REVIEW

G protein-coupled receptors as potential targets for nonalcoholic fatty liver disease treatment

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is a broad-spectrum disease, ranging from simple hepatic steatosis to nonalcoholic steatohepatitis, which can progress to cirrhosis and liver cancer. Abnormal hepatic lipid accumulation is the major manifestation of this disease, and lipotoxicity promotes NAFLD progression. In addition, intermediate metabolites such as succinate can stimulate the activation of hepatic stellate cells to produce extracellular matrix proteins, resulting in progression of NAFLD to fibrosis and even cirrhosis. G protein-coupled receptors (GPCRs) have been shown to play essential roles in metabolic disorders, such as NAFLD and obesity, through their function as receptors for bile acids and free fatty acids. In addition, GPCRs link gut microbiota-mediated connections in a variety of diseases, such as intestinal diseases, hepatic steatosis, diabetes, and cardiovascular diseases. The latest findings show that gut microbiota-derived acetate contributes to liver lipogenesis by converting dietary fructose into hepatic acetyl-CoA and fatty acids. GPCR agonists, including peptides and natural products like docosahexaenoic acid, have been applied to investigate their role in liver diseases. Therapies such as probiotics and GPCR agonists may be applied to modulate GPCR function to ameliorate liver metabolism syndrome. This review summarizes the current findings regarding the role of GPCRs in the development and progression of NAFLD and describes some preclinical and clinical studies of GPCR-mediated treatment. Overall, understanding GPCR-mediated signaling in liver disease may provide new therapeutic options for NAFLD.

Key Words: Nonalcoholic fatty liver disease; G protein-coupled receptors; Metabolism; Bile acids; Short-chain fatty acids; Gut microbiota

Core Tip: Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease. Without effective treatment, NAFLD can progress to fibrosis, cirrhosis, and liver cancer. Currently, there is no effective treatment option. G protein-coupled receptors (GPCRs) have been shown to play essential roles in metabolic disorders, such as NAFLD, through their function as receptors for bile acids and free fatty acids. Therapies such as probiotics and GPCR agonists could be applied to modulate GPCR function to ameliorate liver metabolism syndrome. Herein, this review summarizes the current findings regarding the role of GPCRs in the development and progression of NAFLD.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a broad-spectrum disease characterized by pathological severity ranging from simple hepatic steatosis to nonalcoholic steatohepatitis (NASH)[1]. NAFLD patients with progressive liver fibrosis have a high incidence of developing cirrhosis and hepatocellular carcinoma (HCC)[2]. NAFLD is often associated with other metabolic disorders, including obesity, diabetes, and insulin resistance[3]. Abnormal accumulation of hepatic lipids is the main manifestation of NAFLD. Lipotoxicity caused by toxic free fatty acids, such as palmitic acid, cholesterol, and ceramides, contributes to early-stage NAFLD progression to advanced NASH and advanced liver disease[4]. However, there is still no approved treatment for NAFLD[5]. G protein-coupled receptors (GPCRs) play important roles in metabolic disorders and can respond to various extracellular signals, including fatty acids (FAs)[6,7]. Data are increasingly showing that GPCRs and their signaling pathways are promising targets for NAFLD treatment.

Studies on the gut–liver axis are rapidly contributing to mounting evidence that dysbiosis of gut microbiota contributes to NAFLD progression *via* multiple mechanisms, including the secondary bile acid-induced senescence-associated secretory phenotype of hepatic stellate cells (HSCs)[8], bacterial product-induced proinflammatory responses through Toll-like receptors and toxic products[9,10]. In addition, bile acids (BAs), primarily produced in the liver and metabolized by gut microbiota, have pleiotropic roles in metabolism, including glucose homeostasis, digestion and absorption of dietary lipids, intestinal bacterial growth, and liver regeneration[11]. One of the molecular mechanisms for this BA interaction is with Takeda GPCR 5 and G protein-coupled bile acid receptor-1 (TGR5/GPBAR1) to regulate lipid and glucose metabolism[12,13].

In this review, we focus on the role of GPCRs in NAFLD development and progression by regulating nutrient metabolism. First, we introduce the role of GPCRs in liver metabolism and discuss how GPCR-mediated signaling impacts lipid synthesis, lipid and glucose metabolism, and production of extracellular matrix (ECM) proteins. Then, we summarize the role of GPCRs in NAFLD and advanced liver disease, followed by further discussion on current GPCR-targeted treatments in cellular and animal models for liver disease. Finally, we look to the therapeutic potential of GPCR-mediated signaling in liver disease and current preclinical and clinical trials.

