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Targeting sphingosine-1-phosphate signaling in lung diseases

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ABSTRACT

Sphingosine-1-phosphate (S1P), a simple, bioactive sphingolipid metabolite, plays a key role, both intracellularly and extracellularly, in various cellular processes such as proliferation, survival, migration, inflammation, angiogenesis, and endothelial barrier integrity. The cellular S1P level is low and is tightly regulated by its synthesis and degradation. Sphingosine Kinases (SphKs) 1 and 2, catalyze the ATP-dependent phosphorylation of sphingosine to S1P, while the degradation is mediated by the reversible dephosphorylation catalyzed by the S1P phosphatases and lipid phosphate phosphatases and the irreversible degradation to hexadecenal and ethanolamine phosphate by sphingosine-1-phosphate lyase (S1PL). As a ligand for specific G-protein-coupled receptors, $S1P_{1-5}$, which are differentially expressed in different cell types, S1P generates downstream signals that play crucial role in developmental and disease related pathologies. In addition to acting extracellularly on receptors located on the plasma membrane, S1P can also act intracellularly, independently of $S1P_{1-5}$, affecting calcium homeostasis and cell proliferation. The SphKs /S1P /S1PL metabolic pathway is implicated in numerous human pathologies including respiratory disorders, thereby raising the possibility that manipulating intracellular S1P levels could offer therapeutic potential in ameliorating lung diseases. This review focuses on the prospects of targeting S1P signaling and S1P metabolizing enzymes using small molecule inhibitors, receptor agonists, and antagonists in the treatment of lung diseases.

Contents

Abbreviations: 4-DP, 4′-deoxypridoxine; ABC transporter, ATP-binding cassette transporter; Akt, protein kinase B; ALF4, tetrafluoroaluminate; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ASM, acid sphingomyelinase; BACE1, beta-site APP-cleaving enzyme; BAL, bronchoalveolar lavage; BMDC, bone marrow derived cells; BPD, broncho pulmonary dysplasia; CDK-2, cyclin dependent kinase; CF, Cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; CoA, co enzyme A; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; EC, endothelial cell; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FcεRI, high-affinity receptor for IgG; HAT, histone acetyltransferase; HDAC, histone deacetylase; HLMVEC, human lung microvascular endothelial cells; hTERT, human telomerase reverse transcriptase; HUVEC, human umbilical vein endothelial cell; IL-1β, interleukin-1-beta; IL-4, interleukin-4;; IL-5, interleukin-5; IL-6, interleukin-6; IPF, idiopathic pulmonary fibrosis; JNK, c-Jun N-terminal kinase; LPA, lysophosphatidic acid; LPP, lipid phosphate phosphatase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MPM, malignant pleural mesothelioma; mRNA, messenger RNA; NEM, N-ethylmaleimide; NES, nuclear export signal; NOX, NADPH-oxidase; NSCLC, Non-small cell lung cancer; $P21^{Cip1}$, Cyclin-dependent kinase inhibitor 1A; $P27^{Kip1}$, Cyclin-dependent kinase inhibitor 1B; PASMC, pulmonary artery smooth muscle cell; PDGFR, platelet-derived growth factor receptor; PGE2, prostaglandin E2; PI3K, phosphoinositide-3-kinase; PKCδ, protein kinase C-delta; ROS, reactive oxygen species; S1P, sphingosine-1-phosphate; S1PL, sphingosine-1-phosphate lyase; S1PR, sphingosine-1-phosphate receptor; SAPK, stress-activated protein kinase; SCLC, small cell lung cancer; siRNA, short interfering RNA; SM, sphingomyelin; SphK1, sphingosine kinase 1; SphK2, sphingosine kinase 2; SPT, serine palmitoyltransferase; Spns2, spinster homolog 2; SPP, sphingosine-1-phosphate phosphatase; TGF-β, transforming growth factor-beta; Th-2, T helper 2; THI, 2-acetyl-4-tetrahydroxybutylimidazole; TNF-α, tumor necrosis factor-alpha; TRAF-2, TNF receptor-associated factor 2.

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1. Introduction

Sphingolipids constitute a class of lipids that contain a sphingoid base such as sphingosine, sphinganine (dihydrosphingosine), or phytosphingosine backbone linked to long-chain fatty acids (ceramides). The resulting ceramides can be linked to hydrophilic head groups such as phosphorylcholine (sphingomyelin) (SM), carbohydrate moieties (glycosphingolipids), or a phosphate group (ceramide-1-phosphate) (Weete, 1974). SM is located on the exoplasmic surface of the eukaryotic plasma membrane where it plays a paramount role in protecting the cell surface from external agents (Simons & Ikonen, 1997), and also functions as a signaling lipid (Maceyka et al., 2012). The first step of sphingolipid de novo biosynthesis is the formation of 3-keto-dihydrosphingosine via condensation of L-serine and palmitoyl CoA catalyzed by serine palmitoyltransferase (SPT), the rate limiting enzyme in sphingolipid biosynthesis (Merrill, 2002). 3-Keto-dihydrosphingosine is rapidly reduced to sphinganine (dihydrosphingosine) by ketosphinganine reductase (Stoffel, 1970), followed by ceramide synthase(s) mediated N-acylation to dihydroceramide with different fatty acid chain lengths (Stiban et al., 2010). Mammals exhibit six different acyltransferases encoded by lass-genes that show specificities for different fatty acyl CoAs (Futerman & Riezman, 2005). Dihydroceramides can be desaturated to ceramides, which can be channeled to the synthesis of complex sphingolipids such as SM and glycosphingolipids, or phosphorylated by ceramide kinase to ceramide-1-phosphate (Mitsutake et al., 2006). Mammalian cells do not convert dihydrosphingosine to sphingosine; however sphingosine can be generated from ceramide by ceramidases (Chalfant & Spiegel, 2005). Also, ceramide can be formed from SM in mammalian cells by sphingomyelinase activation in response to extracellular stimuli such as TNF- α or growth factors (Dbaibo et al., 1993). Sphingosine generated from ceramide is converted to sphingosine-1-phosphate (S1P) by sphingosine kinase (SphK) 1 and/or 2 (Fig. 1).

