Journal of Advanced Research 59 (2024) 173–187

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Review

Bile acid and nonalcoholic steatohepatitis: Molecular insights and therapeutic targets

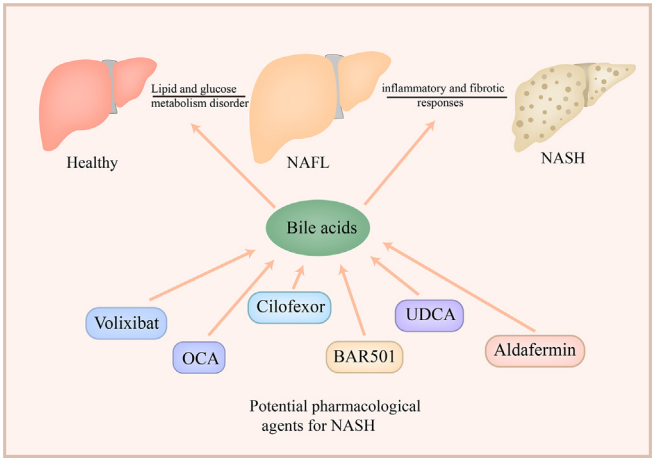
Zilu Cheng [a], Yixiong Chen [a], Bernd Schnabl [b], Huikuan Chu [a,*], Ling Yang [a,*]

[a] Division of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei Province 430022, China
[b] Department of Medicine, University of California San Diego, La Jolla, CA, USA

HIGHLIGHTS

- Bile acid serves as a pivotal signaling molecule.
- Bile acid has a salutary effect on hepatic metabolic disorders by activating FXR and TGR5.
- Bile acid also exerts anti-inflammation and anti-fibrosis properties.
- Bile acid is emerging as a potential biomarker for the stratification of NAFLD.
- Some pharmacological agents targeting bile acid and its associated pathways show great potential in NASH treatment.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 30 March 2023
Revised 6 June 2023
Accepted 20 June 2023
Available online 23 June 2023

Keywords:
Bile acid
Takeda G-protein coupled receptor 5
farnesoid X receptor
Dysbiosis

ABSTRACT

Background: Nonalcoholic steatohepatitis (NASH) has been the second most common cause of liver transplantation in the United States. To date, NASH pathogenesis has not been fully elucidated but is multifactorial, involving insulin resistance, obesity, metabolic disorders, diet, dysbiosis, and gene polymorphism. An effective and approved therapy for NASH has also not been established. Bile acid is long known to have physiological detergent function in emulsifying and absorbing lipids and lipid-soluble molecules within the intestinal lumen. With more and more in-depth understandings of bile acid, it has been deemed to be a pivotal signaling molecule, which is capable of regulating lipid and glucose metabolism, liver inflammation, and fibrosis. In recent years, a plethora of studies have delineated that disrupted bile acid homeostasis is intimately correlated with NASH disease severity.
Aims: The review aims to clarify the role of bile acid in hepatic lipid and glucose metabolism, liver

Abbreviations: CDCA, chenodeoxycholic acid; CA, sterol 27-hydroxylase; BSEP, bile salt export pump; ASBT, apical sodium-dependent bile salt transporter; CDCArg, Chenodeoxycholyl-arginine ethyl ester conjugate; CKK, cholecystokinin; CYP7B1, oxysterol 7α-hydroxylase; CYP27A1, sterol 27-hydroxylaseex; CYP7A1, cholesterol 7α-hydroxylase; FXR, farnesoid X receptor; FGF15, fibroblast growth factor15; FA, fatty acid; DCA, deoxycholic acid; GLP1, glucagon-like peptide1; FGFR4, FGF receptor 4; HSC, hepatic stellate cell; HFD, high-fat diet; HCC, hepatocellular carcinoma; LCA, lithocholic acid; I-BABP, bile acid binding protein; LPS, lipopolysaccharide; MRP2, multidrug resistance-associated protein2; MCP1, monocyte chemoattractant protein1; MCD, methionine/choline-deficient; MCA, muricholic acid; NASH, nonalcoholic hepatitis; OATPs, organic anion-transporting polypeptides; NTCP, sodium taurocholate co-transporting polypeptide; NF-kB, nuclear factor kappa B; NAFLD, nonalcoholic fatty liver disease; OCA, Obeticholic acid; PPARα, peroxisome proliferator-activated receptor alpha; PEPCK, phosphoenolpyruvate carboxykinase; OSTα/β, organic solute transporter α/β; SREBP1c, sterol regulatory binding protein1c; SHP, small heterodimer partner; PPAR γ, peroxisomal proliferator-activated receptor γ; TG, triglyceride; TGR5, VLDL, very-low-density lipoprotein; Takeda, G-protein coupled receptor 5.

* Corresponding authors.
E-mail addresses: 2012XH0827@hust.edu.cn (H. Chu), yanglinguh@hust.edu.cn (L. Yang).

https://doi.org/10.1016/j.jare.2023.06.009

Nonalcoholic hepatitis

inflammation, as well as liver fibrosis, and discusses the safety and efficacy of some pharmacological agents targeting bile acid and its associated pathways for NASH.

Key scientific concepts of review: Bile acid has a salutary effect on hepatic metabolic disorders, which can ameliorate liver fat accumulation and insulin resistance mainly through activating Takeda G-protein coupled receptor 5 and farnesoid X receptor. Moreover, bile acid also exerts anti-inflammation and anti-fibrosis properties. Furthermore, bile acid has great potential in nonalcoholic liver disease stratification and treatment of NASH.

Contents

Introduction

Nonalcoholic hepatitis (NASH) is identified as an aggressive modality of nonalcoholic fatty liver disease (NAFLD), which is composed of a series of hepatic metabolic conditions [1]. The predominant features of NASH are steatosis, inflammation, and hepatic damage, with fibrosis or not [2]. The prevalence of NAFLD in adults is 17 %–33 %, of which 33 %–50 % putatively develop NASH. Moreover, 15 %–25 % of NASH patients probably suffer from liver fibrosis or cirrhosis after 10–15 years [3,4]. In most cases, NASH patients present asymptomatic, which raises the risk of developing cirrhosis or hepatocellular carcinoma (HCC) [5–7]. Currently, NASH has also emerged as the second most common cause of liver transplantation, which urgently warrants effective diagnostic and therapeutic interventions [8–12]. To date, NASH pathogenesis is not completely elucidated. The widely accepted hypothesis is "multiple parallel hits", regarding NASH as a sequential combination of parallel insults, implicated in obesity, insulin resistance, inflammatory cascades, and fibrosis, which usually acts on genetically predisposed individuals [13]. Recent studies reported that altered bile acid metabolism participates in the pathological progress of NASH [14,15].

Bile acids are mainly made up of primary bile acids and secondary bile acids. Enterohepatic circulation contributes to the homeostasis of bile acids [16]. Bile acids not only play a critical role in emulsifying and absorbing lipid-soluble molecules within the intestine, along with other biliary constituents [17], but also participate in the modulation of lipid and glucose metabolism, liver inflammation and, fibrosis through binding to Takeda G-protein coupled receptor 5 (TGR5) and farnesoid X receptor (FXR) [17–19].

At present, no approved pharmacological therapy is available despite that there is an urgent need for the treatment of NASH [20]. Mounting evidence has indicated that altered bile acids concentration and composition closely correlate with the disease's occurrence and severity [14,15]. Furthermore, bile acid derivatives or compounds are hopeful to become therapeutic agents for NASH via the activation and modulation of FXR and TGR5 [21–23]. Therefore, it appears plausible that bile acids and its associated signaling

pathways have the potential to be pharmacological targets for therapeutic interventions. By systematically collecting recent literatures, we summarize the role of bile acids in lipid and glucose metabolism, liver inflammation and fibrosis, and its associated signaling pathways. This sheds lights on the therapeutic potential of bile acids as pharmaceuticals or their related pathways as target for NASH patients.

Bile acids

Synthesis

Primary bile acids are synthesized from cholesterol within hepatocytes, which mainly depends on the classical and alternative pathway [16]. Roughly 75 % of total bile acids are synthesized under the classical pathway in humans [24], while the alternative pathway in rodents is in charge of synthesysing half of the total bile acids [25]. In the classical pathway, hydroxylation of cholesterol at C-7 position is catalyzed by cholesterol 7α-hydroxylase (CYP7A1), which is only distributed in the liver and is the rate-limiting enzyme of bile acid synthesis. 7α-hydroxycholesterol then undergoes further modification by sterol 27-hydroxylase (CYP27A1), ultimately forming cholic acid (CA) and chenodeoxycholic acid (CDCA) [26]. In contrast, CYP27A1 is able to effectively catalyze the first rate-limiting step in the alternative pathway, and oxysterol 7α-hydroxylase (CYP7B1) participates in the subsequent 7α-hydroxylation, which is in charge of the synthesis of most CDCA [27]. Of note, bile acids composition and synthesis in mice are quite distinct from that in humans [28–30]. Specifically, the primary bile acids in mice are made up of CA and α- and β-muricholic acids (MCA), which are mainly converted from CDCA via 6β-hydroxylation catalyzed by CYP2C70 [28]. Most importantly, the conversion of CDCA (endogenous FXR agonist) to MCA (FXR antagonist) can alter the signaling properties of bile acids in mice [29]. The primary bile acids in humans are conjugated with taurine and glycine at a ratio of 1–3, respectively, whereas in mice, the majority of primary bile acids are conjugated with taurine [30]. After conjugating with glycine or taurine, primary bile acids subsequently are excreted from hepatocytes, and reach the duodenum via the biliary tract. Conjugated bile acids ultimately undergo deconjugation and dihydroxylation by intestinal bacteria in the large intestine [31]. In humans, conjugated bile acids are deconjugated by bacterial bile salt hydrolase, which is mainly expressed in *Bifidobacteria, Lactobacillus, Clostridium* and *Bacteroides* [32]. Then unconjugated bile acids are further dehydroxylated by 7α-dehydroxylase predominantly expressed in *Eubacterium* and *Clostridium*, resulting in the generation of secondary bile acids from primary bile acids, converting CDCA to lithocholic acid (LCA) as well as CA to deoxycholic acid (DCA) [32–34]. Moreover, *Clostridium, Escherichia, Eubacterium* and *Bacteroides* can diversify secondary bile acids via pepimerization [35]. Similarly, α-MCA and β-MCA in mice are also transformed into their corresponding secondary bile acids following the consecutive deconjugation and dihydroxylation by intestinal bacteria, including hyodeoxy-cholic acid, murideoxycholic acid, and ω-MCA. Furthermore, the enzyme CYP2A12 in mice was believed to convert secondary bile acids back to primary bile acids in a recent study, which was not found in humans [25].

In addition to the afore-mentioned proverbial biosynthetic pathways of bile acids, there are also some novel pathways that are in charge of unique bile acids production. In a recent study, researchers analyzed the intestinal microbiome of centenarians and found that *Odoribacteraceae* played a critical role in the production of isoallo-LCA, which exhibited antimicrobial prosperities against multidrug-resistant Gram-positive bacteria, including *Clostridioides difficile* and *Enterococcus faecium* [36]. And the enzymes 3β-hydroxysteroid dehydrogenase and 5α-reductase produced a notable effect in this process [36].

Transport

Primary bile acids conjugated with taurine or glycine are excreted from hepatocytes to bile canaliculi against the concentration gradient via the bile salt export pump (BSEP), which is able to specifically bind to conjugated bile acids and is exclusively distributed in hepatocytes [37]. Organic anions, which constitute part of bile, along with sulfated bile acids, are transported from hepatocytes into the bile duct mainly mediated by multidrug resistance-associated protein2 (MRP2) [38]. Moreover, a part of bile acids (mostly during cholestasis) is excreted into the systematic circulation with the assistance of organic solute transporter α/β (OSTα/β) and MRP3 expressed on the basolateral membrane of hepatocytes [39]. Under fasting conditions, bile acids enter the gallbladder and further concentrate here owing to high pressure resistance provided by the sphincter of Oddi. After food consumption, the stored bile acids are excreted into the duodenum with gallbladder contraction and Oddi sphincter relaxation stimulated by cholecystokinin [40]. The reabsorption of roughly 95 % of bile acids mainly depends on the apical sodium-dependent bile salt transporter (ASBT) in the terminal ileum [41–43]. Bile acids bind to the bile acid binding protein (I-BABP) intracellularly, then the OSTα/β heterodimer localized on the basolateral membranes secretes bile acids into the portal circulation [44–46]. It is worth noting that MRP3, at least in rodents, putatively makes contributions to the efflux of bile acids from enterocytes [47], similar to the OSTα/β heterodimer on the basolateral side. After entering the portal vein, bile acids are taken in hepatocytes mediated through organic anion-transporting polypeptides (OATPs) and sodium taurocholate co-transporting polypeptide (NTCP) distributed on the basolateral membrane [48–51]. The afore-mentioned process is termed enterohepatic circulation (Fig. 1). In the colon, approximately 5 % of bile acids undergo deconjugation and dihydroxylation by intestinal bacteria and are ultimately converted to secondary bile acids, including LCA and DCA [32–34]. LCA and DCA are passively reabsorbed in the colon or lost daily in feces [52]. Owing to the almost equal amounts of bile acids de novo synthesized within hepatocytes as well as lost in feces [53], the bile acid pool remains in a steady state.