EFFECT OF GPCRS ON LIVER METABOLISM

GPCRs, the largest family of membrane proteins, mediate cellular responses to various stimuli and play essential roles in most patho/physiological processes[14]. Some GPCRs can be activated by energy metabolites, such as FAs, saccharides, lactates, and ketone bodies[15]. Increasing evidence indicates that GPCRs play pivotal roles in liver metabolism by modulating diverse signaling pathways[16,17], including the Hedgehog,

Wnt, Notch, and transforming growth factor-β pathways[18]. GPCRs are receptors of short-, medium-, and long-chain FAs and can regulate the secretion of gut hormones, lipid and glucose metabolism, and generation of ECM proteins (Figure 1). Herein, we discuss how GPCRs mediate liver metabolism *via* these ligands.

### Medium-chain fatty acids and long-chain fatty acids

Long-chain fatty acids (LCFAs) with more than 16 carbons are the most common fatty acids in Western diets and are commonly associated with inflammation and lipid accumulation[19]. In contrast, consuming diets rich in medium-chain fatty acids with 8-12 carbons can increase energy expenditure and decrease fatty acid accumulation. Oleate, an unsaturated (18:1) LCFA, can stimulate glucagon-like peptide 1 (GLP-1) secretion from an immortalized murine enteroendocrine cell line of GLUTag cells through their receptors *via* upregulating GPR40 (FFAR1) and GPR41 (FFAR3)[20]. Another study showed that GPR120 (FFA4) functions as a receptor for LCFA to regulate the secretion of GLP-1 from the gastrointestinal tract[21]. GLP-1 shows anti-inflammatory activity, including suppression of inflammatory cytokine expression in macrophages[22]. Accumulating evidence indicates that GLP-1 receptor agonists, GLP-1, and glucagon receptor co-agonists are treatment options for NAFLD[23,24]. The GPR40 agonist GW9508 decreased oleic acid-induced lipid accumulation in liver cancer cell line HepG2 cells *via* activating mitogen-activated protein kinase signaling, to downregulate the expression of sterol regulatory element-binding protein 1[25]. The effect of GW9508 on sterol regulatory element-binding protein 1 was diminished in GPR40-knockdown HepG2 cells. Moreover, GW9508 attenuated liver X receptor-induced hepatic lipid accumulation *via* activating the mitogen-activated protein kinase signaling pathway[26]. Another report showed that GPR40-deficient mice were protected against conjugated linoleic acid-induced accumulation of triglycerides in the liver[27], which might be associated with the secretion of insulin from the pancreas[28]. GPR120, as a receptor for unsaturated LCFAs, plays an essential role in liver metabolism. Ichimura *et al*[29] reported that GPR120-deficient mice showed a marked increase in hepatic lipids with a 10% greater bodyweight increase than wild-type mice[29]. Gpr43$^{-/-}$ mice were obese compared to wild-type mice with an increase in short-chain fatty acid (SCFA)-producing bacteria in the gut and increased concentrations of fecal SCFA and plasma acetate[30]. In addition, a specific deficiency of GPR43 in the adipose tissue attenuated high-fat diet (HFD)-induced liver steatosis.

SCFAs

SCFAs, including acetate, propionate, and butyrate, are the main metabolites of gut microbiota under an anaerobic microenvironment. SCFAs fuel intestinal cells and modulate the gut immune response *via* activating GPCRs (*e.g.*, GPR41/FFAR3 and GPR43/FFAR2) and inhibiting histone deacetylase[31]. In addition, GPCRs modulate SCFA-mediated inflammatory responses. For example, an antagonist of GPR41 or GPR43 alone as well as in combination were able to recover the inhibiting effect of acetate on lipopolysaccharides/tumor necrosis factor alpha-induced interleukin (IL)-6 and IL-8 production in human umbilical vein endothelial cells[32]. GPR41/43 are also involved in the effect of butyrate and propionate on IL-6 production but not IL-8 production. A new finding showed that microbial acetate contributed to liver lipogenesis by converting dietary fructose into hepatic acetyl-CoA and fatty acids[33]. SCFAs are also associated with the ameliorating effect of fructo-oligosaccharides on steatohepatitis and chronic inflammation[34].

