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Review Article

Sphingosine-1-phosphate signaling and the gut-liver axis in liver diseases☆

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ABSTRACT

The liver is the central organ involved in lipid metabolism and the gastrointestinal (GI) tract is responsible for nutrient absorption and partitioning. Obesity, dyslipidemia and metabolic disorders are of increasing public health concern worldwide, and novel therapeutics that target both the liver and the GI tract (gut-liver axis) are much needed. In addition to aiding fat digestion, bile acids act as important signaling molecules that regulate lipid, glucose and energy metabolism via activating nuclear receptor, G protein-coupled receptors (GPCRs), Takeda G protein receptor 5 (TGR5) and sphingosine-1-phosphate receptor 2 (S1PR2). Sphingosine-1-phosphate (S1P) is synthesized by two sphingosine kinase isoforms and is a potent signaling molecule that plays a critical role in various diseases such as fatty liver, inflammatory bowel disease (IBD) and colorectal cancer. In this review, we will focus on recent findings related to the role of S1P-mediated signaling pathways in the gut-liver axis.

1. Introduction

Sphingolipids were discovered in the late 1800s and named after the mysterious Sphinx due to their puzzling biological function.[1] Like other lipids, sphingolipids were initially thought to be structural components that make up cellular membranes. Not until in the 1990s when sphingosine and its sphingoid derivatives proved to be important signaling molecules that mediate biological function such as cellular differentiation, migration, survival and metabolism.[2,3] Moreover, the phosphorylated sphingosine moiety, sphingosine-1-phosphate (S1P), demonstrated to be a potent activator of various cellular signaling through its S1P receptors (S1PRs). S1P is synthesized by sphingosine kinases (SphKs).[4,5] Genetically modified mouse studies have uncovered many important physiological roles of S1P-mediated signaling in various human diseases including pulmonary arterial hypertension, diabetes, liver diseases, gastrointestinal (GI) diseases and cancer.[6–8] In addition, the development of pharmacological drugs targeting S1P signaling pathways has allowed the modulation of critical cellular pathways while providing an avenue for the treatment of various diseases.[9]

The ever-increasing obesity epidemic in the Western countries has attracted special attention to the liver and the GI tract (gut-liver axis) for their physiologic roles in lipid metabolism and nutrient partitioning. Concurrently, S1P signaling emerges as one of the key players in metabolic diseases, various liver pathologies including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and liver fibrosis, and GI diseases such as inflammatory bowel disease (IBD) and colorectal cancer.[10–12] Moreover, only recently have researchers begun to take a more holistic view of the liver and gut diseases as a single disease organ system rather than two separate disease entities. Technological advances in deep genetic sequencing and biochemical techniques have provided a wealth of information in understanding the gut microbiome and how it contributes not only to GI disorders, but how it contributes to diseases affecting other organs in the body including the liver, brain and lung.[13,14] In this review, we will focus on S1P signaling in the gut-liver axis and its promising role in the development of novel therapeutics to treat various liver and GI-related disorders.

2. S1P signaling

S1P is a potent signaling molecule that activates various cellular signaling pathways.[15] As shown in Fig. 1, S1P is generated through a

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series of steps beginning with the hydrolysis of ceramide into sphingosine by ceramidase.[16] Sphingosine is phosphorylated to its active form S1P by two sphingosine kinase isoforms (SphK1 and SphK2).[17] SphK1 generates cytosolic S1P while SphK2 contains a nuclear localization signal that allows the synthesis of nuclear S1P, which has been identified as a potent inhibitor of histone deacetylase.[18] In addition, SphKs are differentially expressed with SphK1 highly expressed in the spleen and lung while SphK2 in the liver, brain, kidney and heart.[19] S1P can directly mediate cellular response pathways intracellularly and several intracellular S1P targets have been identified including the activation of tumor necrosis factor (TNF) receptor-associated factor 2 (TRAF2) which plays a key role in the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activation pathway.[20–24] S1P plays a critical role in regulating epithelial barrier function, vascular tone, inflammatory response and S1P level is therefore tightly regulated. Along with erythrocytes and platelets, the liver plays a central role in S1P regulation and contributes to the S1P level in plasma. S1P plasma concentration in humans is approximately 1 μM and is associated with apolipoprotein M (ApoM), a component of high-density lipoprotein (HDL) that is bound to S1P. ApoM-S1P level has been shown to decrease during sepsis and inflammation underscoring the importance of S1P level for endothelial barrier.[25,26]

Interestingly, S1P can also be transported out of the cell through ATP-binding cassette (ABC) transporters or by major facilitator superfamily member spinster 2 (Spns2).[20] Once exported out of the cell, S1P can activate a family of five different S1PRs (S1PR1-5).[27–30] Since their discovery, these S1PRs have been reported to carry out various important cellular functions.[31] S1PR1 is important for its role in immune cell trafficking and angiogenesis. S1PR1 deletion is proved to be embryonically lethal.[32–34] S1PR2 deficient mice have been shown to develop spontaneous seizures and fatty liver.[35,36] S1PR3 plays a key role in lung barrier integrity and vascular endothelial function.[37] S1PR4 is highly expressed in leukocytes and regulates T cell cytokine production.[38] S1PR5 is expressed in oligodendrocytes; however, its function remains largely unknown.[39] The discovery of these S1PRs and their biological functions has made targeting the S1P signaling pathways attractive novel therapeutic candidates for various diseases. To date, various agonists and antagonists of the S1PRs and SphKs have been developed.[40] These pharmacologic modulators of the S1P-mediated signaling pathways have been reported to have promising results for liver fibrosis. Fingolimod (FTY720), a modulator of the S1PRs except S1PR2, is currently being used to treat multiple sclerosis.[41] In addition, Amiselimod (MT-1303) targets S1PR2 and is in phase II clinical trials for the treatment of Crohn's disease (CD).[42] Yeliva (ABC294640) is a specific SphK2 inhibitor in phase II clinical trials and has been shown to have promising results as an anti-cancer and anti-inflammatory agent.[43]