Regulation

A steady bile acid pool is maintained under normal conditions as afore-mentioned. Several different mechanisms in the liver and the intestine participate in the modulation of bile acid homeostasis via the activation of FXR, which pertains to the ligand-activated transcriptional nuclear receptor superfamily [54]. When bile acid concentration increases, the synthesis of bile acidis inhibited in the liver. To be more specific, the small heterodimer partner (SHP) induced by FXR in hepatocytes, not only represses the liver-related homolog1, but also inhibits the hepatocyte nuclear factor 4α [55,56]. The two inhibited nuclear receptors further repress the CYP7A1 gene proximal promoter mainly by binding to the bile acid response element-I, thus inhibiting the transcription of CYP7A1 gene [53]. Equally, FXR in the intestine can inhibit hepatic CYP7A1 gene transcription by inducing fibroblast growth factor15 (FGF15) production, an endocrine hormone, which binds to the heterodimeric receptor beta-Klotho and the FGF receptor 4 (FGFR4) that is mainly localized on the hepatocyte surface [57,58]. FGF19, the human orthologue of murine FGF15, represses CYP7A1 gene transcription by activating FGFR4/β-Klotho receptor simultaneously [58–60]. Furthermore, intrahepatic bile acid accumulation

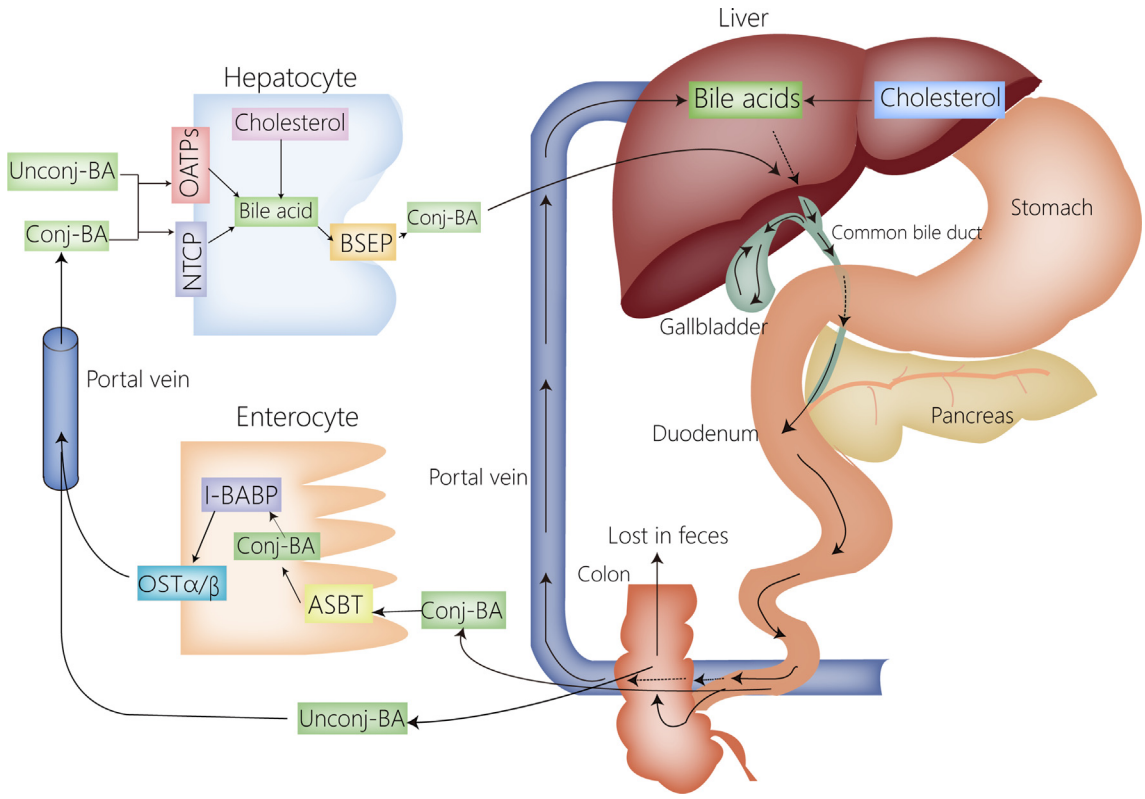


Fig. 1. Enterohepatic circulation. Conjugated bile acid is excreted from hepatocyte to bile duct via BSEP, predominantly actively reabsorbed at the terminal ileum by ASBT expressed on the apical membrane of the enterocyte, then the OSTα/β heterodimer on the basolateral mediates bile acid secretion into portal circulation. At length, bile acid is taken in hepatocyte through NTCP and OATPs. The reminder of bile acid is deconjugated and dehydroxylated by intestinal bacteria in the large intestine, and then some are daily lost in feces, while others are passively reabsorbed into portal circulation. OSTα/β: organic solute transporter α/β; BSEP: bile salt export pump; OATPs: organic anion-transporting polypeptides; NTCP: sodium taurocholate co-transporting polypeptide; ASBT: apical sodium-dependent bile salt transporter; MRP2: multidrug resistance-associated protein2.

Table 1
The function of bile acid-activated FXR and TGR5 in regulating lipid and glucose metabolism, hepatic inflammation, as well as fibrosis.

Receptor	Lipid metabolism	Glucose metabolism	Inflammation	Fibrosis
FXR [72–81,85–88,102,103,107–110]	Lipogenesis↓ β-oxidation↑ serum HDL level↓ TG-rich lipoproteins↓	Gluconeogenesis↓ Glycogen synthesis↑	NF-kB↓ Pro-inflammatory cytokines↓ NLRP3 inflammasome↓ MCP1 expression↓ Infiltration of inflammatory cells↓	PPAR γ↑ HSC activation↓ Collagen deposition↓
TGR5 [19,75,82–84,104–106]		GLP-1 secretion↑ Insulin secretion↑ Insulin resistance↓ Glucose uptake and removal↑	Pro-inflammatory cytokines↓ IL-10↑ MCP1 expression↓ Infiltration of inflammatory cells↓	

↑signifies increase; ↓signifies decrease; FXR: farnesoid X receptor; TGR5: Takeda G receptor 5; NF-kB: nuclear factor kappa B; HDL: high-density lipoprotein; TG: triglycerides; PPAR γ: peroxisomal proliferator-activated receptor γ; MCP1: Monocyte chemoattractant protein1; HSC: hepatic stellate cell; GLP1: glucagon-like peptide 1.

also can stimulate the production of FGF19 in humans in an autocrine manner [59,61]. Different from humans, FGF15 is not expressed in mice hepatocytes and this autocrine mechanism is also absent [57,61]. Moreover, FXR was believed to have the capacity to enhance the degradation of CYP7A1 mRNA [62]. The synthesis of bile acids is suppressed through inhibiting CYP7A1 gene transcription, which counteracts the elevated bile acid concentration.

In addition, FXR also regulates bile acid transport to maintain bile acid pool. To be more specific, in hepatocytes, BSEP is induced and NTCP is inhibited by FXR, which reduces the accumulation of bile acids [63,64]. Moreover, I-BABP and OSTα/β induction and ASBT inhibition by FXR in the enterocyte [65–67] prevent bile acid uptake and promote bile acid efflux, which is of great benefit to confer protection against cellular injury and compromised intestinal tight junction [68–71].

Bile acids: important molecules in regulating lipid and glucose metabolism

Regulation of lipid metabolism

Several researches have observed that FXR-deficient (FXR–/–) mice developed hepatic steatosis or hypertriglyceridemia [72,73], which indicated that FXR was closely related to hepatic lipid metabolism. Collectively, bile acid-activated FXR and its associated signaling pathways regulate lipogenesis, fatty acid (FA) oxidation, as well as triglyceride (TG) and cholesterol clearance (Table 1,

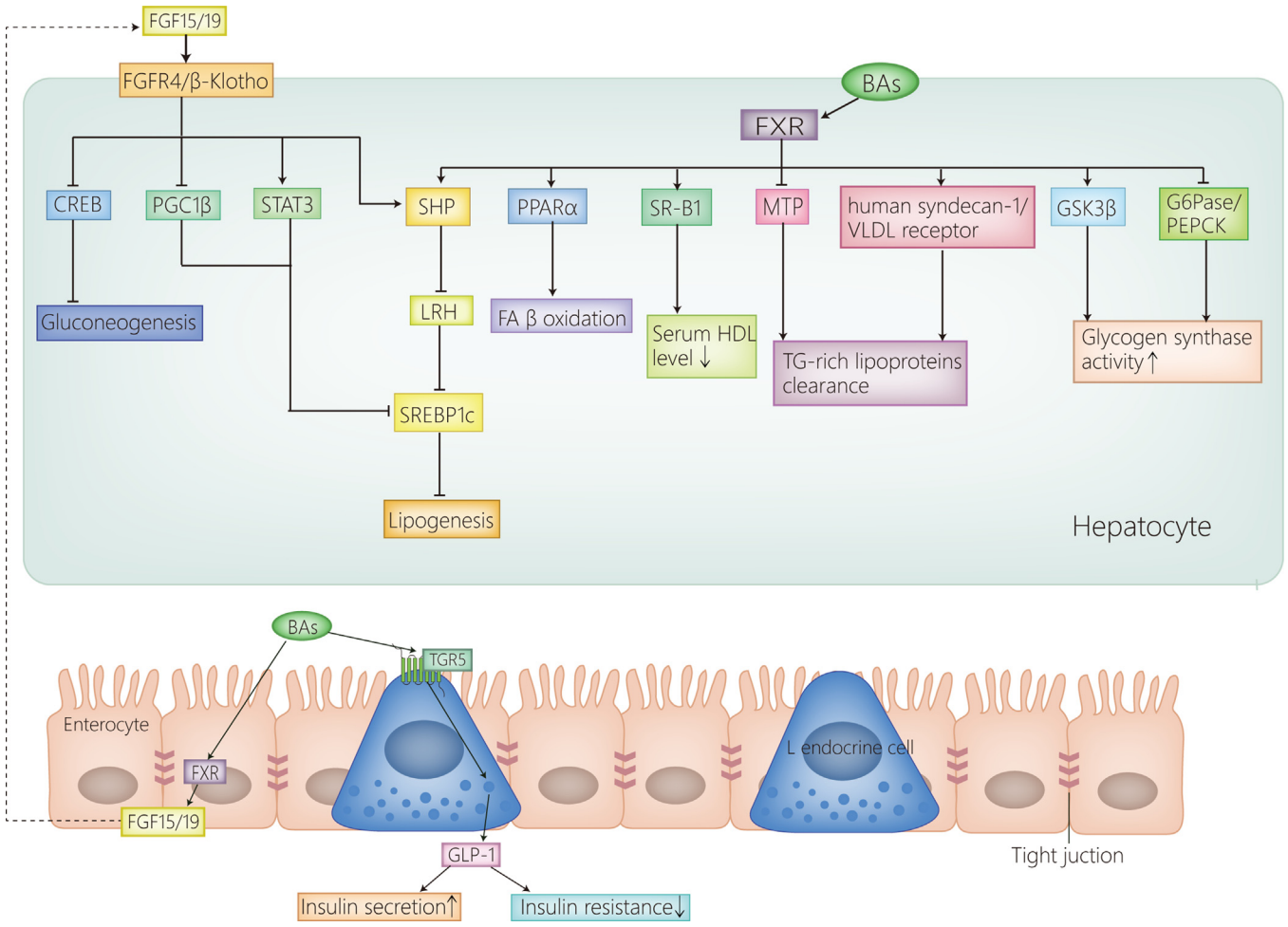


Fig. 2. The associated mechanisms of bile acids in regulating lipid and glucose metabolism. Activated FXR by bile acids in the hepatocyte represses LRH, mediated by SHP, further inhibits the transactivation of SREBP1c, which regulates some critical genes associated with lipogenesis, thereby reducing hepatic de novo lipogenesis. Moreover, activated FXR in the enterocyte induces FGF15/19 production, which can bind to the FGFR4/β-Klotho receptor expressed on hepatocytes, not only enhancing SHP, but also repressing SREBP1c directly by inducing STAT3 and inhibiting PGC1β, thus regulating lipogenesis in the liver. Furthermore, FGF15/19 can reduce hepatic gluconeogenesis via the inhibition of CREB. FXR in the hepatocyte also promotes β oxidation by inducing PPARα, reduces serum HDL level by inducing SR-B1, contributes to TG-rich lipoproteins clearance by inducing human syndecan-1 and VLDL receptor as well as inhibiting MTP, and improves the activity of glycogen synthase by promoting the phosphorylation of GSK3β and repressing G6Pase and PEPCK. Additionally, bile acids activate TGR5 on L endocrine cells to stimulate the secretion of GLP1, which further induces insulin secretion and ameliorates insulin resistance. SREBP1c, sterol regulatory binding protein1c; SHP, small heterodimer partner; LRH, liver receptor homologue; FXR, farnesoid X receptor; FGF15/19, fibroblast growth factor15/19; FGFR4, fibroblast growth factor receptor 4; PGC1β, peroxisome proliferator-activated receptor-γ coactivator1β; STAT3, signal transducer and activator of transcription3; PPARα, peroxisome proliferator-activated receptor alpha gene; CREB, cAMP regulatory element-binding protein; SR-B1, scavenger receptor class B type I; HDL, high-density lipoprotein; TG, triglyceride; MTP, microsomal transfer protein; VLDL, very-low-density lipoprotein; PEPCK, phosphoenolpyruvate carboxykinase; GLP1, glucagon-like peptide1; TGR5, Takeda G-protein coupled receptor 5.

Fig. 2). FXR represses hepatic de novo lipogenesis by restraining liver receptor homologue 1 expression mediated by SHP, further inhibiting the transactivation of sterol regulatory binding protein1c (SREBP1c) [74]. SREBP1c serves as a critical regulator of genes involved in lipogenesis [75]. Moreover, as a signaling molecule induced by FXR, FGF19 represses SREBP1c in the intestine indirectly by enhancing SHP expression, and directly by inhibiting peroxisome proliferator-activated receptor-γ coactivator 1β as well as enhancing signal transducer and activator of transcription 3 [76] (Fig. 2).