2. Sphingosine-1-phosphate metabolism and signaling

Cellular levels of S1P are tightly regulated by its synthesis from sphingosine through the activation of SphKs and degradation through reversible dephosphorylation of S1P to sphingosine by S1P phosphatases (SPPs), lipid phosphate phosphatases (LPPs), or irreversible degradation by a pyridoxal phosphate-dependent S1P lyase (S1PL) to Δ2 hexadecenal and ethanolamine phosphate (Saba & Hla, 2004). In unstimulated cells, the balance between S1P production and degradation results in relatively low intracellular levels of S1P. Erythrocytes and platelets have much higher levels of S1P compared to other cells and this is due to lack of S1PL (Ito et al., 2007). S1P is also transported from inside the cell to outside by ABC transporters (Mitra et al., 2006; Sato et al., 2007; Kim et al., 2009; Kobayashi et al., 2009), and the recently identified spinster homolog 2 (Spns2) transporter (Kawahara et al., 2009; Fukuhara et al., 2012; Hisano et al., 2012). In the last two decades, S1P garnered much deserved research attention as it has emerged as a bioactive lipid mediator of diverse cellular processes such as cell growth, and survival (Olivera et al., 1999), motility (Van Brocklyn et al., 2003; Xu et al., 2006; Berdyshev et al., 2011), cytoskeletal organization (Garcia et al., 2001), endothelial permeability (Wang & Dudek, 2009), vascular tone (Levkau, 2008), adherens junctions (Mehta et al., 2005), tight junctions assembly (Lee et al., 1999a, 2006), autophagy (Lavieu et al., 2006; Huang & Natarajan, 2015), immune regulation (Chi, 2011; Spiegel & Milstien, 2011; Walzer et al., 2007) and morphogenesis (Lee et al., 1999a). These pleotropic actions of S1P are attributed to its unique inside-out (extracellular), and intracellular signaling, highlighting its role as a signaling sphingolipid. Intracellularly, S1P is known to act as a second messenger and plays a role in calcium homeostasis; however very little is known regarding intracellular targets of S1P. Release of S1P in human lung endothelial cells by the photolysis of caged S1P significantly enhanced endothelial cell (EC) barrier function, which was independent of $S1P_1$, but was dependent on

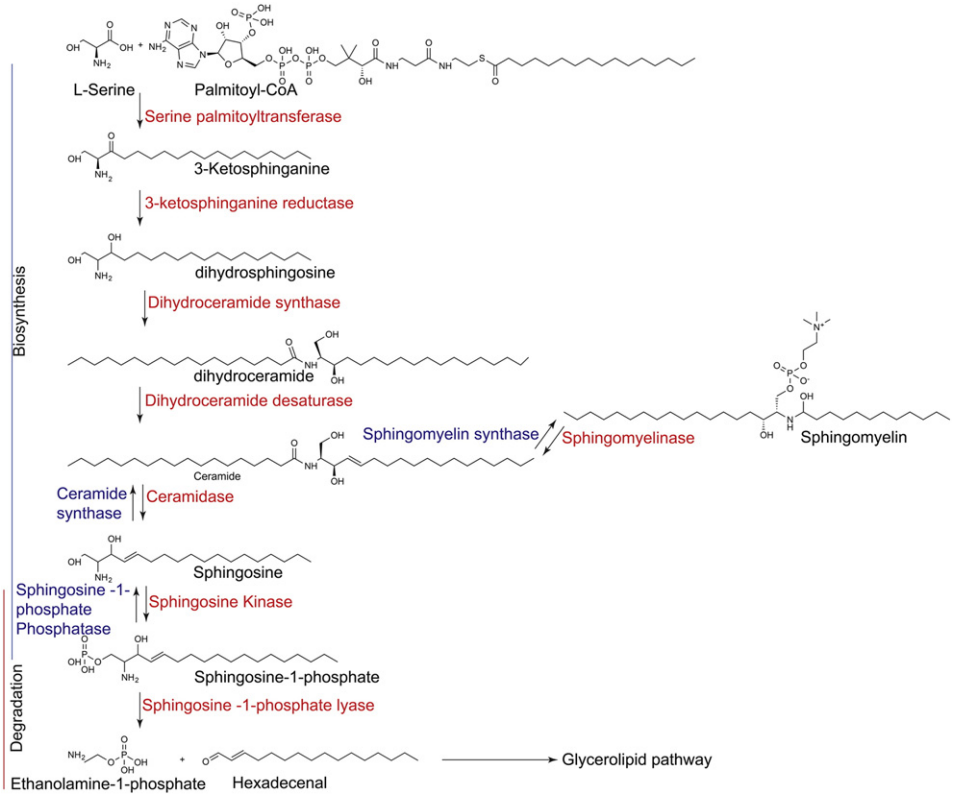

Fig. 1. De novo Sphingolipid Metabolism in mammalian cells. Illustration of the key enzymatic steps in the biosynthesis, degradation and recycling of sphingoid bases.