3. SphKs/S1P in hepatic lipid metabolism

Metabolic diseases such as obesity, diabetes, NAFLD/NASH and cardiovascular diseases remain at the top of the list in Western countries for its ever-increasing morbidity and mortality.[44–46]

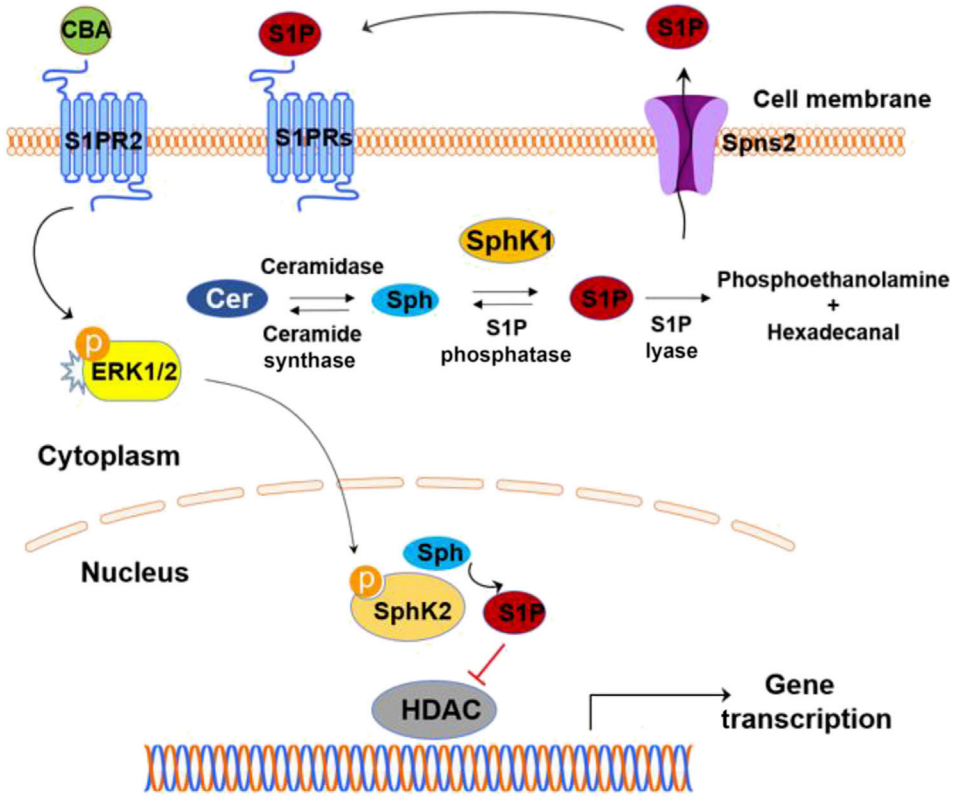

Fig. 1. S1P mediated signaling pathways. Sphingosine can be phosphorylated to form S1P by SphK1 in the cytosol or SphK2 in the nucleus. Cytosolic S1P can be exported by transporters (ABCA1, ABCC1, and Spns2) to activate five different S1P receptors (S1PR1-5). In addition, conjugated bile acids can also activate S1PR2. Sphingosine can form ceramide by ceramidase or S1P can be degraded by S1P lyase to form phosphoethanolamine and hexadecanal. Activation of S1PR2 can activate ERK1/2 which leads to the generation of nuclear S1P by SphK2. Nuclear S1P is a strong inhibitor of HDAC1/2 activity leading to the upregulation of gene transcription. Abbreviations: CBA, conjugated bile acid; Cer, ceramide; ERK, extracellular regulated protein kinases; HDAC, histone deacetylases; S1P, sphingosine-1-phosphate; S1PRs, sphingosine-1-phosphate receptors; Sph, sphingosine; SphK1, sphingosine kinase 1; SphK2, sphingosine kinase 2; Spns2, spinster 2.

SphKs have recently been shown to play a critical role in lipid metabolism and lipid-related disorders.[47,48] Circulating S1P in the plasma is bound to HDL and albumin.[15] Interestingly, atherosclerosis protection has been observed when S1P is released from HDL.[49,50] Studies were performed on apolipoprotein E (*ApoE*) knockout mice where inhibiting or silencing S1PR2 reduced atherosclerotic plaque formation.[51] This observation is further substantiated by another study using FTY720, an analogue of S1P, effectively attenuating atherosclerosis in rodents.[52–56] Furthermore, it has been previously reported that sphingolipids are linked to diabetes, and SphKs/S1P signaling plays an important role in insulin resistance and hepatic lipid metabolism.[6,47,48,57,58] In addition, evidence suggests that SphK1 level, but not SphK2, is increased in *ob*/*ob* mouse adipocytes and during adipogenesis.[59]