Bile acids

Toxic BAs can cause hepatocyte death by directly activating cell death receptors or inducing oxidative damage, resulting in mitochondrial dysfunction, endoplasmic reticulum stress, and cell death[35]. Conversely, BAs can activate nuclear farnesoid X receptor and GPCR signaling to protect against liver and gastrointestinal inflammation[36,37]. TGR5 is widely expressed in different nonparenchymal liver cells, altering expression in response to BAs like lithocholic acid. TGR5 deletion increased the sensitivity of cholic acid feeding and bile duct ligation-induced liver injury in the endothelin-1 associated signaling pathway[38]. Administration of parenteral nutrition increased liver weight, the infiltration of macrophages, and inflammatory cytokine IL-6 expression[39] in TGR5$^{-/-}$ mice compared to wild-type mice. Meanwhile, unconjugated primary BAs and secondary BAs were increased due to the elevated abundance of *Bacteroides* and *Parabacteriodes* in the gut. Another study showed that BA-activated Mas-related GPCR4 played a critical role in cholestatic itch[40].
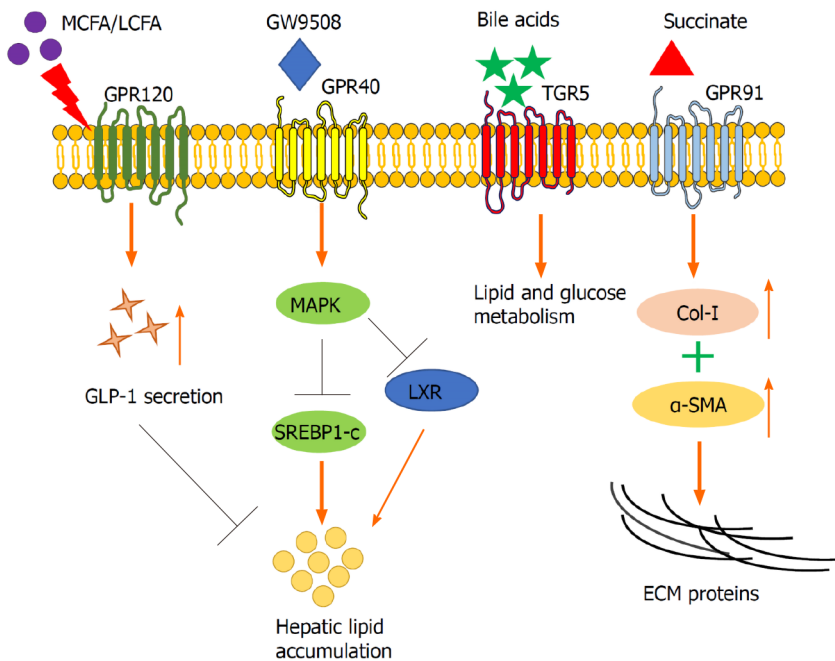
Figure 1 The role of G protein-coupled receptors in liver metabolism and the generation of extracellular matrix proteins. G protein-coupled receptors are receptors of diverse molecules, such as fatty acids, bile acids, and other agonists (*e.g.*, GW9508). They can regulate hepatic lipid and glucose metabolism and extracellular matrix (ECM) production *via* directly modulating hepatic cells (hepatocytes and hepatic stellate cells), and indirectly regulating gut hormones (*e.g.*, glucagon-like peptide-1, GLP-1). α-SMA: α-smooth muscle actin; Col-I: Collagen type I; LCFA: Long-chain fatty acid; LXR: Liver X receptor; MAPK: Mitogen-activated protein kinase; MCFA: Medium-chain fatty acid; SREBP1-c: Sterol regulatory element-binding protein 1.

Gut hormones

Gut hormones, such as peptide-YY and GLP-1, can be modulated through GPCRs to regulate insulin secretion in obese subjects[21,41]. For instance, SCFAs can stimulate incretin hormone GLP-1 secretion *via* GPR43 in the intestinal L cells to impact insulin sensitivity and appetite[42]. GLP-1 can regulate hepatic steatosis by preventing HFD-induced very-low-density lipoprotein overproduction and insulin resistance[43], accompanying the reduction in the mRNA and protein expression of sterol regulatory element-binding protein 1c, stearoyl-CoA desaturase-1, and fatty acid synthase.

Others

Conditional deletion of GPRC6a in hepatocytes by cross-breeding Alb-Cre and Gprc6a^flox/flox^ mice resulted in abundant liver fat accumulation and glycogen depletion[44]. In addition, GPRC6a depletion altered the production of FGF-21 and its release, which controlled systemic energy homeostasis. Exposure of succinate upregulated the expression of GPR91 in primary and immortalized HSCs accompanying the increased expression of ECM proteins. Inhibiting GPR91 expression by lentivirus harboring shRNA reduced succinate-mediated HSC activation[45].

EFFECT OF GPCRS IN NAFLD, NASH, AND HCC

GPCRs

To date, some GPCRs have been shown to play critical roles in liver diseases (Table 1). Herein, we summarize some crucial GPCRs with potential clinical value at different stages of liver diseases, ranging from NAFLD to HCC. For instance, GPR120 is a functional receptor for ω-3 fatty acids that show strong anti-inflammatory and anti-insulin resistance effects. Oh *et al*[46] reported that GPR120 agonist cpdA treatment increased insulin sensitivity and glucose tolerance and decreased hepatic steatosis in HFD-induced obese mice[46].

