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Sphingosine Kinases/Sphingosine 1-Phosphate Signaling in Hepatic Lipid Metabolism

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Abstract

The ever-increasing prevalence of metabolic diseases such as dyslipidemia and diabetes in the western world continues to be of great public health concern. Biologically active sphingolipids, such as sphingosine 1-phosphate (S1P) and ceramide, are important regulators of lipid metabolism. S1P not only directly functions as an active intracellular mediator, but also activates multiple signaling pathways *via* five transmembrane G-protein coupled receptors (GPCRs), S1PR1-5. S1P is exclusively formed by sphingosine kinases (SphKs). Two isoforms of SphKs, SphK1 and SphK2, have been identified. Recent identification of the conjugated bile acid-induced activation of S1PR2 as a key regulator of SphK2 opened new directions for both the sphingolipid and bile acid research fields. The role of SphKs/S1P-mediated signaling pathways in health and various human diseases has been extensively reviewed elsewhere. This review focuses on recent findings related to SphKs/S1P-medaited signaling pathways in regulating hepatic lipid metabolism.

Keywords

Sphingolipids; Sphingosine 1-phosphate; Sphingosine kinase; G protein-coupled receptor; Hepatic lipid metabolism; Metabolic diseases

2. Introduction

Sphingosine forms the backbone of most sphingolipids and was initially recognized as a component of the plasma membrane lipid bilayer. The advent of large scale data analyses including genomics and proteomics paved way for the identification of many regulatory receptors and enzymes involved in sphingolipid metabolism (1). Since then, sphingosine and its derivative sphingolipids have emerged as important signaling molecules in the regulation of different biological processes including migration, differentiation, cell survival and lipid metabolism. The phosphorylated derivative of sphingosine, sphingosine 1-phosphate (S1P),

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has attracted the attention of investigators for its potency as an activator of cell signaling and regulator of cell survival, growth, and immune cell trafficking which are important in inflammatory diseases and various cancers (2, 3). In addition, studies with genetically modified mouse models have provided physiological insight into the functions of sphingolipids and have yielded many important advances in the understanding of the role of sphingolipid-mediated signaling pathways in various human diseases, including inflammation, cancer, pulmonary arterial hypertension, diabetes, nonalcoholic fatty liver disease (NAFLD), and metabolic diseases (4–6)

S1P represents a key signaling sphingolipid molecule. It is exclusively formed by the phosphorylation of sphingosine *via* the action of sphingosine kinases (SphKs). Two major isoforms of SphK (SphK1 and SphK2) have been isolated and characterized. SphK1 and SphK2 have diverse and compensatory biological activities. S1P is not only an intracellular messenger, but also a natural ligand for five specific cell surface G-protein-coupled receptors (GPCRs). During the last two decades, numerous agonists and antagonists of S1P receptors (S1PRs) and chemical inhibitors of SphKs have been developed. One notable discovery is FTY720 (fingolimod), a modulator of the S1PRs except S1PR2, has been approved for the treatment of multiple sclerosis (7). However, the role of SphKs and S1P in lipid metabolism remains largely unknown. In this review, we will focus on the current understanding of the role of SphKs/S1P-mediated signaling pathways in regulating hepatic lipid metabolism and the development of potential therapeutics for the treatment of metabolic disorders by targeting SphKs and S1PRs.

3. Sphingosine Lipid Metabolism

Sphingolipids are lipids that contain the sphingoid backbone and can be N-acylated to form ceramide which occupies a central position in the biosynthetic pathway of sphingolipid metabolism (8). The first step in *de novo* synthesis of sphingolipids is the condensation of serine and palmitoyl CoA by the enzyme serine palmitoyltransferase to form 3-ketosphinganine. This reaction takes place in the endoplasmic reticulum (ER) and represents the rate-limiting step of this biosynthetic pathway. Subsequent reactions involve the N-acylation of 3-ketosphinganine and reduction to sphinganine. Sphinganine is further fatty acylated by ceramide synthesis to generate dihydroceramide followed by desaturation by dihydroceramide desaturase to form ceramide, which is the precursor of the majority of complex sphingolipids (9). Ceramide is membrane-bound molecule with very low aqueous solubility. It requires transport from ER to the Golgi complex by ceramide transfer protein or vehicular transport, where it serves as a substrate for the production of sphingolipids such as glycosphospholipids, sphingomyelin and sphingosine. In addition, ceramide can be converted to an important cell signaling molecule, ceramide 1-phosphate, by ceramide kinase. Furthermore, sphingosine can be converted to S1P by SphKs (10, 11).