While studies have implicated SphKs in hepatic lipid metabolism, the functions of SphK1 and SphK2 seem to differ and are less clear. Lipid metabolism is maintained through homeostasis by various physiologic reactions such as fatty acid synthesis, fatty acid oxidation, bile acid production and the synthesis of cellular components that require lipids.[60] Mouse studies reveal that a high-fat high-glucose diet results in increased hepatic lipid accumulation along with decreased SphK1 level, but not SphK2.[48] Interestingly, knocking out *SphK1* protected mice from lipid accumulation and inflammation.[61] Genetic deletion of *SphK1* attenuated hepatic steatosis in high-fat diet fed mice through downregulating the expression of peroxisome proliferator-activated receptor gamma (PPARγ) in the liver.[47] The observed steatotic accumulation is mediated by the activation of S1PR2 and S1PR3, but not S1PR1.[47] Moreover, SphK1 expression is elevated in high-fat high-glucose fed mice and human NASH patients.[61]

The function of SphK2 is less well-characterized and seems to have an opposing function to SphK1. The physiologic role of SphK2 has been demonstrated to be involved in regulating immune cell function and inflammation.[62,63] However, the exact role remains unclear in various disease settings. Recent studies have demonstrated that SphK2 is a key regulator of hepatic lipid metabolism.[64] Previously, we reported that *SphK2* deficient mice on a high-fat diet developed overt fatty liver compared to wild type. Key lipid metabolism genes such as sterol regulatory element binding protein 1c (SREBP1c), fatty acid synthase (FAS), low-density lipoprotein receptor (LDLR), farnesoid X receptor (FXR), and PPARγ are significantly downregulated in both *S1PR2*$^{-/-}$ and *SphK2*$^{-/-}$ mice.[64] Another group also demonstrated that the activation of SphK2 by endoplasmic reticulum (ER) stress attenuates hepatic steatosis and insulin resistance.[57] These studies suggest that the differential subcellular localization between SphK1 and SphK2 may play a different mechanistic function in regulating hepatic lipid metabolism.

4. Role of S1P in GI diseases

Several studies have demonstrated a critical role for S1P in endothelial barrier function and inflammation.[65,66] Activation of S1P-mediated signaling pathways has been linked to colitis, IBD and colorectal cancer.[11] Chronic state of inflammation in the gut increases the relative risk of developing cancer and there has been an impetus for finding suitable pharmacologic targets to attenuate the inflammatory response in the gut. However, S1P activation is not all deleterious and S1P has been shown to have a protective role in various tissues including the heart, brain, lung and kidney.[67–70] S1P enhances endothelial function in the lung and attenuates acute lung injury in animal models.[71] In addition, S1P has been shown to protect the heart from ischemia-reperfusion injury.[72] Despite the wealth of literature on S1P's role in promoting endothelial barrier integrity, only recently have studies turned to elucidating the role of S1P in intestinal epithelial barrier function.

IBD is a disease caused by a dysregulation of host immune function in the GI tract and affects up to 0.5% of the population in Western countries. IBD is subdivided into two disease entities, ulcerative colitis (UC) and CD.[73,74] UC is characterized by continuous inflammation of the mucosa with crypt abscesses while CD is more characteristic of skip lesions in the GI tract with cobblestoning.[75,76] Symptoms of IBD include diarrhea, bloody stool and abdominal pain and medical management of IBD involves immunosuppression.[77] The early drugs used to treat IBD utilize glucocorticoids, sulfasalazine/5-aminosalicylic acid and methotrexate to attenuate the inflammatory response.[78–80] However, these drugs acted nonspecifically and unwanted systemic side effects were apparent. With advances in immunotherapy, the next generation of drugs were specific monoclonal antibodies directed at tumor necrosis factor alpha (TNFα) such as infliximab and adalimumab.[81] However, anti-TNFα proved to be effective in only a subset of patients and the efficacy diminished with time. With the increased knowledge in the pathophysiology behind IBD and its cause is due to lymphocyte trafficking and immune cell dysfunction, the quest for drug targets that directly inhibit these pathways has received substantial attention.

In this regard, S1P has the potential to be an effective drug target due to its role in lymphocyte egress and T cell differentiation.[82] Moreover, S1PR2, S1PR3 and S1PR5 have been suggested to play a role in macrophage and natural killer cell trafficking.[83] Clinical studies have shown that interleukin 6 (IL-6), TNFα, NFκB, and signal transducer and activator of transcription 3 (STAT3) expressions in IBD patients are elevated.[84]

Accordingly, S1P has been shown to mediate TNFα activation and subsequently the NFκB pathway. Genetic studies supported this notion when *SphK1* deficient mice were partially protected against dextran sulfate sodium (DSS)-induced colitis.[85] Furthermore, data demonstrating the importance of S1P in IBD is a pediatric case study on IBD analyzing the gene expression levels of proteins involved in S1P metabolism. The critical findings of this study showed an upregulation of S1P synthetic genes (*SphK1*, *SphK2*), signaling (S1PR1, S1PR2, S1PR4) and degradation (SGPL1) in colon biopsies of IBD patients with moderate to severe symptoms compared to control or patients in remission. Moreover, ceramide and ceramide-1-phosphate (C1P) levels were significantly elevated in IBD patients compared to control.[86]