GPR49, an orphan GPCR with unknown ligands, is highly expressed in human HCC cell lines PLC/PRF/5 and HepG2[47]. In addition, overexpression of GPR49 has been shown in HCC tissue with a mutation of beta-catenin exon three. Another orphan GPCR receptor, GPR137, is also broadly expressed in human liver cancer cell lines,

Table 1 The role of G protein-coupled receptors in nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and hepatocellular carcinoma

Liver disease	GPCRs	Expression	Ref.
NAFLD/Steatosis	GPR120	GPR120 agonist cpdA treatment increased insulin sensitivity and glucose tolerance and decreased hepatic steatosis in HFD-induced obese mice	[46]
HCC	GPR49	GPR49 is highly expressed in human HCC cell lines PLC/PRF/5 and HepG2; overexpression of GPR49 in HCC tissue with a mutation of beta-catenin exon 3 was also shown	[47]
HCC	GPR137	Knockdown of GPR137 in HepG2 cells induced cell cycle arrest and cell apoptosis. Additionally, low expression of GPR137 indicated the progression of human HCC and a low survival rate	[49]
NAFLD/Steatosis	GPR132	GPR132 was involved in hepatic lipid metabolism and gallstone formation in mice because GPR132-deficient mice fed a lithogenic diet quickly developed gallstones and had a high cholesterol saturation index	[51]
NAFLD/Steatosis	GPR55	GPR55-deficient (GPR55$^{-/-}$) mice showed impaired insulin signaling and had a significant increase in total body fat and liver fatty acid synthase, resulting in the development of hepatic steatosis	[53]
NASH/Fibrosis	GPR91	Succinate in the fatty liver can activate HSC *via* GPR91 receptor, resulting in NASH progression	[45]
Liver injury/Fibrosis	GPBAR1	GPBAR1 is an upstream regulator of the axis expression of chemokine CCL2 and its receptor CCR2 in the interface of liver sinusoidal cells	[54]

GPCRs: G protein-coupled receptors; HCC: Hepatocellular carcinoma; HFD: High-fat diet; HSC: Hepatic stellate cell; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis.

such as HepG2 and Bel7404. The depletion of GPR137 by lentivirus-mediated RNA interference in these two cell lines remarkably inhibited the proliferation and colony formation capacity[48]. Knockdown of GPR137 in HepG2 cells resulted in cell cycle arrest and cell apoptosis, suggesting that targeting GPR137 can inhibit cancer growth. Moreover, low expression of GPR137 indicated the progression of human HCC and low survival rates[49].

GPR132 or G2A receptor is a proton-sensing GPCR and plays an important role in cell cycle and proliferation, oncogenesis, and the immune response[50]. GPR132 is also involved in hepatic lipid metabolism and gallstone formation in mice because GPR132-deficient mice fed a lithogenic diet quickly developed gallstones and had a high cholesterol saturation index[51].

Not all GPCRs have a protective effect against liver disease. Succinate was increased in fatty liver cells of high fat/calorie diet plus high fructose and glucose in drinking water-fed mice[45]. Exposure of succinate upregulated the expression of GPR91 in primary and immortalized HSCs and increased the expression of ECM proteins of these cells. Inhibiting GPR91 expression by lentivirus harboring shRNA reduced succinate-mediated HSC activation. Meanwhile, the expression of GPR91 was correlated with the severity of fibrosis in human NASH biopsy specimens[45]. GPR55 and its endogenous ligand, l-α-lysophosphatidylinositol are positively correlated with obesity and type 2 diabetes (T2D)[52]. Moreover, GPR55-deficient (GPR55$^{-/-}$) mice showed impaired insulin signaling evidenced by reduced phosphorylation of protein kinase B and its downstream targets and had a significant increase in total body fat and liver fatty acid synthase, which can result in the development of hepatic steatosis[53]. In the same study, the author also found that lysophosphatidylinositol activated rat H4IIE liver cells and human HepG2 liver cells *via* GPR55 to enhance insulin-dependent protein kinase B phosphorylation. Deletion of GPBAR1, a GPCR for secondary BAs, accelerated the severity of liver injury caused by acetaminophen[54]. Further, GPBAR1 agonism mediated the axis expression of chemokine CCL2 and its receptor CCR2 in the interface of liver sinusoidal cells.

GPCR signaling and regulatory proteins

Generally, GPCRs are linked to distinct families of G proteins, including Gs, Gi, and Gq[55]. For example, the glucagon receptor most highly expressed in hepatocytes is linked to the stimulatory G proteins, Gs. Heterotrimeric G proteins are involved in the signaling of approximately 800 GPCR family members[56]. Some of these signaling pathways play an important role in liver metabolism. For instance, $G\alpha_{12}$ protein ($G\alpha_{12}$) ablation significantly increases fasting-induced fat accumulation in the liver of mice, and $G\alpha_{12}$ expression is also decreased in liver biopsies of NAFLD patients[16]. A mechanistic study showed that $G\alpha_{12}$ regulated mitochondrial respiration through modulating sirtuin 1 and peroxisome proliferator-activated receptor alpha expression. Moreover, the expression of $G\alpha_{12}$ has been associated with the overall survival of HCC

patients[57]. Understanding the role of G proteins in the liver also helps unlock the role of GPCRs in liver metabolism and disease progression.