4. Sphingosine Kinases

SphKs belong to the class of lipid kinases that contain five conserved domains and are evolutionarily conserved. Two mammalian isoforms have been identified, SphK1 and SphK2 (12). Human SphKs are encoded by two distinct genes, SPHK1 and SPHK2, which are

located on chromosome 17 and 19, respectively (13). Human SphK1 and SphK2 share 80% similarity in amino acid sequence and 50% similarity in nucleotide sequence identity. SphK2 has 200 additional amino acids at the N-terminal region, containing a nuclear targeting sequence. The predicted molecular weights for SphK1 and SphK2 are 42 kDa and 68 kDa, respectively (14). SphK1 is highly expressed in cells in the lung and spleen, whereas SphK2 is more abundant in liver, kidney, brain and heart (15). Moreover, the intracellular localization of SphK1 and SphK2 is closely linked to their physiological functions. SphK1 predominately resides in the cytoplasm under normal physilogical conditions and upon various stimuli such as activation of mitogen-activated protein kinase (MAPK) by cytokines and growth factors, SphK1 is activated and translocated from the cytosol to the plasma membrane to carry out its catalytic conversion of sphingosine to S1P. Activation of SphK1 is associated with promotion of cell proliferation, survival, migration, differentiation, angiogenesis and inflammation (16–18). In contrast, SphK2 is mainly localized in the nucleus (19). Nuclear S1P produced by SphK2 has been shown to inhibit histone deacetylases (HDAC1/2) activity, leading to increased histone acetylation and increased gene transcriptional activity (20). The subcellular localization of SphK2 and its function are less well-studied. In addition, SphK2 is also found in mitochondria, where it binds with high affinity and specificity to prohibitin 2, a highly-conserved protein that regulates mitochondrial assembly and function (21). Activation of SphK2 has also been shown to increase mitochondrial membrane permeability and promote cytochrome c release (22, 23).

5. Sphingosine 1-Phosphate Signaling

Sphingosine 1-phosphate (S1P) is a simple sphingolipid but potent activator of cellular signaling pathways. S1P plays a role in various cellular processes including cell proliferation, differentiation, angiogenesis, inflammation and cancer (24). Like most signaling molecules, intracellular S1P level is tightly regulated by its synthesis and degradation. S1P is exclusively synthesized *via* phosphorylation of the 1-hydroxyl group on sphingosine either by SphK1 or SphK2 in response to diverse stimuli, including inflammatory cytokines, growth factors, and activation of GPCRs. S1P can be converted back to sphingosine by S1P specific phosphatase in the cytosol or degraded by S1P lyase to ethanolamine phosphate and hexadecanal (25). Unlike sphingosine, which is sufficiently hydrophobic to diffuse cross membranes, S1P is a more hydrophilic molecule, which requires specific transporters to be exported to the extracellular space. Several membrane-associated transporters have been identified as active S1P transporters, including ATP-binding cassette (ABC) transporters, ABCA1 and ABCC1, and spinster homologue 2 (Spns2) (26–29). The exported S1P can activate the S1P-specific GPCRs on the cell membrane to induce various physiological responses (Figure 1) (30).