Chronic intestinal inflammation has been linked to colorectal cancer and reports demonstrated that S1P mediates pro-inflammatory cytokines such as TNFα.[87,88] Interestingly, colon biopsies from colorectal cancer patients showed an elevation of SphK1 level.[89] It is believed that the NFκB and STAT3 are activated which enhances the survival of intestinal epithelial cells. In a feedback loop, NFκB and STAT3 induce pro-inflammatory cytokines IL-6 and TNFα, effectively reinforcing inflammation-induced tumorigenesis.[90] S1P and SphK1 have been implicated in colorectal cancer through its association with TNFα. TNFα promotes the translocation of SphK1 to the plasma membrane to produce S1P. Moreover, it has been suggested that SphK1 and intracellular SphK1 can stimulate the E3 ligase activity of TRAF2, contributing to the activation of NFκB pathway leading to inflammation and anti-apoptotic signals.[91]

5. Molecular mechanisms of S1P signaling in gut-liver axis

Numerous studies demonstrating the causal relationship of diseases affecting the gut also impacting the liver. Since blood from the GI tract drains to the liver via the hepatic portal system, bacterial products, cytokines and various biological signal molecules in

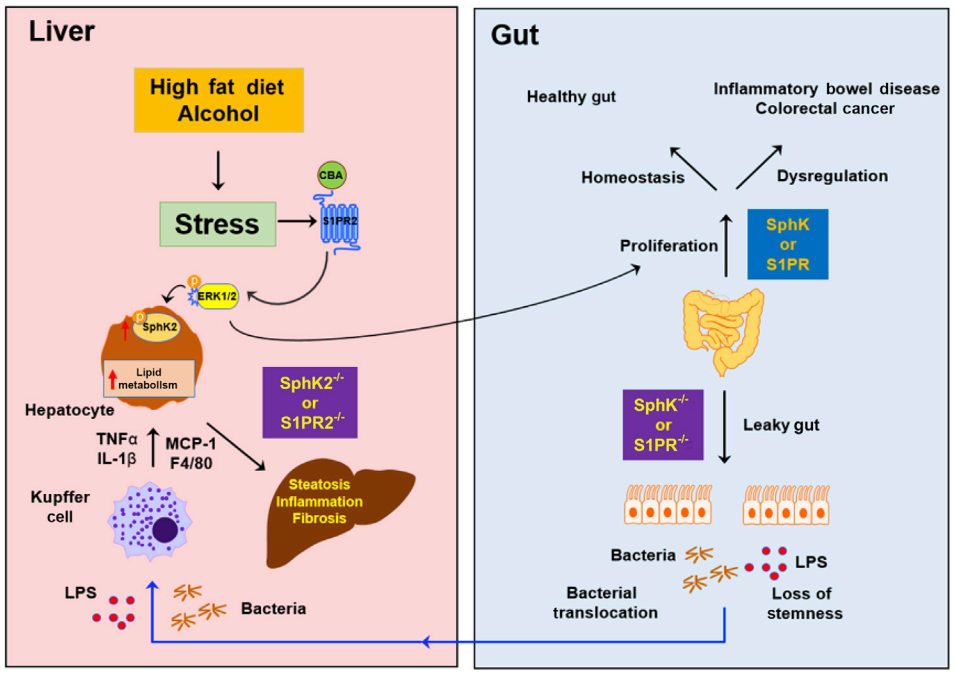

Fig. 2. Schematic diagram of S1P signaling in the gut-liver Axis. In response to stressors such as high-fat diet or alcohol, S1PR2-mediated activation of Sphk2 leads to the upregulation of hepatic lipid metabolism. In the absence of S1PR2 or SphK2, fatty liver (steatosis), inflammation or fibrosis may result when challenged with stressors. In the gut, S1P promotes epithelial stem cell growth and proliferation. Under physiologic conditions, this promotes a healthy gut but when S1P production is dysregulated, this could result in the promotion of inflammatory bowel disease (IBD) or colorectal cancer. In the absence of S1P, there is a loss of stemness in the gut resulting in leaky gut. Bacteria and bacterial products such as LPS travel to the liver through the portal circulation to sensitize resident liver macrophages (Kupffer cells). Kupffer cells release pro-inflammatory cytokines (TNFα, IL-1β, MCP-1, F4/80) that further potentiate liver injury. Abbreviations: CBA, conjugated bile acid; ERK, extracellular regulated protein kinases; F4/80, EGF-like module-containing mucin-like hormone receptor-like 1; IL-1β, interleukin 1 beta; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein 1; S1PR, sphingosine-1-phosphate receptor; SphK, sphingosine kinase; TNFα, tumor necrosis factor alpha.

the gut could very well produce a disease state in the liver.[92,93] With the ever-increasing body of knowledge on S1P in gut and liver pathology, we will highlight potential mechanisms of how S1P signaling could produce pathologies in both the gut and liver.