Furthermore, activated FXR can induce peroxisome proliferator-activated receptor alpha gene expression (PPARα), thus promoting FA β-oxidation [77]. FXR also promotes high-density lipoprotein (HDL) removal in the blood via the upregulation of scavenger receptor class B type I expression [78], which is able to regulate cholesterol ester uptake from HDL [79]. FXR enhances the clearance of TG-rich lipoproteins by inducing human syndecan-1 and very-low-density lipoprotein (VLDL) receptor [75]. By inhibiting microsomal transfer protein expression, FXR makes great contributions to TG assembly with apolipoprotein B as VLDL triglycerides [80]. In addition, conjugated bile acids reduce hepatic lipid content via S1PR2/SphK2/S1P signaling axis [81].

In summary, FXR in the hepatocyte inhibits hepatic de novo lipogenesis by repressing SREBP1c [74,75], promotes FA β-oxidation by inducing PPARα expression [77], reduces cholesterol levels by enhancing HDL removal in the blood [78], and accelerates the clearance of TG-rich lipoproteins by inducing human syndecan-1 and VLDL receptor, and inhibiting MTP expression [75,80]. Meanwhile, FXR in the intestine stimulates the secretion of FGF19, which can subsequently activate the FGFR4/β-Klotho receptor on the hepatocytes, allowing it to both directly and indirectly repress SREBP1c, thus contributing to the inhibition of hepatic lipogenesis [76].

Regulation of glucose metabolism

Bile acids are involved in glucose metabolism through regulating hepatic glycogen synthesis, hepatic gluconeogenesis, systemic

glucose levels, and BAT thermogenesis (Table 1, Fig. 2). Bile acid-activated TGR5 makes great contributions to the modulation of insulin sensitivity and glucose metabolism, which is extensively distributed in various tissues, including liver, gallbladder, gut, and muscle [19]. The activation of TGR5-mediated signaling pathway stimulates the secretion of glucagon-like peptide1 (GLP1) from intestinal L endocrine cells, which conversely modulates insulin secretion in a glucose-dependent way, and is conducive to the development of pancreatic β cell [74,75]. GLP-1 has been identified as a potent hormone [82] whose ability to ameliorate insulin resistance and liver damage has been widely recognized [19]. Moreover, TGR5 located on BAT can also be activated by bile acids, which then activate D2, PRDM16, and UCP1 in BAT sequentially, ultimately resulting BAT thermogenesis [83]. The thermogenesis in BAT showed a positive correlation with glucose uptake and removal, thus strikingly improving glucose metabolism [84].

In addition, FXR knock-out mice develop insulin resistance and fatty liver, as well as elevated plasma free fatty acid and serum glucose levels [85]. Hepatic gluconeogenesis can be inhibited by suppressing the expression of several critical transcription factors mediated by SHP via the activation of FXR [86]. FGF15/19 induced by activated FXR in the intestine dephosphorylates and inactivates cAMP regulatory element-binding protein, further inhibiting gluconeogenesis-associated genes expression [87]. Additionally, hepatic FXR activation stimulates the phosphorylation of GSK3β, and suppresses G6Pase and phosphoenolpyruvate carboxykinase (PEPCK) expression, thus increasing the activity of glycogen synthase [75]. However, increased PEPCK expression and elevated glucose level were induced by a FXR agonist in a different study, which mainly utilized human and rat hepatocytes, as well as the livers from mice [88]. Therefore, species difference among humans and mice putatively exists [89,90], and can partly explain the conflicting evidence.

In summary, the activation of TGR5 expressed on L endocrine cells stimulates GLP1 secretion, which is conducive to the insulin secretion and the improvement of insulin resistance [74,75]. The activated TGR5 in BAT enhances BAT thermogenesis, and thus increases glucose uptake and removal [84]. Moreover, FGF15/19 induced by activated FXR in the enterocytes bind to the FGFR4/β-Klotho receptor on the hepatocytes, and then inhibit gluconeogenesis by dephosphorylating and inactivating of CREB [87]. They can also promote the activity of glycogen synthase by phosphorylating GSK3β and by suppressing G6Pase and PEPCK expression [75]. Of note, increased PEPCK expression and elevated glucose level were induced by FXR agonist in a different study that mainly utilized human and rat hepatocytes, as well as the livers from mice [88]. The controversial results can be partly explained by the theory of species difference [89,90].

The relationship between bile acid and the intestinal microbiota

The intestinal microbiota colonizes human intestine and coexists in harmony with the host and affects physiological and pathological condition of the host [91], including obesity, metabolic syndrome, and other associated diseases [17]. Germ-free mice were less likely to develop high-fat diet (HFD)-induced obesity [17,92]. However, using intestinal microbiota transplants from subjects with NAFLD to germ-free animal models induced the development of fatty liver disease, indicating that the intestinal microbiota intimately correlated with NAFLD/NASH pathogenesis. Moreover, a recent study has illustrated that flaxseed-mediated changes in bile acid-related signaling pathways contributed to NASH improvements by the regulation of intestinal microbiota [20], further unraveling the relationship between bile acids and intestinal microbiota in NASH animal models.

Collectively, bile acids shape the intestinal microbiota, which conversely takes part in the regulation of biochemical and biological properties of bile acids. As bile acids have detergent properties over the plasmatic membrane and DNA structure, they show a potent antimicrobial effect and reduce the intestinal permeability to endotoxin [29,93–95]. Decreased bile flow during biliary obstruction contributes to bacterial overgrowth, disrupted intestinal barrier, and bacterial translocation in animal models and humans [96–98]. This further confirms the antimicrobial effects of bile acids. Additionally, bile acids also have the capability to directly remodel the intestinal microbiota by antimicrobial effects and indirectly by the induction of antimicrobial peptides secretion by FXR, like angogenin1 [92,99]. In the large intestine, primary bile acids undergo deconjugation and dihydroxylation with the assistance of some intestinal bacteria species, including *Clostridium, Bacteroides* and *Escherichia* [69,100]. Therefore, dysbiosis may alter bile acid composition and disrupt bile acid homeostasis, thus exerting great influence on bile acid-related pathways, including FXR signaling pathway and TGR5 signaling pathway [101]. Herein, the intestinal microbiota can affect the metabolic responses and lead to the increase of unconjugated bile acids in the circulation [100], which is able to repress the antibacterial function of conjugated bile acids, resulting in bacteria overgrowth that augments bile acid deconjugation, thereby promoting the translocation of intestinal microbiota and the occurrence of endotoxemia [101].

In summary, bile acids restrict the overgrowth of intestinal pathobionts owing to its detergent properties over DNA structure and the plasmatic membrane [29,92–94]. And they also have the capability to induce the secretion of antimicrobial peptides by activating FXR [92,99]. In contrast, the intestinal bacteria participate in secondary bile acids biotransformation [69,100]. Therefore, dysbiosis putatively disrupts bile acid homeostasis and alters bile acid composition, thereby exerting great influence on the bile acid-related pathways, including FXR signaling pathway and TGR5 signaling pathway [101]. Herein, it appears reasonable to speculate that the intestinal bacteria contribute to the pathogenesis of NASH putatively by altering bile acid-associated signaling pathways.

Bile Acid: A critical mediator in Anti-Inflammation and Anti-Fibrosis

FXR and TGR5 activated by bile acids distributed in some immune cells exhibit anti-inflammatory and anti-fibrotic properties (Table 1). To mitigate liver inflammation, activated FXR inhibits the expression of several proinflammatory genes by repressing the nuclear factor kappa B (NF-kB), which also reduces the expression of proinflammatory cytokines [102]. Moreover, FXR activation shows a negative correlation with NLRP3 inflammasome via its direct interaction with NLRP3 and IL-1β, which also downregulates proinflammatory cytokines secretion [103]. Of note, activated TGR5 can also inhibit NLRP3 inflammasome via the TGR5-cAMP-PKA signaling pathway [104,105], thus decreasing proinflammatory cytokines secretion. In addition, TGR5 has the capacity to promote anti-inflammatory cytokines production in macrophages via TGR5-PKA-CREB signaling axis, such as IL-10 [75], and ameliorate liver inflammation induced by lipopolysaccharide (LPS) [105]. -Furthermore, TGR5 negatively regulates the expression of monocyte chemoattractant protein1 (MCP1) [75], which is identified as an important chemokine that is capable of modulating monocytes/macrophages migration and infiltration [106]. A FXR agonist WAY-362450, administrated in an NASH model induced by continuous exposure to the methionine/choline-deficient (MCD) diet, restrained MCP1 expression, thus remarkably mitigat-

ing liver inflammatory cell infiltration [107]. Moreover, FGF19 induced by FXR in the intestine improves inflammation through regulating the inhibitor of NF-kB activity [108].

In addition, the activated FXR by bile acids in hepatic stellate cells (HSCs) putatively directly suppresses liver fibrosis through triggering the expression of the anti-fibrotic gene, like peroxisomal proliferator-activated receptor γ that is intimately associated with HSCs inactivation [109,110]. In addition, FXR activation in HSCs negatively modulates collagen deposition partly by inhibiting TGF-β/SMAD3 and Jun D/AP1 signaling pathway in a SHP-dependent way [75].

To sum up, hepatic FXR inhibits the expression of proinflammatory cytokines via the repression of associated genes [75]. TGR5 induces anti-inflammatory cytokines secretion, represses the expression of proinflammatory cytokines, as well as mitigates the infiltration of monocytes/macrophages, thus remarkably ameliorating inflammation in the liver [75,105,106]. Moreover, FGF19 induced by FXR in the intestine confers protection against inflammation by modulating the inhibitor of NF-kB activity [108]. Furthermore, activated FXR in HSCs is capable of alleviating hepatic fibrosis through inducing anti-fibrotic genes expression and reducing collagen deposition [75,109,110].

Bile acids contribute to the development of NASH

As mentioned above, TGR5 and FXR activation by bile acids hampers the pathological development of NASH. However, in several studies, bile acids also contribute to the disease's progression [111–114]. In a NASH rat model with exposure to high fat and high cholesterol (HFC) diet, the administration of CA exacerbated hepatic steatosis, inflammation, and fibrosis dose-dependently [111]. Consistently, the expression of mRNA associated with inflammatory responses and fibrogenesis in CA diet group was much higher than that of the controls [111]. In another animal study, DCA and LCA were both confirmed to downregulate the expression of MTTP, ACOX1 and PNPLA3, which regulate lipid metabolism by promoting hepatic lipid accumulation [112]. Moreover, at pathological concentration, bile acids acted as potent inflammagens and stimulated the secretion of proinflammatory cytokines and chemokines from hepatocytes, which facilitated the shift from simple steatosis to NASH [113]. Furthermore, several recent studies have found that patients with NASH tended to have elevated 12α-OH bile acids level, which is often related to unhealthy high BMI status [115]. 12α-OH bile acids also had the ability to strongly bind to TGR5 and further activate p38 MAPK and ERK1/2, thus contributing to HSCs proliferation and fibrosis-associated markers expression [114]. More interestingly, when administrated with bile acids, normal human hepatic cell lines exhibited more potent proliferation properties, which link bile acids to liver carcinogenesis [116]. Taken together, higher bile acid concentration can also contribute to the pathogenesis of NASH.

Bile acid: A potential biomarker for the stratification of NAFLD

NASH is an aggressive modality of NAFLD, which putatively progress to fibrosis, cirrhosis, or HCC if untreated [1]. Fibrosis is regarded as the most significant presage for liver-related adverse events or the mortality in long-term longitudinal studies [117]. Although the histopathological biopsy is the reference standard to diagnose hepatic fibrosis [118,119], it is invasive, potentially painful and costly [120]. Therefore, there is an urgent need to find effective noninvasive methods for the early recognition of fibrosis.

Some studies have found that compared to the controls, there was an increment of circulating bile acids in NAFLD patients [121]. However, these patients tended to have insulin resistance, metabolic syndrome and T2DM, which have been confirmed to correlate with bile acid profiles [122]. Herein, it is difficult to assert that NAFLD has an association with alterations of circulating bile acid profiles. Interestingly, a substantial body of evidence have reported that bile acid profiles were related to hepatic fibrosis severity in NAFLD/NASH patients [123–125]. Caussy et al. [123] found that the fibrosis stage of NAFLD was associated with fasting total bile acids levels in a dose-dependent way. Nimer et al. [124]'s findings indicated that NAFLD patients with higher grades of inflammation often had increased conjugated primary bile acids. Puri et al. [125] suggested that there was a close relationship between the increment of fasting circulating total conjugated CA and the increased possibility of advanced fibrosis stage ($F \geq 2$ vs F0-F1) and NAFLD activity score (NAS) ≥ 4. Therefore, it appears plausible to utilize bile acid profiling in the stratification of NAFLD patients, which warrants further investigations.

Potential bile acid-based therapies for NASH

In pace with the pandemic of obesity and metabolic syndrome worldwide, NASH is currently emerging as the major cause of chronic and end stage liver disorder [126,127]. Although weight reduction and lifestyle modification are conducive to the improvement of histological conditions in NAFLD/NASH patients, only 10 %–20 % of patients can achieve the desired benefits owing to the difficulty to permanently persist in a healthy lifestyle and effective exercise [128]. Up to date, no approved pharmacological agents for patients with NASH are available [129]. Of note, bile acids have taken an important part in the pathogenesis of NASH, which open new perspectives on the potential therapies which target the bile acids and its associated signaling pathways (Fig. 3, Table 2).