Identification of the S1P-specific GPCRs represents an important milestone in understanding S1P-mediated biological functions. Since the discovery of the first S1PR, S1PR1 (formerly named as EDG1) in 1998 (31), a total of five GPCRs have been identified as S1P-specific receptors (S1PR1-5) (20, 32–34). S1PRs are differentially expressed in different tissues and the expression levels vary under different physiological and pathological conditions (35). S1PR1 is ubiquitously expressed and deletion of S1PR1 is embryonically lethal (36). S1PR1 has been shown to play a key role in immune cell trafficking and angiogenesis (37, 38).

S1PR2 is important for the development of the auditory and vestibular system (39). Unlike S1PR1, deletion of S1PR2 is not lethal, however mice deficient in S1PR2 have been shown to develop spontaneous seizures (40). S1PR3 is highly expressed in the brain, heart, lung, spleen, kidney, liver, intestine and skeletal muscle (41). In addition, it plays a role in vascular endothelial function and lung barrier integrity (42). S1PR4 is expressed in leukocytes and regulates T cell cytokine production (43). S1PR5 is highly expressed in oligodendrocytes, however the function of S1PR5 remains unknown (44). The various biological functions of S1P in different cells and tissues are largely due to the different expression patterns of S1PR subtypes and the various G proteins they couple with (45). The crystal structure of S1PR1 made a significant advancement in the understanding of S1P-mediated signaling (46). The S1P receptor subtype-specific agonists and antagonists have become novel therapeutic candidates for various diseases (47, 48).

6. SphKs and S1P in Lipid Metabolism

Dyslipidemia associated with metabolic diseases is complex and involves dysregulation of metabolic pathways of various lipid species (9, 49). In addition to phospholipid metabolites, sphingolipid metabolites are also involved in the regulation of metabolic lipid homeostasis (9). The function of SphKs in regulating cell proliferation, differentiation and migration as well as the inflammatory response has been studied extensively, but only until recently have studies demonstrated an eminent role for SphKs in regulating lipid metabolism (50–53). S1P is present in the circulation and bile and mainly associated with high density lipoproteins (HDL) and albumin (24). HDL-mediated release of S1P has been shown to have protective effects against atherosclerosis (54, 55). S1P-mediated activation of the inflammatory response represents a key event in atherosclerotic disease progression. Both pharmacologic inhibition and genetic silencing of S1PR2 attenuated atherosclerotic lesion formation in apolipoprotein E knockout mice ($ApoE^{-/-}$) (56). Interestingly, several studies have shown that FTY720, a synthetic S1P analogue, reduces atherosclerosis in rodent models (57–61). A recent study has shown that the SphK1/S1P axis plays a critical role in hypoxia-mediated pulmonary hypertension (HPH). Pharmacological inhibition of SphK1 and S1PR2 or genetic deletion of SphK1 prevented the development of HPH in rodent HPH models (62). FTY720 is also found to reduce cholesterol and sphingolipid accumulation in Niemann-Pick type C (NPC) mutant fibroblasts by upregulating the expression of NPC1 and NPC2 and reducing cholesterol accumulation (63).

Obesity is closely associated with diabetes, nonalcoholic fatty liver disease (NAFLD)/ nonalcoholic steatohepatitis (NASH), and cardiovascular diseases (64). Numerous studies have reported that dysregulation of sphingolipid metabolism is linked to diabetes (4). However, most studies in this area are focused on ceremide (65–67) and only a few studies have examined the involvement of SphKs/S1P signaling in obesity-related diseases. It has been reported that the expression of SphK1, but not SphK2, is elevated in mouse 3T3-L1 adipocytes during adipogenesis and in *ob/ob* mouse adipose tissue (68). Recently, several studies reported that SphK/S1P-signaling plays an important role in hepatic lipid metabolism and insulin resistance (4, 50,52, 53, 69). However, there is a discrepancy regarding the role of SphK1 in the regulation of hepatic lipid metabolism in recent studies. NAFLD is characterized by aberrant accumulation of lipids in hepatocytes. Hepatic lipid homeostasis is

