Published in final edited form as:

Hepatology. 2015 April ; 61(4): 1118–1120. doi:10.1002/hep.27616.

Sphingosine-1-phosphate receptor 2: a novel bile acid receptor and regulator of hepatic lipid metabolism?

John Y. L. Chiang

Northeast Ohio Medical University

Dysregulation of hepatic lipid metabolism is a major contributing factor for the development of hepatic steatosis and pathogenesis of non-alcoholic fatty liver disease (NAFLD), diabetes and obesity. Bile acids have lipid-lowering effects but the underlying mechanisms are very complex and not fully understood [review in ¹]. It has been known for a long time that bile acid pool size is inversely correlated to serum triglyceride levels in human patients. Bile acid sequestrants reduce bile acid pool size but increase serum triglycerides. Conversely, bile acid treatment in hypertriglyceridemia and gallstone patients decreased serum triglycerides and VLDL production. The discovery of farnesoid X receptor (FXR) as a bile acid-activated receptor has generated a plethora of research to study the roles of bile acids in the regulation of hepatic lipid metabolism in recent years [review in ²].

FXR is activated by primary bile acids, chenodeoxycholic acid and cholic acid, to inhibit bile acid synthesis by a feedback mechanism (Fig 1). In the liver, FXR induces the small heterodimer partner (SHP), which inhibits cholesterol 7 α -hydroxylase (CYP7A1) gene transcription and bile acid synthesis. In the intestine, FXR induces fibroblast growth factor 15 (FGF15, or a human orthologue FGF19), which is secreted into blood circulation to hepatocytes to activate the FGF receptor 4 (FGFR4) that activates the mitogen activated protein kinase (MAPK)/extracellular receptor kinase 1/2 (ERK1/2) pathway to inhibit CYP7A1. CA and synthetic FXR agonists have been shown to reduce serum triglycerides in diabetic and obese mice. Consistently, FXR^{-/-} mice have increased serum triglycerides and pro-atherogenic lipoprotein profiles.

FXR signaling may regulate hepatic lipid metabolism by several mechanisms. It has been reported that activation of FXR by bile acids or FXR agonists inhibits steroid response element binding protein-1c (SREBP-1c)-mediated hepatic lipogenesis. It was suggested that the FXR/SHP pathway might inhibit expression of the genes in lipogenesis and VLDL metabolism (Fig 1). FXR agonists stimulate triglyceride clearance. Transgenic overexpression of FGF19 has been shown to increase metabolic rate in mice, but the mechanism is not clear. More importantly, recent studies showed that bile acids and FXR agonists had an anti-inflammatory function through the inhibition of NF κ B-mediated inflammatory cytokine production in hepatocytes and enterocytes ^{3, 4}. However, how FXR signaling inhibits NF- κ B activity is not clear. Expression of the SREBP-1c and its target

Corresponding address John Y. L. Chiang, Ph.D. Department of Integrative Medical Sciences, College of Medicine, Northeast Ohio Medical University, 4209 SR 44, Rootstown, OH 44272, jchiang@neomed.edu, Fax: 330-325-5910.

Potential conflict of interest: none

genes is not reduced in FXR^{-/-} mice, suggesting that FXR-independent mechanisms may also be involved in the triglyceride-lowering effect of bile acids.

Secondary bile acids (lithocholic acid and deoxycholic acid) and their taurine conjugates are activators of Gαs protein-coupled receptor, TGR5 (aka Gpbar1). In the digestive tract, TGR5 is expressed in the gallbladder epithelium and in the intestine. In the liver, TGR5 is expressed in Kupffer cells and sinusoidal endothelial cells, as well as in cholangiocytes, but not in hepatocytes. Activation of TGR5 signaling stimulates energy metabolism in brown adipose tissue, protects the intestinal barrier function and alleviates inflammation in animal models of inflammatory bowel diseases. However, TGR5^{-/-} mice have no obvious liver metabolic phenotype. Activation of TGR5 has been shown to protect liver from inflammation but the underlying mechanism is not clear. TGR5 agonists increase insulin secretion from β cells and glycogen like peptide-1 secretion from enteroendocrine cells, and may contribute to the amelioration of liver inflammation and insulin resistance.