FXR and TGR5 agonist

FXR agonist

Obeticholic acid (OCA), as one kind of selective and potent synthetic steroidal FXR agonist, putatively contributes to NASH improvement [23]. In animal experiments, OCA exhibited properties that ameliorate liver steatosis, inflammation, fibrosis, as well as insulin resistance [130,131]. In two phase 2 trials, both conducted in the double-blind, placebo-controlled, parallel group [22,132], OCA could increase insulin sensitivity, ameliorate histological and biochemical characteristics of NASH, and reduce markers of liver inflammation and fibrosis, and NAS in NAFLD/NASH patients compared with placebo without cirrhosis. In a phase 3 study [133], the interim analysis after 18 months showed that, compared with placebo, the fibrosis condition in NASH patients with F2-F3 or F1 fibrosis was partly improved whereas NASH histological features were not mitigated with OCA treatment. However, in these trials, an increase in pruritus in NASH patients after OCA treatment has been observed, as well as an increase of LDL-c and a decrease of HDL-c [21], which positively correlated with atherosclerotic risk, thereby restricting the use of OCA. To test whether OCA was still effective and safe for NASH patients with cirrhosis, another phase 3 study investigated the efficacy of OCA combined with statins, which ultimately drew a conclusion that OCA treatment in subjects with compensated cirrhosis or not was confirmed to be comparably safe at doses up to 25 mg [129]. These evidences offer the promise of OCA treatment in NASH.

Cilofexor belongs to one kind of non-steroidal FXR agonists. In a NASH animal model, it showed anti-fibrotic effects [23]. In a phase 2 DBRCT [134], in the 100 mg group treated with cilofexor, total and primary serum bile acids decreased moderately while secondary bile acids decreased significantly, with no alteration in liver

Table 2
Bile acid-based therapies for NASH.

Category	Agents	Study types	Therapeutic implications	Adverse effects	Ref
FXR agonist	OCA	Animal study; phase 2 and 3 study	Ameliorating histological and biochemical characteristics of NASH	Pruritus; LDL-c increment; HDL-c reduction	[21,22,129–133]
	Cilofexor	Animal study; phase 2 study	Inhibiting liver fibrosis	Pruritus; LDL-c increment; HDL-c reduction	[21,23,134,135]
	Tropifexor	Animal study; phase 1 and 3 study	Alleviating hepatic steatosis and restoring gut microbiota	Pruritus; LDL-c increment; HDL-c reduction	[23,129,136,137]
	SU5	Animal study	Improving hepatic steatosis and inflammation		[138]
	EDP-305	Phase 2 study	Reducing ALT and hepatic fat content	Pruritus; diarrhea; dizziness; headache; and vomiting	[139]
	PX-104	Phase 2 study	Reducing liver enzymes and improving insulin sensitivity		[140]
	Vonafexor	Phase 2a study	Reducing liver enzymes, hepatic fat content, and bodyweight	Pruritus; LDL-c increment	[141]
	Nidufexor	Animal study	Reducing hepatic steatosis, inflammation, as well as fibrosis		[142]
	MET409	Phase 1b study	Reducing liver fat contents	Lower risk of pruritus and LDL-c increment compared to other FXR agonists	[143]
TGR agonist	BAR501	Animal study	Treating the vascular component of NASH	Pruritus; gallbladder distention	[144–147]
Dual FXR and TGR5 agonist	INT-767	Animal study	Attenuating hepatic steatosis or inflammation		[148,149]
	BAR502	Animal study	Improving lipid metabolism		[150–152]
Bile acid sequestrant	Sevelamer	Animal study	Alleviating hepatic steatosis, inflammation, and fibrosis		[154]
Bile acid conjugate	CDCArg	Animal study	Mitigating hepatic steatosis; increasing insulin sensitivity		[155]
	Aramchol	Phase 2 study	Reducing liver fat content		[156]
NorUDCA		Animal study, phase 2 study	Reducing ALT		[157,163]
FGF19 analogue	Aldafermin	Phase 2 study	Reducing hepatic steatosis and fibrosis	Diarrhea; abdominal pain; frequent bowel movements; nausea; hepatocyte proliferation	[129,164–167]
ASBT inhibitor	SC-435	Animal study	Increasing insulin sensitivity; reducing NAS	Diarrhea; abdominal pain	[168,169]
	Elobixibat	Animal study	Mitigating hepatic inflammation and fibrosis; restoring gut microbiota		[170]

Abbreviations: NASH, nonalcoholic steatohepatitis; FXR, farnesoid X receptor; OCA, Obeticholic acid; LDL-c, low density lipoprotein-cholesterol; HDL-c, high density lipoprotein-cholesterol; ALT, alanine aminotransferase; FGF19, fibroblast growth factor19; TGR5, Takeda G-protein coupled receptor 5; ASBT, apical sodium-dependent bile salt transporter; UDCA, Ursodeoxycholic acid; NAS, nonalcoholic fatty liver disease activity score.

stiffness but a decreasing trend of fibrosis-associated markers in serum, TIMP-1. In another phase 2 trial in NASH patients without cirrhosis [135], serum primary bile acids reduced significantly in both 100 mg and 30 mg treatment, while only in the 30 mg group, total and secondary bile acids decreased relatively and absolutely, respectively. Simultaneously, with Cilofexor, serum pruritus and LDL-c increased, while HDL-c decreased in various trials [21]. These adverse effects also limit Cilofexor's extensive utility in patients with NASH.

Tropifexor is also one synthetic non-steroidal FXR agonists, which could alleviate hepatic steatosis and restore the altered intestinal microbiota in the animal models of NASH [23]. A recent phase 1 study showed that Tropifexor increased the production of FGF19 in a dose-dependent way, which was proven to be safe and well tolerated in humans [136]. In a phase 2 trial (FLIGHT-FXR) [23,129,136], part A/B showed anti-inflammatory and anti-steatotic effects, while part C showed a reduction of hepatic fat content, serum ALT level, and body weight. Of note, Tropifexor treatment also had several adverse effects, such as dose-related pruritus, the early decrease of HDL-c and increase of LDL-c [137]..

SU5 is the obtained analog of Auraptene, which exhibits potent pharmacological effects, and is an excellent safety profile as a novel FXR agonist. In a MCD-induced NASH model, SU5 upregulated the expression of FA β oxidation-associated genes and downregulated the expression of inflammation-related genes and lipid synthesis-related genes [138]. These results indicated that SU5 was likely to be a pharmacological intervention in the treatment for NASH patients.

EDP-305, an oral FXR agonist, was found to decrease hepatic fat content and the serum ALT level of NASH patients in a double-blind phase 2 study, which represents a new avenue for NASH treatment [139]. However, the adverse effects of EDP-305, including pruritus, diarrhea, dizziness, headache, and vomiting, are worthy to be noted and addressed [139].

Four weeks of PX-104 (a synthetic FXR agonist) treatment has been found to reduce liver enzymes and improve insulin sensitivity in NAFLD patients without diabetes, but it exerted little effect on hepatic steatosis in a phase 2 study [140].

Vonafexor, another kind of FXR agonist, had multifaceted salutary effects on patients with suspected fibrotic NASH, including inducing bodyweight loss, reducing liver enzymes, and ameliorating hepatic lipid accumulation [141]. Nidufexor, a novel partial FXR agonist, has been confirmed to reduce hepatic steatosis, inflammation, as well as fibrosis in NASH murine model [142].

Although FXR agonists show great potential in NASH treatment, their adverse effects limit its extensive and long-term utility. Fortunately, MET409, a unique FXR agonist, was found to strikingly reduce liver fat contents at the dose of 50 mg with lower risk of pruritus and LDL-c increment compared to other FXR agonists [143].

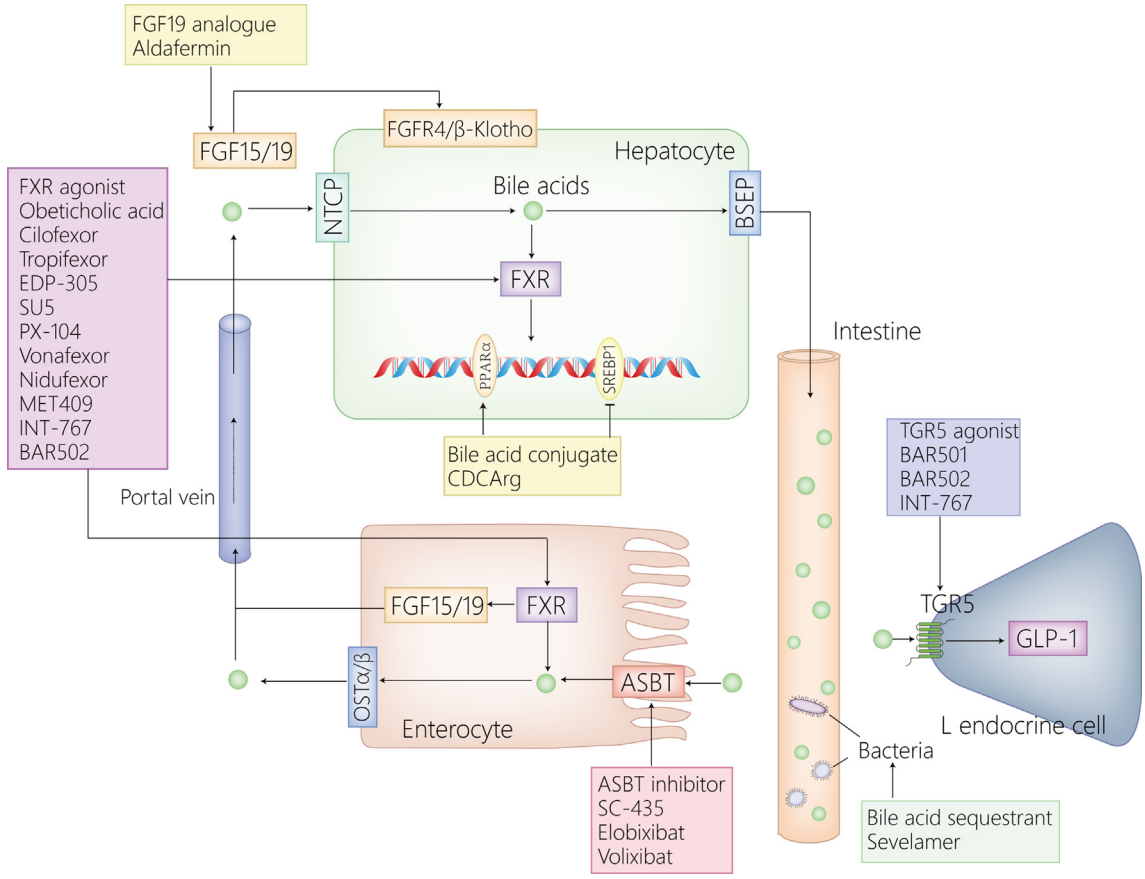


Fig. 3. Bile acids-based therapies for NASH. FXR agonists, including obeticholic acid, cilofexor, tropifexor, SU5 and EDP-305, have been confirmed to alleviate the inflammation and fibrosis condition of NASH by triggering a series of signaling pathways mediated by FXR. BAR501, as a TGR5 agonist, could reverse liver damage. Moreover, the dual FXR and TGR5 agonist, INT-767, was able to attenuate hepatic steatosis and inflammation. Sevelamer, as a bile acid sequestrant, reduced the translocation of LPS from the intestine to the liver by restoring intestinal dysbiosis, which was conducive to ameliorating hepatic inflammation and fibrosis. Bile acid conjugates, such as CDCArg, regulated FXR-targeted genes, like SREBP1 and PPAR α, thus modulating lipid metabolism. Aldafermin, as a kind of FGF19 analogue, improved insulin sensitivity, inhibited de novo lipogenesis and reduced hepatic inflammation and fibrosis by activating the FGFR4/β-Klotho receptor on the hepatocytes. Furthermore, the ASBT inhibitor, including SC-435, Elobixiba, and Volixibat, increased insulin sensitivity, ameliorated hepatic inflammation and fibrosis, as well as reduced NAFLD activity score by enhancing the excretion of bile acids, repressing the expression of the genes involved in lipid synthesis, and inhibiting the expression of proinflammatory cytokines. NASH, nonalcoholic steatohepatitis; SHP, small heterodimer partner; TGR5, Takeda G-protein coupled receptor 5; FXR, farnesoid X receptor; LPS, lipopolysaccharide; FGF15/19, fibroblast growth factor15/19; SREBP1, sterol regulatory binding protein1; CYP7A1, cholesterol 7α-hydroxylase; ASBT: apical sodium-dependent bile salt transporter; FGFR4, fibroblast growth factor receptor 4; BSEP: bile salt export pump; NAFLD, nonalcoholic fatty liver disease; NTCP: sodium taurocholate co-transporting polypeptide; OSTα and OSTβ: organic solute transporter α and organic solute transporter β; GLP1, glucagon-like peptide1.

TGR5 agonist

BAR501 is a potent TGR5 agonist. Some researchers have recently established a mouse model with vascular and liver damage induced by a high fat and fructose diet, and found that BAR501 could reverse the vascular damage and hepatic lipid deposition via the activation of TGR5 [144]. Moreover, BAR501 conferred protection against the thickening of aortic intima-media, which was identified as an effective predictor of cardiovascular outcomes [144]. Herein, BAR501 might be used to treat the vascular component of NASH. However, several properties of TGR5 raised safety concerns about the utility of TGR5 and its compounds in clinical trials, including promoting the development of pruritus, contributing to gallbladder distention, as well as exerting proproliferative and antiapoptotic effects on cholangiocytes [145–147].

Dual FXR and TGR5 agonist

INT-767 was capable of attenuating hepatic steatosis or inflammation when it was administrated in a murine model of NAFLD putatively via the upregulation of anti-inflammatory cytokines like IL-10 and the downregulation of proinflammatory cytokines [148]. Additionally, some researchers established a rabbit model with metabolic syndrome induced by HFD and suggested that INT-767 had the capacity to reverse the alterations in adipose tissue and liver, improve insulin resistance, and promote the differentiation of preadipocytes into metabolically healthy phenotypes [149]. Of note, INT-767 is also not utilized in clinical trials currently owing to its detrimental effects as a TGR5 agonist.