Regulators of G protein signaling (RGS) proteins negatively regulate GPCR signaling. RGS5 can protect against NAFLD and NASH. In the liver, RGS5 is an essential molecule that protects against the progression of NAFLD. RGS5 directly binds to transforming growth factor beta-activated kinase 1 (TAK1) and inhibits its phosphorylation and the subsequent c-Jun N-terminal kinase/p38 pathways. RGS5 is a promising target molecule for fine-tuning the activity of transforming growth factor beta-activated kinase 1 and NAFLD treatment[58].

Activated HSCs are one of the major sources of myofibroblasts in many types of liver injury[59], which produce ECM proteins. GPCR-mediated signaling plays an important role in HSC contraction, migration, and activation. Bahrami *et al*[60] reported that RGS5 can regulate GPCR signaling in HSCs and modulate HSC activation and hepatic fibrogenesis[60]. RGS6$^{-/-}$ mice showed reduced alcohol consumption when given free access to alcohol. RGS6$^{-/-}$ mice were also protected from alcohol-induced hepatic steatosis, cardiac toxicity, dysfunction of the gut barrier, and endotoxemia when they were forced to consume alcohol[61]. Another study showed that overexpression of RGS16, specifically in the liver, displayed fatty liver after overnight fasting but low blood glucose levels compared with wild-type mice[62]. In contrast, RGS16-knockout mice showed a higher rate of fatty acid oxidation in liver extracts compared with wild-type mice, suggesting that RGS16 inhibits GPCR-mediated fatty acid oxidation. Therefore, RGS is a group of therapeutic candidates for modulating GPCRs to treat liver disease.

The signaling of most GPCRs *via* G proteins is regulated by GPCR kinases (GRKs)[63], which also function in the pathogenesis of liver injury. For instance, GRK2 hemizygous (GRK2$^{+/-}$) mice showed a reduced level of triglycerides and a reduced liver-to-body weight ratio compared to wild-type mice when fed a methionine and choline-deficient diet[64]. Increased GRK2 protein and mRNA levels were also detected in human liver biopsies of steatosis and NASH patients. Moreover, high GRK2 expression exaggerated palmitic acid-triggered lipid accumulation in human hepatocytes[64].

Gut microbiota-mediated GPCR expression

The gut–liver axis plays a critical role in the development of liver diseases[65,66]. Gut microbiota-derived metabolites and their associated signaling pathways play important roles in NAFLD development[67]. Rau *et al*[68] reported that SCFA-producing bacteria were dominant in the fecal bacteria of NAFLD patients, accompanying high acetate and propionate in fecal metabolites[68]. These metabolites are associated with immunological features in NAFLD progression. Manipulation of gut microbiota is a promising preventive and therapeutic strategy for NAFLD. For instance, administration of a bacterial cocktail, consisting of three strains of *Bifidobacterium adolescentis* and three strains of *Lactobacillus rhamnosus*, alleviated a high-fat, high-cholesterol diet-induced NAFLD symptom in mice by increasing the concentration of intestinal SCFAs[69]. Similar findings have also been achieved in clinical trials for human patients[70,71]. Gut microbiota-derived metabolites contribute to the development of NAFLD, including SCFAs[68], endogenous alcohol[72,73], and BAs[74,75]. Gut microbiota in the colon is the main source of the production of SCFAs[76,77], which affect lipid and glucose metabolism. It has been demonstrated that both BAs[78] and SCFAs[79] can activate GPCRs to modulate immune responses. Hence, modulating gut microbiota is an attractive strategy to interfere with liver disease.

For example, farnesoid X receptor agonist fexaramine-induced lithocholic acid-producing bacteria *Acetatifactor* and *Bacteroides* impact liver bile acid synthesis, which in turn can enhance the expression of intestinal farnesoid X receptor targeted genes[80]. In hepatocytes, palmitate can be metabolized to sphingosine 1-phosphate (S1P), which binds to different types of S1P receptors (S1PRs) like S1PR1-3 to activate HSCs to myofibroblasts[81]. In addition, S1P can increase the recruitment of bone marrow mesenchymal stem cells *via* activating S1PRs to produce proinflammatory cytokines IL-1β, tumor necrosis factor alpha, and IL-6, resulting in acceleration of the pathophysiological process of liver disease[82]. The S1P-S1PR1 axis is also associated with chronic intestinal inflammation and colitis-associated cancer by modulating IL-6 and transcription factor STAT3[83].