Recent evidence supports the notion that there is a strong interaction between the gut microbiota and the liver. Receiving about 70% of blood from the intestines, the liver encounters majority of bacterial-derived products and antigens from the gut.[94] Concurrently, inflammation is a critical component of liver disease progression with the activation of intrahepatic macrophages, Kupffer cells and the release of pro-inflammatory cytokines.[95] The role of the gut-liver axis is critical in understanding the pathogenesis of alcoholic liver disease. Alcohol disrupts the intestinal barrier via damaging intestinal integrity, tight junctions and changing the gut microbiome. Bacterial endotoxins such as lipopolysaccharide (LPS) drain to the portal circulation and sensitize liver macrophages to release cytokines, chemokines and reactive oxygen species.[96,97] Interestingly, S1P has been shown to promote intestinal epithelial cell proliferation through the activation of S1PR2.[98] Evidence also suggests the activation of serine/threonine protein kinase (Akt) signaling pathway via S1P protects intestinal stem cells from apoptosis.[99]

Bile acids have been shown to activate S1PR2 in different types of cells in the gut and liver. Several studies have demonstrated a unique role for primary and secondary bile acids in regulating gut microbiota under different pathophysiological conditions. It has been shown that secondary bile acids produced by commensal gut bacteria from primary bile acids promote metastatic liver cancer via suppression of natural killer T (NKT) cells in the mouse models of liver cancer metastasis. Treating mice with an antibiotic cocktail to deplete the commensal gut microbiota upregulated NKT cells and promoted a liver-specific antitumor effect.[100] As secondary bile acids are generated from gut bacteria, these results demonstrate an important role for gut microbiota in regulating gut and liver disease. Moreover, it would be interesting for future studies to determine the underlying mechanisms and key signaling molecules that mediate the effects of bile acids in other gut and liver related disorders.

6. Conclusion and future perspectives

As summarized in Fig. 2, our current understanding of S1P-mediating signaling in lipid metabolism and inflammation has provided novel therapeutic targets in the treatment of various liver and GI diseases. Next steps would be to delineate the relationship between SphKs and S1PRs in the gut directly affecting the liver and vice versa. With tissue and cell-specific transgenic mice, we have a greater understanding of the role of SphKs, S1PRs and S1P playing in different organs and under different pathological conditions. Novel chemical inhibitors and agonists of SphKs and S1PRs with high specificity could be potential therapeutic agents for various metabolic diseases.