BAR502 is generally identified as another dual FXR and TGR5 agonist, which has been confirmed to exert salutary effects on NAFLD/NASH. In the NASH model mice induced by HFD, BAR502 was found to improve lipid metabolism by enhancing WAT browning, thus significantly alleviating NASH [150]. Moreover, FXR and TGR5 activation by BAR502 in adipose tissues, liver, and gut were able to inhibit lipid biosynthesis genes in NASH model mice feeding with HFD-F, which was supported by transcriptome analysis [151]. Furthermore, the joint treatment of BAR502 and CDCA was proved to almost completely reverse NASH in an animal study [152].

Interestingly, Notoginsenoside Ft1, a compound derived from traditional Chinese medicine, has been reported to ameliorate insulin resistance and obesity induced by HFD by activating

TGR5 and inhibiting FXR in the intestine [153]. However, whether the compound plays a role in NASH treatment needs further investigation.

Bile acid sequestrant

Sevelamer, a bile acid sequestering resin, was administrated in NASH murine model exposure to the choline-deficient, L-amino acid-defined, high-fat diet. It has been found to significantly alleviate hepatic steatosis, inflammation, and fibrosis by reducing translocated LPS derived from the gut, as Sevelamer could participate in the restoration of dysbiosis, the regulation of LPS absorption, and the repression of bile acid uptake [154].

Bile acid conjugate

CDCArg (Chenodeoxycholyl-arginine ethyl ester conjugate) mitigated hepatic steatosis by the upregulation of PPARα gene expression and the downregulation of SREBP1 expression in a NAFLD murine model induced by HFD, and it also increased insulin sensitivity and affected weight gain directly [155]. Collectively, CDCArg could confer liver protection against the injury induced by HFD without cholesterol toxicity, which offers new hope for NASH treatment.

In a phase 2, randomized, double-blind study, Aramchol, a novel conjugate of bile acid and arachidonic acid, was found to increase adiponectin levels and decrease liver fat content effectively and safely when administrated in NAFLD and NASH patients at a dose of 300 mg [156]. The positive results indicated that Aramchol is putatively a pharmacological intervention in NAFLD/NASH treatment.

Ursodeoxycholic acid and norursodeoxycholic acid

Ursodeoxycholic acid (UDCA) and norUDCA were confirmed to alleviate liver steatosis and fibrosis in a NAFLD/NASH model induced by the Western diet [157]. The administration of norUDCA could also downregulate lipogenic and apoptotic pathways in the genetic NASH mouse mice, thus remarkably alleviating steatosis [158]. In a randomized controlled study for 12 months, high dose UDCA was thought to reduce the levels of serum aminotransferase and fibrosis markers in patients with NASH [159]. But notably, in another randomized and placebo-controlled trial, the overall histology of NASH patients could not be improved by high dose UDCA treatment for 18 months compared with placebo [160]. Similarly, the condition of hepatic steatosis, inflammation and fibrosis of NASH patients who received 2 years of UDCA treatment and that of the placebo group showed no significant difference [161]. Moreover, the UDCA treatment for NAFLD patients was related to hepatic lipid accumulation by exerting its FXR-antagonistic effects in a randomized controlled trial [162]. Therefore, whether UDCA should be included in NASH treatment is still questionable. NorUDCA, a derivative of UDCA, could significantly reduce the serum ALT level of NAFLD patients at a dose of 1500 mg per day after 12 weeks of treatment compared to the control in a double-blind, randomized phase 2 trial [163], which putatively represents a new avenue for NAFLD treatment.

FGF19 analogue

Aldafermin (NGM282), the FXR downstream signaling molecule, belongs to a nontumorigenic variant of FGF19, which has the capacity to inhibit hepatic lipogenesis, increase insulin sensitivity, ameliorate liver inflammation and fibrosis, and rectify mitochondrial dysfunction [129]. Aldafermin treatment broughtabout a reduction of 5 % or more in hepatic fat fraction (MRI-PDFF) in a phase 2 trial over 12 weeks compared to placebo [164]. In another open-label phase 2 trial [165], Aldafermin alleviated fibrosis by one stage or more and reduced NAS remarkably without exacerbation of steatohepatitis. Aldafermin treatment also led to fibrosis improvement without deterioration of NASH in a study group over 24 weeks [129]. However, Aldafermin treatment concomitantly brings about some detrimental events, such as diarrhea, abdominal pain, frequent bowel movements, as well as nausea [165]. Of note, some studies have reported that the activation of FGF19 has been related to hepatocyte proliferation, thus increasing the risk of HCC, which limits FGF19 analogue utility [166,167].

ASBT inhibitor

SC-435, a potent ASBT inhibitor, increased insulin sensitivity and reduced NAS when administrated in HFD-fed mice, by reducing lipid synthesis gene expression and enhancing the excretion of bile acids. However, SC-435 could not significantly reduce hepatic steatosis score in a short term [168]. Furthermore, during long-term treatment, diarrhea and abdominal pain often occur in adults, limiting its applicability [169].

Elobixibat, when administrated in the NASH animal model exposed to MCD, was found to increase the concentration of fecal bile acids, decrease serum bile acids levels, mitigate hepatic inflammation and fibrosis by inhibiting proinflammatory cytokine secretion [170]. Moreover, Elobixibat could also restore the composition of intestinal microbiota and normalize the level of intestinal tight junction protein The results made Elobixibat a candidate for the treatment of NASH.

Volixibat was found to increase fecal bile acid concentrations, influence metabolic associated regulators, and reduce NAS significantly in a NASH murine model exposed to HFD [171]. In phase 1 studies, Volixibat was able to reduce serum cholesterol level and increase fecal bile acids excretion in overweight and obese subjects, which is a possible new NASH treatment option [172]. However, in a double-blind phase 2 trial, Volixibat did not make contributions to the reduction of hepatic content and the improvement of hepatic damage in patients with NASH [173]. The results indicated that Volixibat could not be regarded as an effective agent for NASH treatment.

Conclusion

NAFLD, which occurs in individuals without risk for excessive alcohol consumption, is mainly composed of a spectrum of liver metabolic disorders induced by chronic excessive caloric intake or excessive deposition of lipids, including simple steatosis and NASH. Currently, no approved treatments for NASH are available despite its increasing prevalence. Bile acid-activated FXR and TGR5 have the capacity to regulate bile acid homeostasis, glucose and lipid metabolism via multiple signaling pathways. Additionally, dysbiosis also contributes to the occurrence and progression of NASH by altering bile acid profiles. Moderately increased bile acids are conducive to the improvement of inflammation and fibrosis condition via a host of mechanisms, while excessive bile acids accelerate the pathological process of NASH.

Owing to the intimate relationship between bile acids and NASH disease severity, the analysis of bile acid profile represents a novel avenue for diagnosing and assessing the severity of the disease. It is highly necessary to conduct more research to analyze the characteristics of bile acid disorder and to evaluate the accuracy and feasibility of bile acids as a noninvasive biomarker, particularly when it is used for the diagnosis of liver fibrosis. Currently, although bile acids-based therapies have showed enormous therapeutical potential for NASH in animal experiments and human

phase 2 or 3 trials, extensive efforts are still needed to rigorously evaluate the efficacy and safety of pharmacological agents which target bile acids-mediated signaling pathways, and to address adverse effects of these agents.

Compliance with ethics requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: B.S. has been consulting for Ambys Medicines, Ferring Research Institute, Gelesis, HOST Therabiomics, Intercept Pharmaceuticals, Mabwell Therapeutics, Patara Pharmaceuticals and Takeda. B.S.'s institution UC San Diego has received research support from Axial Biotherapeutics, BiomX, CymaBay Therapeutics, NGM Biopharmaceuticals, Prodigy Biotech and Synlogic Operating Company. B.S. is founder of Nterica Bio. Other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

The authors thank Yixin Zhu for editing the manuscript.

Grant support

The Grant Support are mainly from the National Natural Science Foundation of China (No. 82000561 to HC; No. 81974078, 81570530, 81370550 to LY), Natural Science Foundation of Hubei Province (No. 2019ACA1333 to LY) and the Science Foundation of Union Hospital (No. 2021xhyn005 to HC), and services provided by San Diego Digestive Diseases Research Center (SDDRC) P30 DK120515.

References

[1] Haas JT, Francque S, Staels B. Pathophysiology and mechanisms of nonalcoholic fatty liver disease. Annu Rev Physiol 2016;78:181–205. doi: https://doi.org/10.1146/annurev-physiol-021115-105331.
[2] Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13(4):643–54. doi: https://doi.org/10.1016/j.cgh.2014.04.014.
[3] Takaki A, Kawai D, Yamamoto K. Molecular mechanisms and new treatment strategies for non-alcoholic steatohepatitis (NASH). Int J Mol Sci 2014;15(5):7352–79. doi: https://doi.org/10.3390/ijms15057352.
[4] Castaño-Rodríguez N, Mitchell HM, Kaakoush NO. NAFLD, Helicobacter species and the intestinal microbiome. Best Pract Res Clin Gastroenterol 2017;31(6):657–68. doi: https://doi.org/10.1016/j.bpg.2017.09.008.
[5] Ekstedt M, Franzén LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. Hepatology (Baltimore, MD) 2006;44(4):865–73.
[6] Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. Gastroenterology 1994;107(4):1103–9.
[7] Orman ES, Barritt AS, Wheeler SB, Hayashi PH. Declining liver utilization for transplantation in the United States and the impact of donation after cardiac death. Liver Transpl 2013;19(1):59–68. doi: https://doi.org/10.1002/lt.23547.
[8] Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148(3):547–55. doi: https://doi.org/10.1053/j.gastro.2014.11.039.
[9] Burra P, Becchetti C, Germani G. NAFLD and liver transplantation: disease burden, current management and future challenges. JHEP Rep 2020;2(6):. doi: https://doi.org/10.1016/j.jhepr.2020.100192100192.
[10] Goldberg D, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology 2017;152(5):1090–1099.e1091. doi: https://doi.org/10.1053/j.gastro.2017.01.003.
[11] Holmer M, Melum E, Isoniemi H, Ericzon B-G, Castedal M, Nordin A, et al. Nonalcoholic fatty liver disease is an increasing indication for liver transplantation in the Nordic countries. Liver Int 2018;38(11):2082–90. doi: https://doi.org/10.1111/liv.13751.
[12] Younossi ZM, Stepanova M, Ong J, Trimble G, AlQahtani S, Younossi I, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2021;19(3):580–589.e585. doi: https://doi.org/10.1016/j.cgh.2020.05.064.
[13] Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology (Baltimore, MD) 2010;52(5):1836–46. doi: https://doi.org/10.1002/hep.24001.
[14] Puri P, Daita K, Joyce A, Mirshahi F, Santhekadur PK, Cazanave S, et al. The presence and severity of nonalcoholic steatohepatitis is associated with specific changes in circulating bile acids. Hepatology (Baltimore, MD) 2018;67(2):534–48. doi: https://doi.org/10.1002/hep.29359.
[15] Lake AD, Novak P, Shipkova P, Aranibar N, Robertson D, Reily MD, et al. Decreased hepatotoxic bile acid composition and altered synthesis in progressive human nonalcoholic fatty liver disease. Toxicol Appl Pharmacol 2013;268(2):132–40. doi: https://doi.org/10.1016/j.taap.2013.01.022.
[16] Zhu Y, Liu H, Zhang M, Guo GL. Fatty liver diseases, bile acids, and FXR. Acta Pharm Sin B 2016;6(5):409–12.
[17] Arab JP, Karpen SJ, Dawson PA, Arrese M, Trauner M. Bile acids and nonalcoholic fatty liver disease: molecular insights and therapeutic perspectives. Hepatology (Baltimore, MD) 2017;65(1):350–62. doi: https://doi.org/10.1002/hep.28709.
[18] Kuipers F, Bloks VW, Groen AK. Beyond intestinal soap–bile acids in metabolic control. Nat Rev Endocrinol 2014;10(8):488–98. doi: https://doi.org/10.1038/nrendo.2014.60.
[19] Thomas C, Gioiello A, Noriega L, Strehle A, Oury J, Rizzo G, et al. TGR5-mediated bile acid sensing controls glucose homeostasis. Cell Metab 2009;10(3):167–77. doi: https://doi.org/10.1016/j.cmet.2009.08.001.
[20] Yang C, Wan M, Xu D, Pan D, Xia H, Yang L, et al. Flaxseed powder attenuates non-alcoholic steatohepatitis via modulation of gut microbiota and bile acid metabolism through gut-liver axis. Int J Mol Sci 2021;22(19):10858. doi: https://doi.org/10.3390/ijms221910858.
[21] Kremoser C. FXR agonists for NASH: how are they different and what difference do they make? J Hepatol 2021;75(1):12–5. doi: https://doi.org/10.1016/j.jhep.2021.03.020.
[22] Neuschwander-Tetri BA, Loomba R, Sanyal AJ, Lavine JE, Van Natta ML, Abdelmalek MF, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet 2015;385(9972):956–65. doi: https://doi.org/10.1016/S0140-6736(14)61933-4.
[23] Farooqui N, Elhence A, Shalimar. A current understanding of bile acids in chronic liver disease. J Clin Exp Hepatol 2022;12(1):155–73. doi: https://doi.org/10.1016/j.jceh.2021.08.017.
[24] Asgharpour A, Kumar D, Sanyal A. Bile acids: emerging role in management of liver diseases. Hepatol Int 2015;9(4):527–33. doi: https://doi.org/10.1007/s12072-015-9656-7.
[25] Honda A, Miyazaki T, Iwamoto J, Hirayama T, Morishita Y, Monma T, et al. Regulation of bile acid metabolism in mouse models with hydrophobic bile acid composition. J Lipid Res 2020;61(1):54–69. doi: https://doi.org/10.1194/jlr.RA119000395.
[26] Russell DW, Setchell KD. Bile acid biosynthesis. Biochemistry 1992;31(20):4737–49.
[27] Mihalik SJ, Steinberg SJ, Pei Z, Park J, Kim DG, Heinzer AK, et al. Participation of two members of the very long-chain acyl-CoA synthetase family in bile acid synthesis and recycling. J Biol Chem 2002;277(27):24771–9.
[28] Takahashi S, Fukami T, Masuo Y, Brocker CN, Xie C, Krausz KW, et al. Cyp2c70 is responsible for the species difference in bile acid metabolism between mice and humans. J Lipid Res 2016;57(12):2130–7. doi: https://doi.org/10.1194/jlr.M071183.
[29] Li T, Chiang JY. Bile acid signaling in metabolic disease and drug therapy. Pharmacol Rev 2014;66(4):948–83. doi: https://doi.org/10.1124/pr.113.008201.
[30] Chiang JY. Bile acids: regulation of synthesis. J Lipid Res 2009;50(10):1955–66. doi: https://doi.org/10.1194/jlr.R900010-JLR200.
[31] Johnson MR, Barnes S, Kwakye JB, Diasio RB. Purification and characterization of bile acid-CoA:amino acid N-acyltransferase from human liver. J Biol Chem 1991;266(16):10227–33.
[32] Ridlon JM, Kang D-J, Hylemon PB. Bile salt biotransformations by human intestinal bacteria. J Lipid Res 2006;47(2):241–59.
[33] Björkhem I, Einarsson K, Melone P, Hylemon P. Mechanism of intestinal formation of deoxycholic acid from cholic acid in humans: evidence for a 3-oxo-delta 4-steroid intermediate. J Lipid Res 1989;30(7):1033–9.
[34] Hylemon PB, Melone PD, Franklund CV, Lund E, Björkhem I. Mechanism of intestinal 7 alpha-dehydroxylation of cholic acid: evidence that allo-deoxycholic acid is an inducible side-product. J Lipid Res 1991;32(1):89–96.