In addition to liver disease, gut microbiota-associated products affect other diseases, such as inflammatory bowel disease, diabetes, autoimmune disease, and cardiovascular disease, through GPCRs[84-86]. For example, tryptamine, a tryptophan-derived monoamine produced by gut bacteria like *Bacteroides thetaiotaomicron* can activate the serotonin 5-HT$_4$ receptor, which is uniquely expressed in colonic epithelial

cells to increase ionic flux across colonic epithelium, altering the host gut transmit[87]. Increasing evidence shows that the microbiota plays a crucial role in influencing host appetite and eating-relative behavior[88]. Of note, the gut–liver axis is bidirectional[10,89] because the liver also impacts the components of gut microbiota (Figure 2) by primary BAs, which may result in a change of appetite[90].

GPCR-BASED THERAPIES FOR LIVER DISEASES

GPCRs are a promising therapy for NAFLD treatment (Table 2). Recently, Pi *et al*[44] reported that Gprc6a[Liver-cko] mice (a strain with conditional depletion of GPRC6A in mouse hepatocytes) on a normal diet had excessive liver fat accumulation and impaired glucose and pyruvate tolerance without insulin resistance[44]. Intraperitoneal or oral administration of a peptide hormone metabolitin that binds to GPRC6A significantly ameliorated NAFLD symptoms and inhibited gut triglyceride and cholesterol absorption and insulin resistance *via* activating the 5' AMP-activated protein kinase signaling pathway[91]. Metabolitin treatment was able to stimulate the expression of GLP-1, which further validated the metabolitin-GPRC6A interaction because the GPRC6A receptor functions as an amino acid sensor mediating GLP-1 secretion in the intestinal L cells[92].

Oral administration of a GPR39 agonist, TC-G1008, inhibited liver injury marker glutamic-pyruvic transaminase expression and reduced hepatic cell necrosis in concanavalin A-induced hepatitis liver in mice[93]. Another study showed that an acute dose of TC-G1008 reduced ethanol intake in mice without affecting total fluid intake[94]. GPR40 deficiency was associated with hepatic inflammation and steatosis in low-fat diet-fed mice[95]. Oral administration of a GPR40 full agonist, SCO-267, reduced liver weight, triglyceride and collagen production, and serum alanine amino-transferase without affecting food intake or glucose levels in choline-deficient, L-amino acid-defined, high-fat diet-fed mice[96]. Furthermore, SCO-267 improved mitochondrial function and beta-oxidation, while inhibiting lipogenesis, inflammation, and generation of reactive oxygen species in the liver.

GPR120 agonist III significantly suppressed macrophage infiltration and reactive oxygen species production and reversed hepatic inflammation, endoplasmic reticulum stress, and apoptosis in high-fat, high-cholesterol diet or methionine and choline-deficient-induced steatohepatitis[97]. In addition, GPR120 agonist TUG-891 inhibited lipid accumulation in hepatocytes[98].

Treatment with docosahexaenoic acid, an omega-3 fatty acid, inhibited lipid droplets by interacting with GPR40 in primary hepatocytes *via* reduced expression of lipogenic enzymes, such as fatty acid synthase, acetyl-CoA carboxylase, and stearoyl-CoA desaturase-1[99]. PBI-4547, a fatty acid mimetic, is a GPR84 antagonist. In a mouse model of diet-induced obesity, PBI-4547 treatment ameliorated NAFLD-associated metabolic dysregulation and hepatic steatosis and ballooning, which was depleted in GPR84^{-/-} mice[100]. PBI-4547 increased liver fatty acid oxidation and gene expression of mitochondrial uncoupling proteins. Another study showed that inhibition of GPR84 with antagonists CpdA and CpdB significantly reduced myeloid cell infiltration and ameliorated inflammation and fibrosis in acute liver injury[101]. GPR43-deficient mice became obese when fed a normal diet. In contrast, mice with GPR43 overexpressed specifically in adipose tissue remained lean even on a high-fat diet[30]. Oral administration of compound probiotics ameliorated HFD-induced gut microbe dysbiosis and chronic metabolic inflammation in NAFLD rats *via* GPR43[102].

URGENT NEED FOR CLINICAL TRIALS

GPCRs, as the largest group of transmembrane receptors[103], play important roles in various diseases, including inflammatory bowel diseases[104,105], kidney diseases[106], liver diseases[107], bone disease[6], central nervous system disorders[108], heart diseases[109], and respiratory diseases[110]. To date, about fifty GPCR targeting peptides have been approved to treat metabolic diseases and tumors[111]. With the analysis of public databases, Sriram and Insel[112] reported that about 35% of approved drugs target GPCRs[112]. GPCRs and GPCR-associated proteins consist of about 17% of all protein targets for approved drugs. The application of GPCRs has been tested in clinical trials for metabolic disorders[113,114], including obesity and diabetes.