controlled by the balance of hepatic fatty acid synthesis, dietary fat intakes, adipocyte lipolysis, fatty acid oxidation, and secretion of hepatic lipids (70). Kowalski, *et al.* reported that high-fat-high-glucose diet feeding resulted in accumulation of hepatic lipids and the reduction of total hepatic SphK activity, which was correlated to the down-regulation of SphK1, but not SphK2 (53). However, hepatic overexpression of SphK1 only reduced hepatic triglycerides in low-fat-diet-fed mice, but not in high-fat-diet-fed mice. SphK1/S1P-mediated signaling has been suggested to promote hepatic steatosis and inflammation. Expression of hepatic SphK1 is elevated in both high-fat-high-glucose-fed mice and human NASH patients (71). SphK1$^{-/-}$ mice were protected from high-fat-high-glucose diet-induced hepatic inflammation and lipid accumulation (71). Interestingly, another recent study done by Chen, *et al* reported that deletion of SphK1 ameliorated hepatic steatosis in high-fat-diet fed mice by the down-regulation of peroxisome proliferator-activated receptor gamma (PPARγ) expression in the liver (50). Furthermore, SphK1/S1P-mediated pro-steatotic effect is dependent on S1PR2/S1PR3, not S1PR1 (50). To solve these discrepancies, more in-depth mechanistic approaches will be needed, including liver/hepatocyte-specific deletion and overexpression of SphK1. In contrast to SphK1, the physiological and pathological function of SphK2 is less well-characterized. The role of SphK2 in regulating immune cell function and the inflammatory response is controversial in different disease settings (72, 73). Specific chemical inhibitors of SphK2 have been developed as potential tumor suppressors (74–78). Our recent study demonstrated that SphK2 is a key regulator of hepatic lipid metabolism (51). Both S1PR2$^{-/-}$ and SphK2$^{-/-}$ mice fed on a high-fat-diet rapidly develop overt fatty livers compared to wild type mice. Interestingly, key lipid metabolism genes such as SREBP-1c, FAS, LDLR, FXR and PPARγ are significantly downregulated in both S1PR2$^{-/-}$ and SphK2$^{-/-}$ mice (51). Our recent RNA-seq data further indicated that overexpression of S1PR2 significantly upregulated the expression of SphK2 and key genes in hepatic lipid metabolism (unpublished data). Similarly, another study reported by Lee, et al indicated that activation of SphK2 by endoplasmic reticulum (ER) stress ameliorates hepatic steatosis and insulin resistance (52). High fat diet-induced ER stress results in the upregulation of SphK2 through the activation of ATF4. Consistent with our findings, this study demonstrated that SphK2 is an important regulator of hepatic fatty acid metabolism. In addition, SphK2-medaited activation of AKT signaling pathways protects mice against high-fat-diet-induced glucose intolerance and insulin resistance (52).

7. Bile acid receptors in hepatic lipid metabolism

1) Nuclear receptors

Bile acids are important signaling molecules and play multiple physiological functions including nutrient absorption, regulation of cholesterol, glucose and fatty acid metabolism, maintenance of microbiome homeostasis and intestinal barrier integrity by activating nuclear receptors (79). The FXR and small heterodimer partner (SHP; NR0B2) are the most well-characterized nuclear receptors which play crucial roles in bile acid homeostasis (80, 81). It has been reported that global FXR knock out mice develop liver tumors spontaneously (82). Recent study further showed that liver-specific FXR knock out mice are resistant to spontaneous hepatocarcinogenesis, but susceptible to cholic acid-induced tumor formation (83). However, SHP knock out mice are resistant to bile acid-induced liver damage (84).

Furthermore, double knock out mice of FXR and SHP develop more severe cholestasis and liver injury associated with dysregulation of steroid biosynthesis (85). In addition, FXR and SHP also play important role in regulating hepatic glucose and fatty acid metabolism as well as inflammatory response (79).