[35] Guzior DV, Quinn RA. Review: microbial transformations of human bile acids. Microbiome 2021;9(1):140. doi: https://doi.org/10.1186/s40168-021-01101-1.
[36] Sato Y, Atarashi K, Plichta DR, Arai Y, Sasajima S, Kearney SM, et al. Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians. Nature 2021;599(7885):458–64. doi: https://doi.org/10.1038/s41586-021-03832-5.
[37] Boyer JL. Bile formation and secretion. Compr Physiol 2013;3(3):1035–78. doi: https://doi.org/10.1002/cphy.c120027.
[38] König J, Nies AT, Cui Y, Leier I, Keppler D. Conjugate export pumps of the multidrug resistance protein (MRP) family: localization, substrate specificity, and MRP2-mediated drug resistance. Biochim Biophys Acta 1999;1461 (2):377–94.
[39] 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(4):596–608.
[40] Otsuki M. Pathophysiological role of cholecystokinin in humans. J Gastroenterol Hepatol 2000;15(Suppl):D71–83.
[41] Shneider BL, Dawson PA, Christie DM, Hardikar W, Wong MH, Suchy FJ. Cloning and molecular characterization of the ontogeny of a rat ileal sodium-dependent bile acid transporter. J Clin Invest 1995;95(2):745–54.
[42] Dawson PA, Haywood J, Craddock AL, Wilson M, Tietjen M, Kluckman K, et al. Targeted deletion of the ileal bile acid transporter eliminates enterohepatic cycling of bile acids in mice. J Biol Chem 2003;278(36):33920–7.
[43] Oelkers P, Kirby LC, Heubi JE, Dawson PA. Primary bile acid malabsorption caused by mutations in the ileal sodium-dependent bile acid transporter gene (SLC10A2). J Clin Invest 1997;99(8):1880–7.
[44] Gong YZ, Everett ET, Schwartz DA, Norris JS, Wilson FA. Molecular cloning, tissue distribution, and expression of a 14-kDa bile acid-binding protein from rat ileal cytosol. Proc Natl Acad Sci U S A 1994;91(11):4741–5.
[45] Ballatori N, Christian WV, Lee JY, Dawson PA, Soroka CJ, Boyer JL, et al. OSTalpha-OSTbeta: a major basolateral bile acid and steroid transporter in human intestinal, renal, and biliary epithelia. Hepatology (Baltimore, MD) 2005;42(6):1270–9.
[46] Rao A, Haywood J, Craddock AL, Belinsky MG, Kruh GD, Dawson PA. The organic solute transporter alpha-beta, Ostalpha-Ostbeta, is essential for intestinal bile acid transport and homeostasis. Proc Natl Acad Sci U S A 2008;105(10):3891–6. doi: https://doi.org/10.1073/pnas.0712328105.
[47] Marin JJG, Macias RIR, Briz O, Banales JM, Monte MJ. Bile Acids in Physiology, Pathology and Pharmacology. Curr Drug Metab 2015;17(1):4–29.
[48] Hagenbuch B, Stieger B, Foguet M, Lübbert H, Meier PJ. Functional expression cloning and characterization of the hepatocyte Na+/bile acid cotransport system. Proc Natl Acad Sci U S A 1991;88(23):10629–33.
[49] Hagenbuch B, Meier PJ. Molecular cloning, chromosomal localization, and functional characterization of a human liver Na+/bile acid cotransporter. J Clin Invest 1994;93(3):1326–31.
[50] Meier PJ, Stieger B. Bile salt transporters. Annu Rev Physiol 2002;64:635–61.
[51] Suga T, Yamaguchi H, Sato T, Maekawa M, Goto J, Mano N. Preference of conjugated bile acids over unconjugated bile acids as substrates for OATP1B1 and OATP1B3. PLoS ONE 2017;12(1):. doi: https://doi.org/10.1371/journal.pone.0169719e0169719.
[52] Dowling RH. The enterohepatic circulation of bile acids as they relate to lipid disorders. J Clin Pathol Suppl (Assoc Clin Pathol) 1973;5:59–67.
[53] Li T, Chiang JYL. Bile acid-based therapies for non-alcoholic steatohepatitis and alcoholic liver disease. Hepatobiliary Surg Nutr 2020;9(2):152–69. doi: https://doi.org/10.21037/hbsn.2019.09.03.
[54] Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schütz G, Umesono K, et al. The nuclear receptor superfamily: the second decade. Cell 1995;83(6):835–9.
[55] Goodwin B, Jones SA, Price RR, Watson MA, McKee DD, Moore LB, et al. A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol Cell 2000;6(3):517–26.
[56] Lu TT, Makishima M, Repa JJ, Schoonjans K, Kerr TA, Auwerx J, et al. Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. Mol Cell 2000;6(3):507–15.
[57] Inagaki T, Choi M, Moschetta A, Peng L, Cummins CL, McDonald JG, et al. Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis. Cell Metab 2005;2(4):217–25.
[58] Di Ciaula A, Bonfrate L, Baj J, Khalil M, Garruti G, Stellaard F, et al. Recent advances in the digestive, metabolic and therapeutic effects of farnesoid X receptor and fibroblast growth factor 19: from cholesterol to bile acid signaling. Nutrients 2022;14(23). doi: https://doi.org/10.3390/nu14234950.
[59] Song K-H, Li T, Owsley E, Strom S, Chiang JYL. Bile acids activate fibroblast growth factor 19 signaling in human hepatocytes to inhibit cholesterol 7alpha-hydroxylase gene expression. Hepatology (Baltimore, MD) 2009;49 (1):297–305. doi: https://doi.org/10.1002/hep.22627.
[60] Holt JA, Luo G, Billin AN, Bisi J, McNeill YY, Kozarsky KF, et al. Definition of a novel growth factor-dependent signal cascade for the suppression of bile acid biosynthesis. Genes Dev 2003;17(13):1581–91.
[61] Schaap FG, van der Gaag NA, Gouma DJ, Jansen PLM. High expression of the bile salt-homeostatic hormone fibroblast growth factor 19 in the liver of patients with extrahepatic cholestasis. Hepatology (Baltimore, MD) 2009;49 (4):1228–35. doi: https://doi.org/10.1002/hep.22771.
[62] Tarling EJ, Clifford BL, Cheng J, Morand P, Cheng A, Lester E, et al. RNA-binding protein ZFP36L1 maintains posttranscriptional regulation of bile acid metabolism. J Clin Invest 2017;127(10):3741–54. doi: https://doi.org/10.1172/JCI94029.
[63] Ananthanarayanan M, Balasubramanian N, Makishima M, Mangelsdorf DJ, Suchy FJ. Human bile salt export pump promoter is transactivated by the farnesoid X receptor/bile acid receptor. J Biol Chem 2001;276(31):28857–65.
[64] Denson LA, Sturm E, Echevarria W, Zimmerman TL, Makishima M, Mangelsdorf DJ, et al. The orphan nuclear receptor, shp, mediates bile acid-induced inhibition of the rat bile acid transporter, ntcp. Gastroenterology 2001;121(1):140–7.
[65] Lee H, Zhang Y, Lee FY, Nelson SF, Gonzalez FJ, Edwards PA. FXR regulates organic solute transporters alpha and beta in the adrenal gland, kidney, and intestine. J Lipid Res 2006;47(1):201–14.
[66] Grober J, Zaghini I, Fujii H, Jones SA, Kliewer SA, Willson TM, et al. Identification of a bile acid-responsive element in the human ileal bile acid-binding protein gene. Involvement of the farnesoid X receptor/9-cis-retinoic acid receptor heterodimer. J Biol Chem 1999;274(42):29749–54.
[67] Neimark E, Chen F, Li X, Shneider BL. Bile acid-induced negative feedback regulation of the human ileal bile acid transporter. Hepatology (Baltimore, MD) 2004;40(1):149–56.
[68] Li T, Francl JM, Boehme S, Ochoa A, Zhang Y, Klaassen CD, et al. Glucose and insulin induction of bile acid synthesis: mechanisms and implication in diabetes and obesity. J Biol Chem 2012;287(3):1861–73. doi: https://doi.org/10.1074/jbc.M111.305789.
[69] Ocvirk S, O'Keefe SJ. Influence of bile acids on colorectal cancer risk: potential mechanisms mediated by diet - gut microbiota interactions. Curr Nutr Rep 2017;6(4):315–22. doi: https://doi.org/10.1007/s13668-017-0219-5.
[70] Fu T, Coulter S, Yoshihara E, Oh TG, Fang S, Cayabyab F, et al. FXR regulates intestinal cancer stem cell proliferation. Cell 2019;176(5):1098–1112.e1018. doi: https://doi.org/10.1016/j.cell.2019.01.036.
[71] Ferrebee CB, Li J, Haywood J, Pachura K, Robinson BS, Hinrichs BH, et al. Organic solute transporter α-β protects ileal enterocytes from bile acid-induced injury. Cell Mol Gastroenterol Hepatol 2018;5(4):499–522. doi: https://doi.org/10.1016/j.jcmgh.2018.01.006.
[72] Thomas C, Pellicciari R, Pruzanski M, Auwerx J, Schoonjans K. Targeting bile-acid signalling for metabolic diseases. Nat Rev Drug Discov 2008;7 (8):678–93. doi: https://doi.org/10.1038/nrd2619.
[73] Houten SM, Watanabe M, Auwerx J. Endocrine functions of bile acids. EMBO J 2006;25(7):1419–25.
[74] Trauner M, Claudel T, Fickert P, Moustafa T, Wagner M. Bile acids as regulators of hepatic lipid and glucose metabolism. Dig Dis 2010;28 (1):220–4. doi: https://doi.org/10.1159/000282091.
[75] Fiorucci S, Biagioli M, Sepe V, Zampella A, Distrutti E. Bile acid modulators for the treatment of nonalcoholic steatohepatitis (NASH). Expert Opin Investig Drugs 2020;29(6):623–32. doi: https://doi.org/10.1080/13543784.2020.1763302.
[76] Bhatnagar S, Damron HA, Hillgartner FB. Fibroblast growth factor-19, a novel factor that inhibits hepatic fatty acid synthesis. J Biol Chem 2009;284 (15):10023–33. doi: https://doi.org/10.1074/jbc.M808818200.
[77] Pineda Torra I, Claudel T, Duval C, Kosykh V, Fruchart J-C, Staels B. Bile acids induce the expression of the human peroxisome proliferator-activated receptor alpha gene via activation of the farnesoid X receptor. Mol Endocrinol 2003;17(2):259–72.
[78] Li G, Thomas AM, Williams JA, Kong B, Liu J, Inaba Y, et al. Farnesoid X receptor induces murine scavenger receptor Class B type I via intron binding. PLoS ONE 2012;7(4):. doi: https://doi.org/10.1371/journal.pone.0035895e35895.
[79] Gottlieb A, Canbay A. Why bile acids are so important in non-alcoholic fatty liver disease (NAFLD) progression. Cells 2019;8(11):1358. doi: https://doi.org/10.3390/cells8111358.
[80] Hirokane H, Nakahara M, Tachibana S, Shimizu M, Sato R. Bile acid reduces the secretion of very low density lipoprotein by repressing microsomal triglyceride transfer protein gene expression mediated by hepatocyte nuclear factor-4. J Biol Chem 2004;279(44):45685–92.
[81] Chávez-Talavera O, Tailleux A, Lefebvre P, Staels B. Bile acid control of metabolism and inflammation in obesity, type 2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease. Gastroenterology 2017;152(7):1679–1694. e1673. doi: https://doi.org/10.1053/j.gastro.2017.01.055.
[82] Ding L, Sousa KM, Jin L, Dong B, Kim B-W, Ramirez R, et al. Vertical sleeve gastrectomy activates GPBAR-1/TGR5 to sustain weight loss, improve fatty liver, and remit insulin resistance in mice. Hepatology (Baltimore, MD) 2016;64(3):760–73. doi: https://doi.org/10.1002/hep.28689.
[83] Han X, Guo J, Yin M, Liu Y, You Y, Zhan J, et al. Grape extract activates brown adipose tissue through pathway involving the regulation of gut microbiota and bile acid. Mol Nutr Food Res 2020;64(10):. doi: https://doi.org/10.1002/mnfr.202000149e2000149.
[84] Li M, Li L, Li B, Hambly C, Wang G, Wu Y, et al. Brown adipose tissue is the key depot for glucose clearance in microbiota depleted mice. Nat Commun 2021;12(1):4725. doi: https://doi.org/10.1038/s41467-021-24659-8.
[85] Ma K, Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest 2006;116(4):1102–9.
[86] Yamagata K, Daitoku H, Shimamoto Y, Matsuzaki H, Hirota K, Ishida J, et al. Bile acids regulate gluconeogenic gene expression via small heterodimer partner-mediated repression of hepatocyte nuclear factor 4 and Foxo1. J Biol Chem 2004;279(22):23158–65.
[87] Potthoff MJ, Boney-Montoya J, Choi M, He T, Sunny NE, Satapati S, et al. FGF15/19 regulates hepatic glucose metabolism by inhibiting the CREB-PGC-1α pathway. Cell Metab 2011;13(6):729–38. doi: https://doi.org/10.1016/j.cmet.2011.03.019.