For example, T2D patients aged 20 or older orally received 75 mg of GPR119 agonist DS-8500a daily for 4 wk, resulting in enhanced insulin secretory capacity compared to

Table 2 G protein-coupled receptor-mediated treatment in nonalcoholic fatty liver disease

GPCRs	Treatment	Study	Effect	Ref.
GPRC6A	Metabolitin, a peptide hormone	Mice	Specifically deleting Gprc6a in mouse hepatocytes caused hepatic fat accumulation. Metabolitin can significantly ameliorate NAFLD symptoms and inhibit gut triglyceride and cholesterol absorption and insulin resistance *via* GPRC6A-mediated activation of the 5' AMP-activated protein kinase signaling pathway	[44,91]
GPR39	Agonist TC-G1008	Mice	Oral administration of TC-G1008 inhibited hepatic cell necrosis in concanavalin A-induced hepatitis liver in mice. In addition, acute administration of TC-G1008 reduced ethanol intake	[93,94]
GPR40	Agonist SCO-267	Mice	GPR40 deficiency was associated with hepatic inflammation and steatosis in low-fat diet-fed mice. Oral administration of SCO-267 reduced HFD-induced increase in liver weight, triglyceride and collagen production, and serum alanine aminotransferase	[95,96]
GPR40	Docosahexaenoic acid	Primary hepatocytes, HFD-fed mice	Treatment with DHA, an omega-3 fatty acid, inhibited lipid droplets by interacting with GPR40 in primary hepatocytes *via* reduced expression of lipogenic enzymes. In addition, it significantly reduced the HFD-induced liver steatosis score in mice	[99]
GPR43	Compound probiotics	Rats	Overexpressing GPR43 in adipose tissue kept mice lean on a HFD diet. Compound probiotics can modulate gut microbiota dysbiosis, SCFAs, and their receptors, like GPR43, in NAFLD rats	[30, 102]
GPR84	Antagonist PBI-4547GPR84 Antagonists CpdA and CpdB	Gpr84$^{-/-}$ mice; Wild-type mice	PBI-4547 treatment ameliorated NAFLD-associated metabolic dysregulation, hepatic steatosis and ballooning, which was depleted in Gpr84$^{-/-}$ mice. Inhibition of GPR84 with antagonists CpdA and CpdB significantly reduced myeloid cell infiltration and ameliorated inflammation and fibrosis in acute liver injury	[100, 101]
GPR120	TUG-891Agonist III	Hepatocytes; Mice	Agonist TUG-891 inhibited lipid accumulation in hepatocytes. Agonist III significantly suppressed macrophage infiltration, ROS production, hepatic inflammation, ER stress, and steatohepatitis	[97,98]

DHA: Docosahexaenoic acid; ER: endoplasmic reticulum; GPCRs: G protein-coupled receptors; HFD: High-fat diet; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; ROS: Reactive oxygen species; SCFA: Short-chain fatty acid.

placebo treatment[114]. In addition, DS-8500a significantly reduced total cholesterol, low-density lipoprotein cholesterol, and triglyceride concentrations and significantly increased high-density lipoprotein cholesterol concentrations compared to placebo treatment. No significant treatment-associated adverse events occurred in this trial. Another phase 2 clinical trial showed that daily treatment of GPR40 agonist Fasiglifam for 12 wk significantly improved glycemic control in T2D patients who were not responsible to diet or metformin treatment compared to placebo treatment, evidenced by the reduction of hemoglobin A(1c) from baseline[115]. In addition, Fasiglifam did not cause a higher risk of hypoglycemic events in patients.

However, our current knowledge about the function of GPCRs in liver metabolism disorders is still limited. When considering potential drugs for treatments, even fewer candidates have been tested in clinical trials. Some experimental trials in rodents have been investigated to explore the role of GPCRs in liver diseases, such as GPR40[99] and GPR43[102]. Some of the GPCRs, such as prostaglandin E2 receptors[116] and beta-2 adrenergic receptor[117], have been investigated in preclinical studies using tissue biopsies of human patients. Meanwhile, the side effects of GPCR-targeted molecules need to be considered when designing new therapeutic agents. For example, Fasiglifam increased the ratio of liver enzymes aspartate aminotransferase/alanine transaminase in T2D patients compared to placebo treatment while being evaluated for cardiovascular safety in a phase 3 trial[118].

CONCLUSION

Many GPCRs have critical roles in metabolic disorders, including NAFLD, through their function as receptors for metabolites, such as SCFAs and BAs. GPCR-mediated signaling pathways are involved in hepatic lipid accumulation and fibrogenesis and can also modulate the secretion of gut hormones (*e.g.*, GLP-1), which further impacts liver function, suggesting that GPCRs play a pivotal role in the gut–liver axis. Furthermore, GPCRs and their associated molecules are candidates as biomarkers for NAFLD diagnosis. Overall, GPCRs and their regulating factors provide potential pharmacological targets for NAFLD treatment.