Authors' contributions

E. Kwong wrote and designed the manuscript and figures. H. Zhou designed and edited the manuscript and figures.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. Thudichum JLW. A treatise on the chemical constitution of the brain. With a new historical introd. In: Drabkin David L, ed. *Hamden, Conn. Archon Books*. 1962.
2. Hannun YA, Obeid LM. Principles of bioactive lipid signalling: lessons from sphingolipids. *Nat Rev Mol Cell Biol*. 2008;9:139–150.
3. Spiegel S, Milstien S. The outs and the ins of sphingosine-1-phosphate in immunity. *Nat Rev Immunol*. 2011;11:403–415.
4. Hanada K, Kumagai K, Tomishige N, Yamaji T. CERT-mediated trafficking of ceramide. *Biochim Biophys Acta*. 2009;1791:684–691.
5. Rao RP, Acharya JK. Sphingolipids and membrane biology as determined from genetic models. *Prostag Other Lipid Mediat*. 2008;85:1–16.
6. Ng ML, Wadham C, Sukocheva OA. The role of sphingolipid signalling in diabetesassociated pathologies (Review). *Int J Mol Med*. 2017;39:243–252.
7. Al Fadel F, Fayyaz S, Japtok L, Kleuser B. Involvement of Sphingosine 1-Phosphate in palmitate-induced non-alcoholic fatty liver disease. *Cell Physiol Biochem*. 2016;40:1637–1645.
8. Nagahashi M, Yuza K, Hirose Y, et al. The roles of bile acids and sphingosine-1-phosphate signaling in the hepatobiliary diseases. *J Lipid Res*. 2016;57:1636–1643.
9. Park SJ, Im DS. Sphingosine 1-Phosphate receptor modulators and drug discovery. *Biomol Ther (Seoul)*. 2017;25:80–90.
10. Kleuser B. Divergent role of Sphingosine 1-Phosphate in liver health and disease. *Int J Mol Sci*. 2018;19.
11. Nielsen OH, Li Y, Johansson-Lindbom B, Coskun M. Sphingosine-1-Phosphate signaling in inflammatory bowel disease. *Trends Mol Med*. 2017;23:362–374.
12. Suh JH, Saba JD. Sphingosine-1-phosphate in inflammatory bowel disease and colitis-associated colon cancer: the fat's in the fire. *Transl Cancer Res*. 2015;4:469–483.
13. Ji B, Nielsen J. From next-generation sequencing to systematic modeling of the gut microbiome. *Front Genet*. 2015;6:219.
14. Feng Q, Chen WD, Wang YD. Gut microbiota: an integral moderator in health and disease. *Front Microbiol*. 2018;9:151.
15. Maceyka M, Harikumar KB, Milstien S, Spiegel S. Sphingosine-1-phosphate signaling and its role in disease. *Trends Cell Biol*. 2012;22:50–60.
16. Hanada K. Serine palmitoyltransferase, a key enzyme of sphingolipid metabolism. *Biochim Biophys Acta*. 2003;1632:16–30.
17. Olivera A, Kohama T, Edsall L, et al. Sphingosine kinase expression increases intracellular sphingosine-1-phosphate and promotes cell growth and survival. *J Cell Biol*. 1999;147:545–558.
18. Leclercq TM, Pitson SM. Cellular signalling by sphingosine kinase and sphingosine 1-phosphate. *IUBMB Life*. 2006;58:467–472.
19. Melendez AJ, Carlos-Dias E, Gosink M, Allen JM, Takacs L. Human sphingosine kinase: molecular cloning, functional characterization and tissue distribution. *Gene*. 2000;251:19–26.
20. Mitra P, Oskeritzian CA, Payne SG, Beaven MA, Milstien S, Spiegel S. Role of ABCC1 in export of sphingosine-1-phosphate from mast cells. *Proc Natl Acad Sci U S A*. 2006;103:16394–16399.
21. English D, Welch Z, Kovala AT, et al. Sphingosine 1-phosphate released from platelets during clotting accounts for the potent endothelial cell chemotactic activity of blood serum and provides a novel link between hemostasis and angiogenesis. *FASEB J*. 2000;14:2255–2265.
22. Kawahara A, Nishi T, Hisano Y, Fukui H, Yamaguchi A, Mochizuki N. The sphingolipid transporter spns2 functions in migration of zebrafish myocardial precursors. *Science*. 2009;323:524–527.
23. Fukuhara S, Simmons S, Kawamura S, et al. The sphingosine-1-phosphate transporter Spns2 expressed on endothelial cells regulates lymphocyte trafficking in mice. *J Clin Investig*. 2012;122:1416–1426.
24. Strub GM, Maceyka M, Hait NC, Milstien S, Spiegel S. Extracellular and intracellular actions of sphingosine-1-phosphate. *Adv Exp Med Biol*. 2010;688:141–155.
25. Winkler MS, Nierhaus A, Holzmann M, et al. Decreased serum concentrations of sphingosine-1-phosphate in sepsis. *Crit Care*. 2015;19:372.
26. Frej C, Linder A, Happonen KE, Taylor FB, Lupu F, Dahlbäck B. Sphingosine 1-phosphate and its carrier apolipoprotein M in human sepsis and in Escherichia coli sepsis in baboons. *J Cell Mol Med*. 2016;20:1170–1181.
27. Hait NC, Allegood J, Maceyka M, et al. Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. *Science*. 2009;325:1254–1257.
28. Pyne NJ, McNaughton M, Boomkamp S, et al. Role of sphingosine 1-phosphate receptors, sphingosine kinases and sphingosine in cancer and inflammation. *Adv Biol Regul*. 2016;60:151–159.
29. Karimian G, Buist-Homan M, Schmidt M, et al. Sphingosine kinase-1 inhibition protects primary rat hepatocytes against bile salt-induced apoptosis. *Biochim Biophys Acta*. 2013;1832:1922–1929.
30. Kihara Y, Maceyka M, Spiegel S, Chun J. Lysophospholipid receptor nomenclature review: IUPHAR Review 8. *Br J Pharmacol*. 2014;171:3575–3594.
31. Takuwa Y, Okamoto Y, Yoshioka K, Takuwa N. Sphingosine-1-phosphate signaling in physiology and diseases. *Biofactors*. 2012;38:329–337.