[88] Stayrook KR, Bramlett KS, Savkur RS, Ficorilli J, Cook T, Christe ME, et al. Regulation of carbohydrate metabolism by the farnesoid X receptor. Endocrinology 2005;146(3):984–91.
[89] Zhan L, Liu H-X, Fang Y, Kong B, He Y, Zhong X-B, et al. Genome-wide binding and transcriptome analysis of human farnesoid X receptor in primary human hepatocytes. PLoS ONE 2014;9(9):. doi: https://doi.org/10.1371/journal.pone.0105930e105930.
[90] Thomas AM, Hart SN, Kong B, Fang J, Zhong X-B, Guo GL. Genome-wide tissue-specific farnesoid X receptor binding in mouse liver and intestine. Hepatology (Baltimore, MD) 2010;51(4):1410–9. doi: https://doi.org/10.1002/hep.23450.
[91] Albhaisi SAM, Bajaj JS, Sanyal AJ. Role of gut microbiota in liver disease. Am J Physiol Gastrointest Liver Physiol 2020;318(1):G84–98. doi: https://doi.org/10.1152/ajpgi.00118.2019.
[92] Parséus A, Sommer N, Sommer F, Caesar R, Molinaro A, Ståhlman M, et al. Microbiota-induced obesity requires farnesoid X receptor. Gut 2017;66(3):429–37. doi: https://doi.org/10.1136/gutjnl-2015-310283.
[93] Parlesak A, Schaeckeler S, Moser L, Bode C. Conjugated primary bile salts reduce permeability of endotoxin through intestinal epithelial cells and synergize with phosphatidylcholine in suppression of inflammatory cytokine production. Crit Care Med 2007;35(10):2367–74.
[94] Merritt ME, Donaldson JR. Effect of bile salts on the DNA and membrane integrity of enteric bacteria. J Med Microbiol 2009;58(Pt 12):1533–41. doi: https://doi.org/10.1099/jmm.0.014092-0.
[95] Islam KBMS, Fukiya S, Hagio M, Fujii N, Ishizuka S, Ooka T, et al. Bile acid is a host factor that regulates the composition of the cecal microbiota in rats. Gastroenterology 2011;141(5):1773–81. doi: https://doi.org/10.1053/j.gastro.2011.07.046.
[96] Engen PA, Green SJ, Voigt RM, Forsyth CB, Keshavarzian A. The gastrointestinal microbiome: alcohol effects on the composition of intestinal microbiota. Alcohol Res 2015;37(2):223–36.
[97] Ding JW, Andersson R, Soltesz V, Willén R, Bengmark S. The role of bile and bile acids in bacterial translocation in obstructive jaundice in rats. Eur Surg Res 1993;25(1):11–9.
[98] Lorenzo-Zúñiga V, Bartolí R, Planas R, Hofmann AF, Viñado B, Hagey LR, et al. Oral bile acids reduce bacterial overgrowth, bacterial translocation, and endotoxemia in cirrhotic rats. Hepatology (Baltimore, MD) 2003;37(3):551–7.
[99] Inagaki T, Moschetta A, Lee Y-K, Peng L, Zhao G, Downes M, et al. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. Proc Natl Acad Sci U S A 2006;103(10):3920–5.
[100] Ferslew BC, Xie G, Johnston CK, Su M, Stewart PW, Jia W, et al. Altered bile acid metabolome in patients with nonalcoholic steatohepatitis. Dig Dis Sci 2015;60(11):3318–28. doi: https://doi.org/10.1007/s10620-015-3776-8.
[101] Wahlström A, Sayin SI, Marschall H-U, Bäckhed F. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. Cell Metab 2016;24(1):41–50. doi: https://doi.org/10.1016/j.cmet.2016.05.005.
[102] Wang YD, Chen WD, Wang M, Yu D, Forman BM, Huang W. Farnesoid X receptor antagonizes nuclear factor kappaB in hepatic inflammatory response. Hepatology 2008;48(5):1632–43. doi: https://doi.org/10.1002/hep.22519.
[103] Hao H, Cao L, Jiang C, Che Y, Zhang S, Takahashi S, et al. Farnesoid X receptor regulation of the NLRP3 inflammasome underlies cholestasis-associated sepsis. Cell Metab 2017;25(4):856–867.e855. doi: https://doi.org/10.1016/j.cmet.2017.03.007.
[104] Perino A, Schoonjans K. TGR5 and immunometabolism: insights from physiology and pharmacology. Trends Pharmacol Sci 2015;36(12):847–57. doi: https://doi.org/10.1016/j.tips.2015.08.002.
[105] Wang Y-D, Chen W-D, Yu D, Forman BM, Huang W. The G-protein-coupled bile acid receptor, Gpbar1 (TGR5), negatively regulates hepatic inflammatory response through antagonizing nuclear factor κ light-chain enhancer of activated B cells (NF-κB) in mice. Hepatology (Baltimore, MD) 2011;54(4):1421–32. doi: https://doi.org/10.1002/hep.24525.
[106] Daly C, Rollins BJ. Monocyte chemoattractant protein-1 (CCL2) in inflammatory disease and adaptive immunity: therapeutic opportunities and controversies. Microcirculation 2003;10(3–4):247–57.
[107] 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(2):380–8. doi: https://doi.org/10.1016/j.jhep.2009.03.025.
[108] Schumacher JD, Kong B, Wu J, Rizzolo D, Armstrong LE, Chow MD, et al. Direct and indirect effects of fibroblast growth factor (FGF) 15 and FGF19 on liver fibrosis development. Hepatology (Baltimore, MD) 2020;71(2):670–85. doi: https://doi.org/10.1002/hep.30810.
[109] Fiorucci S, Rizzo G, Antonelli E, Renga B, Mencarelli A, Riccardi L, et al. Cross-talk between farnesoid-X-receptor (FXR) and peroxisome proliferator-activated receptor gamma contributes to the antifibrotic activity of FXR ligands in rodent models of liver cirrhosis. J Pharmacol Exp Ther 2005;315(1):58–68.
[110] Renga B, Mencarelli A, Migliorati M, Cipriani S, D'Amore C, Distrutti E, et al. SHP-dependent and -independent induction of peroxisome proliferator-activated receptor-γ by the bile acid sensor farnesoid X receptor counter-regulates the pro-inflammatory phenotype of liver myofibroblasts. Inflamm Res 2011;60(6):577–87. doi: https://doi.org/10.1007/s00011-010-0306-1.
[111] Ichimura-Shimizu M, Watanabe S, Kashirajima Y, Nagatomo A, Wada H, Tsuneyama K, et al. Dietary cholic acid exacerbates liver fibrosis in NASH model of Sprague-Dawley rats fed a high-fat and high-cholesterol diet. Int J Mol Sci 2022;23(16). doi: https://doi.org/10.3390/ijms23169268.
[112] Hashimoto N, Han KH, Wakagi M, Ishikawa-Takano Y, Ippoushi K, Fukushima M. Bile acids induced hepatic lipid accumulation in mice by inhibiting mRNA expression of patatin-like phospholipase domain containing 3 and microsomal triglyceride transfer protein. Nutr Res 2021;92:12–20. doi: https://doi.org/10.1016/j.nutres.2021.05.006.
[113] Allen K, Jaeschke H, Copple BL. Bile acids induce inflammatory genes in hepatocytes: a novel mechanism of inflammation during obstructive cholestasis. Am J Pathol 2011;178(1):175–86. doi: https://doi.org/10.1016/j.ajpath.2010.11.026.
[114] Xie G, Jiang R, Wang X, Liu P, Zhao A, Wu Y, et al. Conjugated secondary 12α-hydroxylated bile acids promote liver fibrogenesis. EBioMedicine 2021;66:. doi: https://doi.org/10.1016/j.ebiom.2021.103290103290.
[115] Wei M, Huang F, Zhao L, Zhang Y, Yang W, Wang S, et al. A dysregulated bile acid-gut microbiota axis contributes to obesity susceptibility. EBioMedicine 2020;55:. doi: https://doi.org/10.1016/j.ebiom.2020.102766102766.
[116] Xie G, Wang X, Huang F, Zhao A, Chen W, Yan J, et al. Dysregulated hepatic bile acids collaboratively promote liver carcinogenesis. Int J Cancer 2016;139(8):1764–75. doi: https://doi.org/10.1002/ijc.30219.
[117] Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149(2):389–397.e310. doi: https://doi.org/10.1053/j.gastro.2015.04.043.
[118] Abdelmalek MF. Nonalcoholic fatty liver disease: another leap forward. Nat Rev Gastroenterol Hepatol 2021;18(2):85–6. doi: https://doi.org/10.1038/s41575-020-00406-0.
[119] Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan W-K, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol 2020;5(4):362–73. doi: https://doi.org/10.1016/S2468-1253(19)30383-8.
[120] EASL-ALEH Clinical Practice Guidelines. Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63(1):237–64. doi: https://doi.org/10.1016/j.jhep.2015.04.006.
[121] Kalhan SC, Guo L, Edmison J, Dasarathy S, McCullough AJ, Hanson RW, et al. Plasma metabolomic profile in nonalcoholic fatty liver disease. Metabolism 2011;60(3):404–13. doi: https://doi.org/10.1016/j.metabol.2010.03.006.
[122] Qi L, Tian Y, Chen Y. Circulating bile acid profiles: a need for further examination. J Clin Endocrinol Metab 2021;106(11):3093–112. doi: https://doi.org/10.1210/clinem/dgab531.
[123] Caussy C, Hsu C, Singh S, Bassirian S, Kolar J, Faulkner C, et al. Serum bile acid patterns are associated with the presence of NAFLD in twins, and dose-dependent changes with increase in fibrosis stage in patients with biopsy-proven NAFLD. Aliment Pharmacol Ther 2019;49(2):183–93. doi: https://doi.org/10.1111/apt.15035.
[124] Nimer N, Choucair I, Wang Z, Nemet I, Li L, Gukasyan J, et al. Bile acids profile, histopathological indices and genetic variants for non-alcoholic fatty liver disease progression. Metabolism 2021;116:. doi: https://doi.org/10.1016/j.metabol.2020.154457154457.
[125] Gottlieb A, Bechmann L, Canbay A. The presence and severity of nonalcoholic steatohepatitis is associated with specific changes in circulating bile acids. Ann Hepatol 2018;17(3):340–1. doi: https://doi.org/10.5604/01.3001.0011.7378.
[126] Grzych G, Chávez-Talavera O, Descat A, Thuillier D, Verrijken A, Kouach M, et al. NASH-related increases in plasma bile acid levels depend on insulin resistance. JHEP Rep 2021;3(2):. doi: https://doi.org/10.1016/j.jhepr.2020.100222100222.
[127] Tsuchiya T, Naitoh T, Nagao M, Tanaka N, Watanabe K, Imoto H, et al. Increased bile acid signals after Duodenal-Jejunal bypass improve non-alcoholic steatohepatitis (NASH) in a rodent model of diet-induced NASH. Obes Surg 2018;28(6):1643–52. doi: https://doi.org/10.1007/s11695-017-3065-z.
[128] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149(2):367–378.e365. doi: https://doi.org/10.1053/j.gastro.2015.04.005. quiz e314-365.
[129] Rau M, Geier A. An update on drug development for the treatment of nonalcoholic fatty liver disease - from ongoing clinical trials to future therapy. Expert Rev Clin Pharmacol 2021;14(3):333–40. doi: https://doi.org/10.1080/17512433.2021.1884068.
[130] Adorini L, Pruzanski M, Shapiro D. Farnesoid X receptor targeting to treat nonalcoholic steatohepatitis. Drug Discov Today 2012;17(17–18):988–97. doi: https://doi.org/10.1016/j.drudis.2012.05.012.
[131] Cipriani S, Mencarelli A, Palladino G, Fiorucci S. FXR activation reverses insulin resistance and lipid abnormalities and protects against liver steatosis in Zucker (fa/fa) obese rats. J Lipid Res 2010;51(4):771–84. doi: https://doi.org/10.1194/jlr.M001602.
[132] Mudaliar S, Henry RR, Sanyal AJ, Morrow L, Marschall H-U, Kipnes M, et al. Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. Gastroenterology 2013;145(3):574–582.e571. doi: https://doi.org/10.1053/j.gastro.2013.05.042.