2) G protein coupled receptors, TGR5 and S1PR2

Discovery of TGR5, as the first bile acid-specific GPCR, was an important milestone in bile acid research (86). TGR5 is widely expressed including the liver, but absent in hepatocytes. Extensive studies have been done to identify the physiological functions of TGR5 during the last decade (87, 88). However, the role of TGR5 in regulating hepatic lipid metabolism is limited. Identification of conjugated bile acids as activators of S1PR2 opened a new direction for bile acid research (89). S1PR2 is highly expressed in hepatocytes, cholangiocytes and Kupffer cells and is activated by conjugated bile acids, such as taurocholic acid (TCA) (89). TCA-mediated activation of S1PR2 further activates the ERK1/2 and AKT signaling pathways, which are important cellular pathways involved in regulating lipid and glucose metabolism (89, 90). In a chronic bile fistula rat model, infusion of TCA not only activated AKT and ERK1/2 signaling pathway along with glycogen synthase kinase, but also upregulated the expression of SphK2 (51, 91). It has been shown that ERK1/2-mediated activation of SphK2 results in production of S1P in the nucleus, which specifically binds to HDAC1 and HDAC2 and enhances the histone acetylation and gene transcription (20). These studies suggest that cross-talk between bile acids and S1PR2/SphK/S1P-mediated signaling pathways plays a pivotal role in regulating hepatic lipid metabolism. In addition, recent studies showed that conjugated bile acid-mediated activation of S1PR2 is responsible for invasive growth of cholangiocarcinoma cells and bile duct ligation-induced cholestatic liver injury (92–94).

8. Conclusion and Future Perspectives

There have been significant advances in understanding the role of SphKs/S1P-mediated signaling pathways in various human diseases during the last decade. The current understanding of cross-talk between SphKs/S1P-mediated signaling pathways and bile acid-mediated signaling pathways in the regulation of hepatic lipid and glucose metabolism has opened a new direction for the future of sphingolipid and bile acid research. The development of tissue or cell-specific transgenic mice for SphKs and S1PRs is necessary for elucidating the key mechanisms underlying S1P/bile acid-mediated regulation of hepatic lipid metabolism under different physiological and pathological conditions. In addition, resolution of the crystal structures of SphKs and individual S1PRs will enable us to develop more specific activators/inhibitors with less off-target effects as potential novel therapeutics for metabolic disorders.

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Abbreviations

ABC	ATP-binding cassette
AKT	protein kinase B
ApoE	apolipoprotein E
ATF4	activating transcription factor 4
EDG1	endothelial differentiation gene 1
ER	endoplasmic reticulum
ERK	extracellular signal-regulated kinase
FAS	fatty acid synthase
FXR	farnesoid × receptor
GPCRs	G-protein coupled receptors
HDAC	histone deacetylases
HDL	high density lipoprotein
HPH	hypoxia-mediated pulmonary hypertension
LDLR	low-density lipoprotein receptor
MAPK	mitogen-activated protein kinase
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NPC	Niemann-Pick type C
ob/ob	leptin-deficient
PPARγ	proliferator-activated receptor gamma
S1P	sphingosine 1-phosphate
SHP	small heterodimer partner
Sph	sphingosine
SphKs	sphingosine kinases
Spns2	spinster homologue 2
S1PR	sphingosine 1-phosphate receptor
SREBP-1c	sterol regulating element-binding protein 1
TCA	taurocholic acid