32. Allende ML, Proia RL. Sphingosine-1-phosphate receptors and the development of the vascular system. *Biochim Biophys Acta*. 2002;1582:222–227.
33. Liu Y, Wada R, Yamashita T, et al. Edg-1, the G protein-coupled receptor for sphingosine-1-phosphate, is essential for vascular maturation. *J Clin Investig*. 2000;106:951–961.
34. Matloubian M, Lo CG, Cinamon G, et al. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature*. 2004;427:355–360.
35. MacLennan AJ, Carney PR, Zhu WJ, et al. An essential role for the H218/AGR16/Edg-5/LP(B2) sphingosine 1-phosphate receptor in neuronal excitability. *Eur J Neurosci*. 2001;14:203–209.
36. Kwong E, Li Y, Hylemon PB, Zhou H. Bile acids and sphingosine-1-phosphate receptor 2 in hepatic lipid metabolism. *Acta Pharm Sin B*. 2015;5:151–157.
37. Gon Y, Wood MR, Kiosses WB, et al. S1P3 receptor-induced reorganization of epithelial tight junctions compromises lung barrier integrity and is potentiated by TNF. *Proc Natl Acad Sci U S A*. 2005;102:9270–9275.
38. Wang W, Graeler MH, Goetzl EJ. Type 4 sphingosine 1-phosphate G protein-coupled receptor (S1P4) transduces S1P effects on T cell proliferation and cytokine secretion without signaling migration. *FASEB J*. 2005;19:1731–1733.
39. Terai K, Soga T, Takahashi M, et al. Edg-8 receptors are preferentially expressed in oligodendrocyte lineage cells of the rat CNS. *Neuroscience*. 2003;116:1053–1062.
40. Edmonds Y, Milstien S, Spiegel S. Development of small-molecule inhibitors of sphingosine-1-phosphate signaling. *Pharmacol Ther*. 2011;132:352–360.
41. Chun J, Hartung HP. Mechanism of action of oral fingolimod (FTY720) in multiple sclerosis. *Clin Neuropharmacol*. 2010;33:91–101.
42. Vetter M, Neurath MF. Emerging oral targeted therapies in inflammatory bowel diseases: opportunities and challenges. *Therap Adv Gastroenterol*. 2017;10:773–790.
43. Antoon JW, Beckman BS. Sphingosine kinase: a promising cancer therapeutic target. *Cancer Biol Ther*. 2011;11:647–650.
44. Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep*. 2018;20:12.
45. Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol*. 2015;62:S47–S64.
46. Li L, Liu DW, Yan HY, Wang ZY, Zhao SH, Wang B. Obesity is an independent risk factor for non-alcoholic fatty liver disease: evidence from a meta-analysis of 21 cohort studies. *Obes Rev*. 2016;17:510–519.
47. Chen J, Wang W, Qi Y, et al. Deletion of sphingosine kinase 1 ameliorates hepatic steatosis in diet-induced obese mice: role of PPARgamma. *Biochim Biophys Acta*. 2016;1861:138–147.
48. Kowalski GM, Kloehn J, Burch ML, et al. Overexpression of sphingosine kinase 1 in liver reduces triglyceride content in mice fed a low but not high-fat diet. *Biochim Biophys Acta*. 2015;1851:210–219.
49. Potì F, Ceglarek U, Burkhardt R, Simoni M, Nofer JR. SKI-II–a sphingosine kinase 1 inhibitor–exacerbates atherosclerosis in low-density lipoprotein receptor-deficient (LDL-$R^{-/-}$) mice on high cholesterol diet. *Atherosclerosis*. 2015;240:212–215.
50. Potì F, Simoni M, Nofer JR. Atheroprotective role of high-density lipoprotein (HDL)-associated sphingosine-1-phosphate (S1P). *Cardiovasc Res*. 2014;103:395–404.
51. Wang F, Okamoto Y, Inoki I, et al. Sphingosine-1-phosphate receptor-2 deficiency leads to inhibition of macrophage proinflammatory activities and atherosclerosis in apoE-deficient mice. *J Clin Investig*. 2010;120:3979–3995.
52. Luk FS, Kim RY, Li K, et al. Immunosuppression with FTY720 reverses cardiac dysfunction in hypomorphic ApoE mice deficient in SR-BI expression that survive myocardial infarction caused by coronary atherosclerosis. *J Cardiovasc Pharmacol*. 2016;67:47–56.
53. Wang G, Kim RY, Imhof I, et al. The immunosuppressant FTY720 prolongs survival in a mouse model of diet-induced coronary atherosclerosis and myocardial infarction. *J Cardiovasc Pharmacol*. 2014;63:132–143.
54. Huang K, Li SQ, Wang WJ, et al. Oral FTY720 administration induces immune tolerance and inhibits early development of atherosclerosis in apolipoprotein E-deficient mice. *Int J Immunopathol Pharmacol*. 2012;25:397–406.
55. Potì F, Costa S, Bergonzini V, et al. Effect of sphingosine 1-phosphate (S1P) receptor agonists FTY720 and CYM5442 on atherosclerosis development in LDL receptor deficient (LDL-$R^{-/-}$) mice. *Vascul Pharmacol*. 2012;57:56–64.
56. Nofer JR, Bot M, Brodde M, et al. FTY720, a synthetic sphingosine 1 phosphate analogue, inhibits development of atherosclerosis in low-density lipoprotein receptor-deficient mice. *Circulation*. 2007;115:501–508.
57. Lee SY, Hong IK, Kim BR, et al. Activation of sphingosine kinase 2 by endoplasmic reticulum stress ameliorates hepatic steatosis and insulin resistance in mice. *Hepatology*. 2015;62:135–146.
58. Bruce CR, Risis S, Babb JR, et al. Overexpression of sphingosine kinase 1 prevents ceramide accumulation and ameliorates muscle insulin resistance in high-fat diet-fed mice. *Diabetes*. 2012;61:3148–3155.
59. Hashimoto T, Igarashi J, Kosaka H. Sphingosine kinase is induced in mouse 3T3-L1 cells and promotes adipogenesis. *J Lipid Res*. 2009;50:602–610.
60. Brunt EM, Wong VW, Nobili V, et al. Nonalcoholic fatty liver disease. *Nat Rev Dis Primers*. 2015;1:15080.