Another GPCR, sphingosine-1-phosphate receptor 2 (S1PR2) has recently been reported as a conjugated bile acid-activated receptor ⁵. Taurocholic acid (TCA) is the most abundant bile acid in humans and mice and is an efficacious activator of S1PR2 in hepatocytes. S1P activates a S1P family of Gαi-coupled receptors (S1PR1 to 5). S1P kinases (SphK1 and SphK2) phosphorylate sphingosine to S1P. SphK1 is located in the cytosol, whereas SphK2 is localized in the nucleus. In hepatocytes, S1PR2 signaling activates ERK1/2 in the MAPK signaling pathways and AKT in insulin signaling (Fig 1). Sphingolipid metabolites have diverse functions in endothelial cells, including immune response, lymphatic trafficking, and vascular integrity ⁶. In endothelial cells, S1P/S1PRs mediated signaling activates NF-κB in pro-inflammatory responses. The role of S1PR2/SphK2/S1P on hepatic lipid metabolism has not been studied.

In this issue of Hepatology, Nagahashi et al. ⁷ reported a novel finding that the S1PR2/SphK2/S1P signaling pathway might play a key role in control of hepatic lipid metabolism in mice. A previous *in vitro* study reported that the nuclear SphK2-generated S1P bound to and inhibited histone deacetylases 1 and 2 (HDAC1/2) activity and increased histone acetylation and expression of cyclin-dependent kinase inhibitor p21 and cFos of MCF-7 and HeLa cells ⁸. The current *in vivo* study showed that in S1PR2^{-/-} and SphK2^{-/-} mice acetylated histone 3 and histone 4 levels were reduced and these reductions correlated to reduced mRNA expression levels of SREBP-1c and its regulated genes in lipid metabolism and bile acid synthesis genes (not CYP7A1). Furthermore, overexpression of S1PR2 induced these hepatic genes (including CYP7A1) in wild-type and S1PR2^{-/-} mice, but not in SphK2^{-/-} mice suggesting that SphK2 is necessary for mediating S1PR2 signaling in lipid metabolism. A high fat/high cholesterol diet and a lithogenic diet (containing high cholesterol and cholic acid) induced SphK2, but not SphK1 expression in wild-type mouse liver. It is important to note that SphK2^{-/-} mice on a chow diet had markedly elevated serum triglycerides and AST and ALT levels compared to wild type mice. High fat diet feeding increased serum triglycerides and AST and ALT levels in wild-type mice as expected, but did not further increase serum triglyceride and AST/ALT level in SphK2^{-/-} mice. These data may imply that TCA/S1PR2/SphK2/S1P signaling may play a key role in mediating the anti-inflammatory function of bile acids in hepatocytes. It is important to study whether or not

the TCA/S1PR2/ SphK2/S1P signaling pathway modulates NF- κ B-mediated pro-inflammatory cytokine production via epigenetic mechanism in hepatocytes.

Paradoxically, both SHP and CYP7A1 mRNA expression levels were significantly increased in wild-type and S1PR2^{-/-} mice by overexpressing S1PR2. It has been reported that SHP recruits HDAC1/2, histone lysine-specific demethylase 1 (LSD-1), histone methyltransferase G9a and other chromatin modifying enzymes to inhibit CYP7A1 gene transcription⁹. Thus, TCA may activate the SHP/HDAC/LSD1/G9a pathway to inhibit and activate the S1PR2/ SphK2/S1P/HDAC1/2 pathway to induce CYP7A1 expression levels to modulate bile acid homeostasis. Histone acetylation and methylation of the chromatin in gene promoters has emerged as a key mechanism for regulation of liver metabolism.

This study uncovered a novel role of the TCA/S1PR2/SphK2/S1P pathway in control of hepatic lipid metabolism. Further detailed study is needed to: 1) identify the liver metabolic phenotypes and differentially regulated genes and pathways in S1PR2^{-/-} and SphK2^{-/-} mice; 2) confirm the role of the S1PR2/SphK2/S1P pathway in control of hepatic lipid gene expression by epigenetic mechanism; and 3) identify other metabolic pathways and mechanisms that may be involved in the pleiotropic effects of S1P and its implication in pathogenesis of NAFLD. Inhibitors targeted to HDAC and histone methyltransferase activity are currently being developed as drug therapies for treatment of cancer and other human diseases, and may also have potential for treating inflammatory liver-related metabolic diseases, such as NAFLD and diabetes.