TGR5 G-protein coupled bile acid receptor

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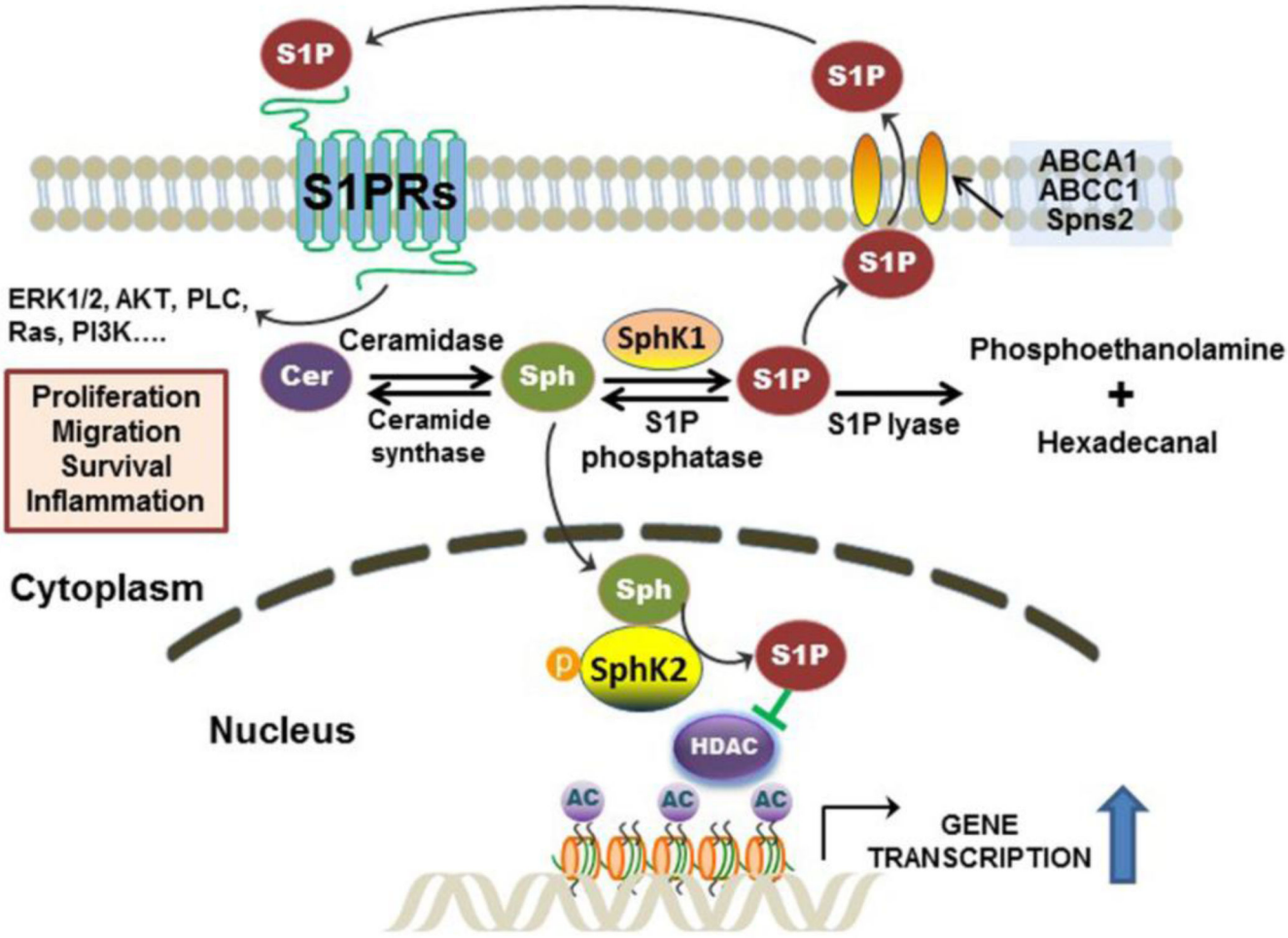

Figure 1. Biosynthetic and signaling pathways of sphingosine 1-phosphate (S1P)

S1P is synthesized by phosphorylation of sphingosine (Sph), which is exclusively mediated by sphingosine kinase 1 (SphK1) in the cytosol and Sphk2 in the nucleus. Cytosolic S1P can be exported by transporters (ABCA1, ABCC1, and Spns2) and activates GPCRs (S1PR1-5) on the cell surface. S1P also can be dephosphorylated by S1P phosphatase back to Sph for ceramide (Cer) synthesis or further degraded by S1P lyase into phosphoethanolamine and hexadecenal. Both SphK1 and SphK2 can be activated by ERK. Nuclear S1P generated by SphK2 inhibits HDAC1/2 activity, which results in increase of histone acetylation and up-regulation of gene transcription.