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Research Article

# Sphingosine 1-phosphate in inflammation

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**Abstract:** Sphingolipids are formed via the metabolism of sphingomyelin, aconstituent of the plasma membrane, or by denovosynthesis. Enzymatic pathways result in the formation of several different lipid mediators, which are known to have important roles in many cellular processes, including proliferation, apoptosis and migration. Several studies now suggest that these sphingolipid mediators, including ceramide, ceramide 1-phosphate and sphingosine 1-phosphate (S1P), are likely to have an integral role in inflammation. This can involve, for example, activation of pro-inflammatory transcription factors in different cell types and induction of cyclooxygenase-2, leading to production of pro-inflammatory prostaglandins. The mode of action of each sphingolipid is different. Increased ceramide production leads to the formation of ceramide-rich areas of the membrane, which may assemble signalling complexes, whereas S1P acts via high-affinity G-protein-coupled S1P receptors on the plasma membrane. Recent studies have demonstrated that in vitro effects of sphingolipids on inflammation can translate into in vivo models. This review will highlight the areas of research where sphingolipids are involved in inflammation and the mechanisms of action of each mediator. In addition, the therapeutic potential of drugs that alter sphingolipid actions will be examined with reference to disease states, such as asthma and inflammatory bowel disease, which involve important inflammatory components. A significant body of research now indicates that sphingolipids are intimately involved in the inflammatory process and recent studies have demonstrated that these lipids, together with associated enzymes and receptors, can provide effective drug targets for the treatment of pathological inflammation.

**Keywords:** Inflammation; Sphingolipids; Sphingosine 1-phosphate

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## 1 S1P Metabolism

Sphingosine, the substrate for S1P synthesis, is produced by degradation of ceramide, not de novo biosynthesis. Subsequently sphingosine can be either re-acylated back to ceramide or phosphorylated by sphingosine kinase (SPHK) 1 and 2 to form S1P. Although both SPHK isoforms synthesize the same product, they display different catalytic properties, subcellular locations, tissue distribution, and possibly have unique and specifi c functions. SPHK1 is highly specifi c for sphingosine and dihydrosphingosine as substrates . It resides in the cytosol but translocates to the plasmalemma upon activation[1]. A signifi cant fraction of cellular SPHK1 (8%) is constitutively released to the extracellular space. The secreted enzyme is active, which enables local production of S1P in the vicinity of its cell surface receptors. SPHK2 is mainly found in the nucleus, but it is also present in the cytosol, internal membranes, and plasmalemma. SPHK2 is not secreted and is ableto phosphorylate a broader range of substrates, including sphingosine, dihydrosphingosine, phytosphingosine, and FTY720.S1P is degraded by three types of enzymes: S1P phosphatase (SPP), S1P lyase (S1PL), and lipid phosphate phosphohydrolase (LPP). In most cells, S1P is irreversibly degraded by S1PL to

  

hexadecenal and ethanolamine1-phosphate [2]. S1P can also be dephosphorylated by two isoforms of SPP (SPP1 and SPP2), which are highly selective for sphingoid base-1-phosphates as substrates, to yield sphingosine.

## 2 Sphingosine 1-phosphate

S1P is to date the best described of the sphingolipid mediators. S1P produced by SK isoenzymes is up-regulated in cells via activation of G-protein-coupled receptors, growth factor receptors and cytokine receptors. SK localization in cells is dependent upon the isoenzyme examined and may be cytoplasmic or plasma membrane-bound. Translocation and plasma membrane targeting following activation have been observed in some cell types dependent upon stimulus. This suggests that S1P can potentially be produced at different intracellular locations varying with the SK isoenzymes activated/expressed, species or cell type examined. However, unlike ceramide and C1P, S1P also occurs naturally in plasma at relatively high concentrations. S1P is known to be an integral and functionally important constituent of lipoproteins, along with the related sphingolipid, SPC. The S1P concentration in plasma is around 200 nM and more than 60% is bound to lipoproteins, with the majority bound to high-denstiy liporteins(86%), Proportionatelylessisboundtolow-densitylipoprotein while oxidation of LDL reduces further the sphingolipid component. It is likely that the S1P component is involved in some of the cytoprotective effects of HDL[3]. In addition to lipoproteins, there is another source of S1P that does not rely on de novo synthesis. A major advance in understanding the physiological and pathophysiological role of S1P was the cloning and characterization of plasma membrane receptors with a high affinity for S1P. These receptors (initially termed EDG receptors, products of the endothelial differentiation gene) are members of the seven-transmembrane, G-protein-coupled superfamily. To date, five subtypes of the S1P receptor (S1P1–5) have been cloned. S1P1–3 are expressed in many cell types with S1P4 and S1P5 restricted to specific cell types. These receptors can couple to multiple heterotrimeric G-proteins (with the exception of S1P1 that couples only to Gai) and therefore have the potential to activate multiple signalling cascades. S1P2 and S1P3 couple preferentially to Gaq (leading to activation of phospholipase C and intracellular $Ca^{2+}$ release) and Ga12/13 (activating the monomeric G-protein RhoA) [4].

## 3 S1P in inflammation

It is now becoming increasingly apparent that sphingolipids can be intimately involved in inflammation. Many studies have demonstrated that, in some cell types, sphingolipids can have specific effects that are integral to regulation of the inflammatory response.

The SK1/S1P pathway has been implicated in inflammation mediated by TNF-α. This TNFα signaling enhances the expression of adhesion molecules, such as vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) . SK1 was shown to be activated by TNF-α in a dose-dependent manner, an event required for TNF–α-mediated adhesion molecule expression in HUVEC cells [5]. Subsequently, Pettus et al. demonstrated a role for sphingolipid metabolism in the inflammatory response in L929 fibroblasts whereby, it was shown that SK1 and S1P are necessary for TNF-α-induced COX2 and PGE2 production[6]. Billich et al. found increased SK1 mRNA synthesis under inflammatory conditions, again, implicating sphingolipids in inflammation[7]. Other inflammatory signaling molecules such as IL-1β, IFN-γ, IgE and C5a, have also been shown to activate SK1, further suggesting the importance of the SK1/S1P pathway in the inflammatory response[8].

In addition to a role for SK1/S1P in TNF-α-mediated signaling, SK1/S1P and the S1PRs have also been shown to regulate numerous types of immune cells involved in inflammatory diseases. For example, SK1 is necessary for TNF-α-mediated responses in human primary monocytes, and it has been suggested, using dimethylsphingosine (DMS), that SK1 is required for catestatin-stimulated migration of monocytes [9,10]. Macrophages stimulated with LPS increase SK1 message and activity, resulting in generation of S1P and induction of COX2[11]. SK1 message and protein have been shown to be increased in LPS-activated microglia [12], perhaps implicating a possible role for the SK1/S1P pathway in neuroinflammation. Also in macrophages, SK1 has been implicated in cytokine production and chemotaxis in response to C5a[13]. Exogenous addition

of low concentrations of sphingosine to C5a-primed neturophils stimulated an oxidative burst, which was attributed to activation of SK and generation of S1P [14]. S1PR transactivation by FcεRI is necessary for mast cell degranulation and migration [15], whereas mast cell degranulation and cytokine production require SK. In addition to the growing literature implicating SK and S1P in inflammation and immune cell functions, the emergence of FTY720 and other S1PR modulators were instrumental to the discovery that S1PRs are essential for migration of lymphocytes [16].

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