References

1. Fuchs C, Claudel T, Trauner M. Bile acid-mediated control of liver triglycerides. *Semin Liver Dis.* 2013; 33:330–342. [PubMed: 24222091]
2. Li T, Chiang JY. Bile acid signaling in metabolic disease and drug therapy. *Pharmacol Rev.* 2014; 66:948–983. [PubMed: 25073467]
3. Zhang S, Wang J, Liu Q, Harnish DC. Farnesoid X receptor agonist WAY-362450 attenuates liver inflammation and fibrosis in murine model of non-alcoholic steatohepatitis. *J Hepatol.* 2009; 51:380–388. [PubMed: 19501927]
4. Gadaleta RM, van Erpecum KJ, Oldenburg B, Willemsen EC, Renooij W, Murzilli S, Klomp LW, et al. Farnesoid X receptor activation inhibits inflammation and preserves the intestinal barrier in inflammatory bowel disease. *Gut.* 2011; 60:463–472. [PubMed: 21242261]
5. Studer E, Zhou X, Zhao R, Wang Y, Takabe K, Nagahashi M, Pandak WM, et al. Conjugated bile acids activate the sphingosine-1-phosphate receptor 2 in primary rodent hepatocytes. *Hepatology.* 2012; 55:267–276. [PubMed: 21932398]
6. Maceyka M, Spiegel S. Sphingolipid metabolites in inflammatory disease. *Nature.* 2014; 510:58–67. [PubMed: 24899305]
7. Nagahashi M, Takabe K, Liu R, Peng K, Wang X, Wang Y, Halt NC, Wang X, Allegood JC, Tamada A, Aoyagi T, Pandak WM, Spiegel S, Hylemon PB, Zhou H. Conjugated bile acid activated S1P receptor 2 is a key regulator of sphingosine kinase 2 and hepatic gene expression. *Hepatology.* 2014
8. Hait NC, Allegood J, Maceyka M, Strub GM, Harikumar KB, Singh SK, Luo C, et al. Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. *Science.* 2009; 325:1254–1257. [PubMed: 19729656]
9. Seok S, Kanamaluru D, Xiao Z, Ryerson D, Choi SE, Suino-Powell K, Xu HE, et al. Bile Acid Signal-induced Phosphorylation of Small Heterodimer Partner by Protein Kinase C ζ Is Critical

for Epigenomic Regulation of Liver Metabolic Genes. J Biol Chem. 2013; 288:23252–23263.
[PubMed: 23824184]

Abbreviation list

CYP7A1	cholesterol 7 α -hydroxylase
ERK1/2	extracellular receptor kinase 1/2
FXR	farnesoid X receptor
FGF15	fibroblast growth factor 15
MAPK	mitogen activated protein kinase
NAFLD	non-alcoholic fatty liver disease
SHP	small heterodimer partner
S1PR	sphingosine-1-phosphate receptor
S1P	sphingosine-1-phosphate
SphK2	S1P kinase 2
SREBP-1c	steroid response element binding protein-1c
TCA	taurocholic acid
TGR5 (aka Gpbar1)	G protein bile acid receptor 1

adipose tissues, TGR5/cAMP signaling may stimulate energy metabolism by inducing a type 2 deiodinase, which activates T_4 to T_3 . In the intestine, TGR5 signaling protects barrier function and inflammation in the intestine, and may indirectly protect hepatocyte against inflammation. Conjugated bile acids, taurocholic acid (TCA) selectively activates a sphingosine-1-phosphate receptor 2 (S1PR2) in hepatocytes. Extracellular signal activates sphingosine kinase 1 (SphK1), which is translocated to plasma membrane to phosphorylate sphingosine to S1P. S1P activates membrane S1PRs by paracrine/autocrine mechanism. Growth factors (epidermal growth factor, FGFR4, etc.) and phorbol esters activate protein kinase C (PKC), which activates ERK1/2 of the mitogen-activated kinase (MAPK) pathway to phosphorylate SphK2. SphK2 is translocated to the nucleus to bind to histone deacetylase 1/2 (HDAC1/2). S1P signaling activates ERK1/2, and AKT in insulin receptor signaling pathway. Nuclear SphK2 generated S1P has been shown to bind to chromatin and inhibits HDAC1/2. Inhibition of HDAC1/2 results in activation of histone acetylases, which stimulate expression of steroid response element binding protein-1c (SREBP-1c), which induces all genes in lipogenesis (fatty acid synthase, acetyl-CoA carboxylase, etc.), and CYP7A1 in bile acid synthesis. On the other hand, the FXR/SHP pathway inhibits SREBP-1c and CYP7A1 gene transcription by recruiting HDAC1/2, histone methyltransferase G9a, and histone lysine-specific demethylase LSD-1 to inhibit lipogenesis and bile acid synthesis. These positive and negative regulations modulate hepatic lipid homeostasis.