There are several advantages to targeting GPCRs to treat NAFLD compared with other NAFLD therapeutics. First, therapeutic candidates or drugs can be easily found.
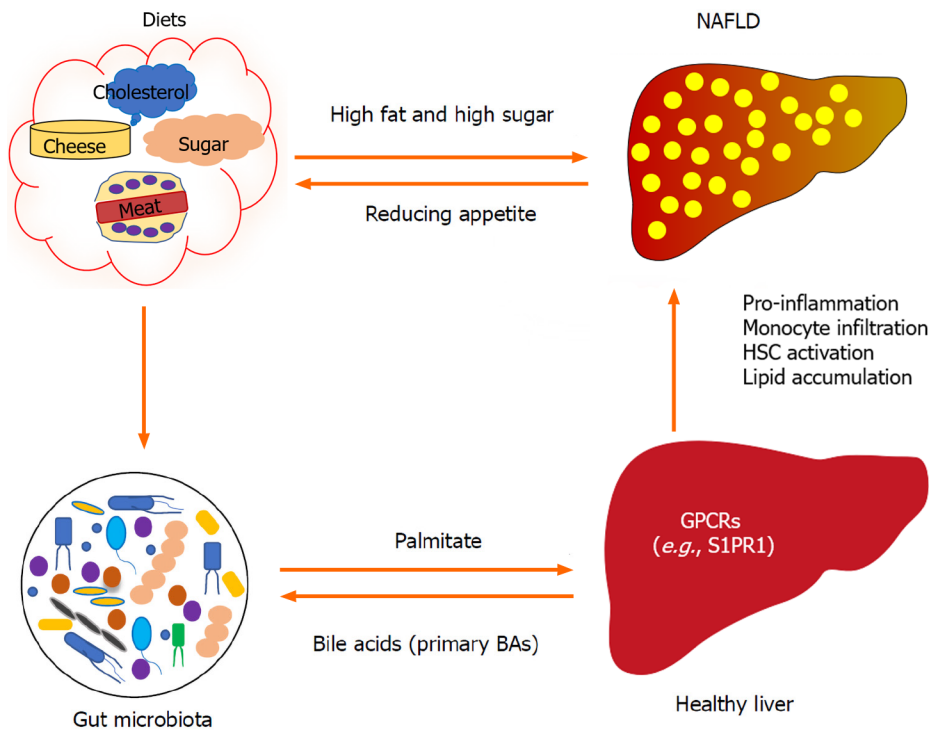
Figure 2 G protein-coupled receptor-mediated interaction of the gut and liver. Gut microbiota-derived metabolites or molecules (*e.g.*, palmitate) impact liver function by being metabolized to sphingosine 1-phosphate in hepatocytes, which can stimulate the activation of hepatic stellate cells (HSCs) and proinflammation *via* sphingosine 1-phosphate receptor 1 (S1PR1). In turn, primary bile acids (BAs) are synthesized in the liver, which can also influence the components of gut microbiota. A high fat and high sugar diet can induce nonalcoholic fatty liver disease (NAFLD) and change gut microbiota. Gut microbiota has been shown to impact appetite, and the progression of NAFLD may also impact the appetite. GPCRs: G protein-coupled receptors.

The data from public databases (ChEMBL, Guide to PHARMACOLOGY/GtoPdb, and DrugBank) show that about 35% of approved drugs target GPCRs[112]. Second, functional selection of GPCR ligands helps minimize the potential side effects of selected treatment[119]. Third, GPCRs are implicated in the development and progression of NAFLD, including lipid metabolism, proinflammation, and fibrosis. Therefore, targeting GPCR can be applied to different stages of NAFLD therapy, ranging from simple steatosis to NASH. However, current GPCR-mediated treatments in hepatic steatosis, liver fibrosis, and liver cancer are mainly performed either in cells or animals. Few preclinical and clinical trials in humans have been carried out so far. More work is needed to unmask the role of GPCRs in the clinic.

The structures of GPCRs are critically important for de novo design of GPCR targeting drugs. However, only about 60 GPCR structures have been resolved with the advanced technologies like X-ray crystallography and cryo-electron microscopy[120]. A new protocol has optimized the precrystallization process for resolving GPCR structures *via* X-ray crystallography[121]. Some technologies such as cell-based electrical impedance also help identify GPCR-targeting molecules[122]. In addition, computer-based design of GPCR allosteric receptors helps reveal the unknown GPCR signaling pathways and the relative molecular mechanism[123]. In conclusion, advanced technologies help unravel the clear role of each GPCR in both physiological and pathological environment to accelerate GPCR-mediated therapy.

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