
10. Stahelin RV, Hwang JH, Kim JH, Park ZY, Johnson KR (2005) The mechanism of membrane targeting of human sphingosine kinase 1. *J Biol Chem* 280: 43030-43038.
11. Edmonds Y, Milstien S, Spiegel S (2011) Development of small-molecule inhibitors of sphingosine-1-phosphate signaling. *Pharmacol Ther* 132: 352-360.

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