61. Geng T, Sutter A, Harland MD, et al. SphK1 mediates hepatic inflammation in a mouse model of NASH induced by high saturated fat feeding and initiates proinflammatory signaling in hepatocytes. *J Lipid Res*. 2015;56:2359–2371.
62. Neubauer HA, Pitson SM. Roles, regulation and inhibitors of sphingosine kinase 2. *FEBS J*. 2013;280:5317–5336.
63. Xu T, Li L, Huang C, Peng Y, Li J. Sphingosine kinase 2: a controversial role in arthritis. *Rheumatol Int*. 2014;34:1015–1016.
64. Nagahashi M, Takabe K, Liu R, et al. Conjugated bile acid-activated S1P receptor 2 is a key regulator of sphingosine kinase 2 and hepatic gene expression. *Hepatology*. 2015;61:1216–1226.
65. Kunisawa J, Kiyono H. Immunological function of sphingosine 1-phosphate in the intestine. *Nutrients*. 2012;4:154–166.
66. Oskouian B, Saba J. Sphingosine-1-phosphate metabolism and intestinal tumorigenesis: lipid signaling strikes again. *Cell Cycle*. 2007;6:522–527.
67. Hofmann U, Burkard N, Vogt C, et al. Protective effects of sphingosine-1-phosphate receptor agonist treatment after myocardial ischaemia-reperfusion. *Cardiovasc Res*. 2009;83:285–293.
68. Couttas TA, Kain N, Daniels B, et al. Loss of the neuroprotective factor Sphingosine 1-phosphate early in Alzheimer's disease pathogenesis. *Acta Neuropathol Commun*. 2014;2:9.
69. Peng X, Hassoun PM, Sammani S, et al. Protective effects of sphingosine 1-phosphate in murine endotoxin-induced inflammatory lung injury. *Am J Respir Crit Care Med*. 2004;169:1245–1251.
70. Perry HM, Huang L, Ye H, et al. Endothelial Sphingosine 1-Phosphate Receptor-1 mediates protection and recovery from acute kidney injury. *J Am Soc Nephrol*. 2016;27:3383–3393.
71. Mehaffey JH, Charles EJ, Narahari AK, et al. Increasing circulating sphingosine-1-phosphate attenuates lung injury during ex vivo lung perfusion. *J Thorac Cardiovasc Surg*. 2018;156:910–917.
72. Morel S, Christoffersen C, Axelsen LN, et al. Sphingosine-1-phosphate reduces ischaemia-reperfusion injury by phosphorylating the gap junction protein Connexin43. *Cardiovasc Res*. 2016;109:385–396.
73. Dubinsky M, Braun J. Diagnostic and prognostic microbial biomarkers in inflammatory bowel diseases. *Gastroenterology*. 2015;149:1265–1274 (e3).
74. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology*. 2014;146:1489–1499.
75. Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med*. 2011;365:1713–1725.
76. Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med*. 2009;361:2066–2078.
77. Larsen S, Bendtzen K, Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. *Ann Med*. 2010;42:97–114.
78. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106:590–599.
79. Nielsen OH, Munck LK. Drug insight: aminosalicylates for the treatment of IBD. *Nat Clin Pract Gastroenterol Hepatol*. 2007;4:160–170.
80. Nielsen OH, Coskun M, Steenholdt C, Rogler G. The role and advances of immunomodulator therapy for inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol*. 2015;9:177–189.
81. Nielsen OH, Ainsworth MA. Tumor necrosis factor inhibitors for inflammatory bowel disease. *N Engl J Med*. 2013;369:754–762.
82. Garris CS, Blaho VA, Hla T, Han MH. Sphingosine-1-phosphate receptor 1 signalling in T cells: trafficking and beyond. *Immunology*. 2014;142:347–353.
83. Aoki M, Aoki H, Ramanathan R, Hait NC, Takabe K. Sphingosine-1-Phosphate signaling in immune cells and inflammation: roles and therapeutic potential. *Mediat Inflamm*. 2016;2016:8606878.
84. Nagahashi M, Hait NC, Maceyka M, et al. Sphingosine-1-phosphate in chronic intestinal inflammation and cancer. *Adv Biol Regul*. 2014;54:112–120.
85. Snider AJ, Kawamori T, Bradshaw SG, et al. A role for sphingosine kinase 1 in dextran sulfate sodium-induced colitis. *FASEB J*. 2009;23:143–152.
86. Suh JH, Degagné É, Gleghorn EE, et al. Sphingosine-1-Phosphate signaling and metabolism gene signature in pediatric inflammatory bowel disease: a matched-case control pilot study. *Inflamm Bowel Dis*. 2018;24:1321–1334.
87. Oskouian B, Sooriyakumaran P, Borowsky AD, et al. Sphingosine-1-phosphate lyase potentiates apoptosis via p53- and p38-dependent pathways and is down-regulated in colon cancer. *Proc Natl Acad Sci U S A*. 2006;103:17384–17389.
88. Bao Y, Guo Y, Zhang C, Fan F, Yang W. Sphingosine kinase 1 and Sphingosine-1-Phosphate signaling in colorectal cancer. *Int J Mol Sci*. 2017;18.
89. Kawamori T, Kaneshiro T, Okumura M, et al. Role for sphingosine kinase 1 in colon carcinogenesis. *FASEB J*. 2009;23:405–414.
90. Pyne NJ, Pyne S. Sphingosine 1-phosphate is a missing link between chronic inflammation and colon cancer. *Cancer Cell*. 2013;23:5–7.
91. Alvarez SE, Harikumar KB, Hait NC, et al. Sphingosine-1-phosphate is a missing cofactor for the E3 ubiquitin ligase TRAF2. *Nature*. 2010;465:1084–1088.
92. Paolella G, Mandato C, Pierri L, Poeta M, Di Stasi M, Vajro P. Gut-liver axis and probiotics: their role in non-alcoholic fatty liver disease. *World J Gastroenterol*. 2014;20:15518–15531.
93. Fukui H. Gut-liver axis in liver cirrhosis: how to manage leaky gut and endotoxemia. *World J Hepatol*. 2015;7:425–442.
94. Compare D, Coccoli P, Rocco A, et al. Gut–liver axis: the impact of gut microbiota on non alcoholic fatty liver disease. *Nutr Metabol Cardiovasc Dis*. 2012;22:471–476.
95. Nolan JP. The role of intestinal endotoxin in liver injury: a long and evolving history. *Hepatology*. 2010;52:1829–1835.
96. Szabo G, Bala S. Alcoholic liver disease and the gut-liver axis. *World J Gastroenterol*. 2010;16:1321–1329.
97. Szabo G, Petrasek J. Gut-liver axis and sterile signals in the development of alcoholic liver disease. *Alcohol Alcohol*. 2017;52:414–424.
98. Chen T, Huang Z, Liu R, Yang J, Hylemon PB, Zhou H. Sphingosine-1 phosphate promotes intestinal epithelial cell proliferation via S1PR2. *Front Biosci (Landmark Ed)*. 2017;22:596–608.
99. Greenspon J, Li R, Xiao L, et al. Sphingosine-1-phosphate protects intestinal epithelial cells from apoptosis through the Akt signaling pathway. *Dig Dis Sci*. 2009;54:499–510.
100. Ma C, Han M, Heinrich B, et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science*. 2018:360.