[133] Younossi ZM, Ratziu V, Loomba R, Rinella M, Anstee QM, Goodman Z, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2019;394(10215):2184–96. doi: https://doi.org/10.1016/S0140-6736(19)33041-7.
[134] Trauner M, Gulamhusein A, Hameed B, Caldwell S, Shiffman ML, Landis C, et al. The nonsteroidal farnesoid X receptor agonist cilofexor (GS-9674) improves markers of cholestasis and liver injury in patients with primary sclerosing cholangitis. Hepatology (Baltimore, MD) 2019;70(3):788–801. doi: https://doi.org/10.1002/hep.30509.
[135] Patel K, Harrison SA, Elkhashab M, Trotter JF, Herring R, Rojter SE, et al. Cilofexor, a nonsteroidal FXR agonist, in patients with noncirrhotic NASH: a phase 2 randomized controlled trial. Hepatology (Baltimore, MD) 2020;72(1):58–71. doi: https://doi.org/10.1002/hep.31205.
[136] Badman MK, Chen J, Desai S, Vaidya S, Neelakantham S, Zhang J, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel non-bile acid FXR agonist tropifexor (LJN452) in healthy volunteers. Clin Pharmacol Drug Dev 2020;9(3):395–410. doi: https://doi.org/10.1002/cpdd.762.
[137] Sanyal AJ, Lopez P, Lawitz EJ, Lucas KJ, Loeffler J, Kim W, et al. Tropifexor for nonalcoholic steatohepatitis: an adaptive, randomized, placebo-controlled phase 2a/b trial. Nat Med 2023;29(2):392–400. doi: https://doi.org/10.1038/s41591-022-02200-8.
[138] Wen F, Bian D, Wu X, Liu R, Wang C, Gan J. SU5, a new Auraptene analog with improved metabolic stability, ameliorates nonalcoholic fatty liver disease in methionine- and choline-deficient diet-fed db/db mice. Chem Biol Drug Des 2022;99(3):504–11. doi: https://doi.org/10.1111/cbdd.14021.
[139] Ratziu V, Rinella ME, Neuschwander-Tetri BA, Lawitz E, Denham D, Kayali Z, et al. EDP-305 in patients with NASH: a phase II double-blind placebo-controlled dose-ranging study. J Hepatol 2022;76(3):506–17. doi: https://doi.org/10.1016/j.jhep.2021.10.018.
[140] Traussnigg S, Halilbasic E, Hofer H, Munda P, Stojakovic T, Fauler G, et al. Open-label phase II study evaluating safety and efficacy of the non-steroidal farnesoid X receptor agonist PX-104 in non-alcoholic fatty liver disease. Wien Klin Wochenschr 2021;133(9–10):441–51. doi: https://doi.org/10.1007/s00508-020-01735-5.
[141] Ratziu V, Harrison SA, Loustaud-Ratti V, Bureau C, Lawitz E, Abdelmalek M, et al. Hepatic and renal improvements with FXR agonist vonafexor in individuals with suspected fibrotic NASH. J Hepatol 2023;78(3):479–92. doi: https://doi.org/10.1016/j.jhep.2022.10.023.
[142] Chianelli D, Rucker PV, Roland J, Tully DC, Nelson J, Liu X, et al. Nidufexor (LMB763), a novel FXR modulator for the treatment of nonalcoholic steatohepatitis. J Med Chem 2020;63(8):3868–80. doi: https://doi.org/10.1021/acs.jmedchem.9b01621.
[143] Harrison SA, Bashir MR, Lee KJ, Shim-Lopez J, Lee J, Wagner B, et al. A structurally optimized FXR agonist, MET409, reduced liver fat content over 12 weeks in patients with non-alcoholic steatohepatitis. J Hepatol 2021;75(1):25–33. doi: https://doi.org/10.1016/j.jhep.2021.01.047.
[144] Carino A, Marchianò S, Biagioli M, Bucci M, Vellecco V, Brancaleone V, et al. Agonism for the bile acid receptor GPBAR1 reverses liver and vascular damage in a mouse model of steatohepatitis. FASEB J 2019;33(2):2809–22. doi: https://doi.org/10.1096/fj.201801373RR.
[145] Alemi F, Kwon E, Poole DP, Lieu T, Lyo V, Cattaruzza F, et al. The TGR5 receptor mediates bile acid-induced itch and analgesia. J Clin Invest 2013;123(4):1513–30. doi: https://doi.org/10.1172/jci64551.
[146] Li T, Holmstrom SR, Kir S, Umetani M, Schmidt DR, Kliewer SA, et al. The G protein-coupled bile acid receptor, TGR5, stimulates gallbladder filling. Mol Endocrinol 2011;25(6):1066–71. doi: https://doi.org/10.1210/me.2010-0460.
[147] Reich M, Deutschmann K, Sommerfeld A, Klindt C, Kluge S, Kubitz R, et al. TGR5 is essential for bile acid-dependent cholangiocyte proliferation in vivo and in vitro. Gut 2016;65(3):487–501. doi: https://doi.org/10.1136/gutjnl-2015-309458.
[148] McMahan RH, Wang XX, Cheng LL, Krisko T, Smith M, El Kasmi K, et al. Bile acid receptor activation modulates hepatic monocyte activity and improves nonalcoholic fatty liver disease. J Biol Chem 2013;288(17):11761–70. doi: https://doi.org/10.1074/jbc.M112.446575.
[149] Comeglio P, Cellai I, Mello T, Filippi S, Maneschi E, Corcetto F, et al. INT-767 prevents NASH and promotes visceral fat brown adipogenesis and mitochondrial function. J Endocrinol 2018;238(2):107–27. doi: https://doi.org/10.1530/JOE-17-0557.
[150] Carino A, Cipriani S, Marchianò S, Biagioli M, Santorelli C, Donini A, et al. BAR502, a dual FXR and GPBAR1 agonist, promotes browning of white adipose tissue and reverses liver steatosis and fibrosis. Sci Rep 2017;7:. doi: https://doi.org/10.1038/srep42801.
[151] Carino A, Marchianò S, Biagioli M, Fiorucci C, Zampella A, Monti MC, et al. Transcriptome analysis of dual FXR and GPBAR1 agonism in rodent model of NASH reveals modulation of lipid droplets formation. Nutrients 2019;11(5):1132. doi: https://doi.org/10.3390/nu11051132.
[152] Marchianò S, Biagioli M, Morretta E, Di Giorgio C, Roselli R, Bordoni M, et al. Combinatorial therapy with BAR502 and UDCA resets FXR and GPBAR1 signa ling and reverses liver histopathology in a model of NASH. Sci Rep 2023;13(1):1602. doi: https://doi.org/10.1038/s41598-023-28647-4.
[153] Ding L, Yang Q, Zhang E, Wang Y, Sun S, Yang Y, et al. Notoginsenoside Ft1 acts as a TGR5 agonist but FXR antagonist to alleviate high fat diet-induced obesity and insulin resistance in mice. Acta Pharm Sin B 2021;11(6):1541–54. doi: https://doi.org/10.1016/j.apsb.2021.03.038.
[154] Tsuji Y, Kaji K, Kitade M, Kaya D, Kitagawa K, Ozutsumi T, et al. Bile acid sequestrant, sevelamer ameliorates hepatic fibrosis with reduced overload of endogenous lipopolysaccharide in experimental nonalcoholic steatohepatitis. Microorganisms 2020;8(6):925. doi: https://doi.org/10.3390/microorganisms8060925.
[155] Voloshin I, Hahn-Obercyger M, Anavi S, Tirosh O. L-arginine conjugates of bile acids-a possible treatment for non-alcoholic fatty liver disease. Lipids Health Dis 2014;13:. doi: https://doi.org/10.1186/1476-511X-13-6969.
[156] Safadi R, Konikoff FM, Mahamid M, Zelber-Sagi S, Halpern M, Gilat T, et al. The fatty acid-bile acid conjugate Aramchol reduces liver fat content in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2014;12(12):2085–2091.e2081. doi: https://doi.org/10.1016/j.cgh.2014.04.038.
[157] Marchianò S, Biagioli M, Roselli R, Zampella A, Di Giorgio C, Bordoni M, et al. Beneficial effects of UDCA and norUDCA in a rodent model of steatosis are linked to modulation of GPBAR1/FXR signaling. Biochim Biophys Acta Mol Cell Biol Lipids 2022;1867(11):. doi: https://doi.org/10.1016/j.bbalip.2022.159218159218.
[158] Beraza N, Ofner-Ziegenfuss L, Ehedego H, Boekschoten M, Bischoff SC, Mueller M, et al. Nor-ursodeoxycholic acid reverses hepatocyte-specific nemo-dependent steatohepatitis. Gut 2011;60(3):387–96. doi: https://doi.org/10.1136/gut.2010.223834.
[159] Ratziu V, de Ledinghen V, Oberti F, Mathurin P, Wartelle-Bladou C, Renou C, et al. A randomized controlled trial of high-dose ursodesoxycholic acid for nonalcoholic steatohepatitis. J Hepatol 2011;54(5):1011–9. doi: https://doi.org/10.1016/j.jhep.2010.08.030.
[160] Leuschner UF, Lindenthal B, Herrmann G, Arnold JC, Rössle M, Cordes HJ, et al. High-dose ursodeoxycholic acid therapy for nonalcoholic steatohepatitis: a double-blind, randomized, placebo-controlled trial. Hepatology 2010;52(2):472–9. doi: https://doi.org/10.1002/hep.23727.
[161] Lindor KD, Kowdley KV, Heathcote EJ, Harrison ME, Jorgensen R, Angulo P, et al. Ursodeoxycholic acid for treatment of nonalcoholic steatohepatitis: results of a randomized trial. Hepatology 2004;39(3):770–8. doi: https://doi.org/10.1002/hep.20092.
[162] Mueller M, Thorell A, Claudel T, Jha P, Koefeler H, Lackner C, et al. Ursodeoxycholic acid exerts farnesoid X receptor-antagonistic effects on bile acid and lipid metabolism in morbid obesity. J Hepatol 2015;62(6):1398–404. doi: https://doi.org/10.1016/j.jhep.2014.12.034.
[163] Traussnigg S, Schattenberg JM, Demir M, Wiegand J, Geier A, Teuber G, et al. Norursodeoxycholic acid versus placebo in the treatment of non-alcoholic fatty liver disease: a double-blind, randomised, placebo-controlled, phase 2 dose-finding trial. Lancet Gastroenterol Hepatol 2019;4(10):781–93. doi: https://doi.org/10.1016/s2468-1253(19)30184-0.
[164] Harrison SA, Rinella ME, Abdelmalek MF, Trotter JF, Paredes AH, Arnold HL, et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet 2018;391(10126):1174–85. doi: https://doi.org/10.1016/S0140-6736(18)30474-4.
[165] Harrison SA, Rossi SJ, Paredes AH, Trotter JF, Bashir MR, Guy CD, et al. NGM282 improves liver fibrosis and histology in 12 weeks in patients with nonalcoholic steatohepatitis. Hepatology (Baltimore, MD) 2020;71(4):1198–212. doi: https://doi.org/10.1002/hep.30590.
[166] Uriarte I, Latasa MU, Carotti S, Fernandez-Barrena MG, Garcia-Irigoyen O, Elizalde M, et al. Ileal FGF15 contributes to fibrosis-associated hepatocellular carcinoma development. Int J Cancer 2015;136(10):2469–75. doi: https://doi.org/10.1002/ijc.29287.
[167] Nicholes K, Guillet S, Tomlinson E, Hillan K, Wright B, Frantz GD, et al. A mouse model of hepatocellular carcinoma: ectopic expression of fibroblast growth factor 19 in skeletal muscle of transgenic mice. Am J Pathol 2002;160(6):2295–307.
[168] Rao A, Kosters A, Mells JE, Zhang W, Setchell KDR, Amanso AM, et al. Inhibition of ileal bile acid uptake protects against nonalcoholic fatty liver disease in high-fat diet-fed mice 357ra122. Sci Transl Med 2016;8(357). doi: https://doi.org/10.1126/scitranslmed.aaf4823.
[169] Rao A, van de Peppel IP, Gumber S, Karpen SJ, Dawson PA. Attenuation of the hepatoprotective effects of ileal apical sodium dependent bile acid transporter (ASBT) inhibition in choline-deficient l-amino acid-defined (CDAA) diet-fed mice. Front Med (Lausanne) 2020;7:. doi: https://doi.org/10.3389/fmed.2020.0006060.
[170] Yamauchi R, Takedatsu H, Yokoyama K, Yamauchi E, Kawashima M, Nagata T, et al. Elobixibat, an ileal bile acid transporter inhibitor, ameliorates non-alcoholic steatohepatitis in mice. Hepatol Int 2021;15(2):392–404. doi: https://doi.org/10.1007/s12072-020-10107-0.
[171] Salic K, Kleemann R, Wilkins-Port C, McNulty J, Verschuren L, Palmer M. Apical sodium-dependent bile acid transporter inhibition with volixibat improves metabolic aspects and components of non-alcoholic steatohepatitis in Ldlr-/-.Leiden mice. PLoS ONE 2019;14(6):. doi: https://doi.org/10.1371/journal.pone.0218459e0218459.
[172] Palmer M, Jennings L, Silberg DG, Bliss C, Martin P. A randomised, double-blind, placebo-controlled phase 1 study of the safety, tolerability and pharmacodynamics of volixibat in overweight and obese but otherwise healthy adults: implications for treatment of non-alcoholic steatohepatitis. BMC Pharmacol Toxicol 2018;19(1):10. doi: https://doi.org/10.1186/s40360-018-0200-y.
[173] Newsome PN, Palmer M, Freilich B, Sheikh MY, Sheikh A, Sarles H, et al. Volixibat in adults with non-alcoholic steatohepatitis: 24-week interim

analysis from a randomized, phase II study. J Hepatol 2020;73(2):231–40. doi: https://doi.org/10.1016/j.jhep.2020.03.024.

Ling Yang, M.D., Ph.D. Division of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Ling Yang presided over 4 National Natural Science Foundation projects, 1 provincial major special project, and published more than 30 articles in the top journals in the field of digestion such as Gastroenterology, Hepatology, J Clinical Investment, J Hepatology, which were widely cited by Nature, Cell and other magazines.

Huikuan Chu, M.D. Division of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Huikuan Chu presided over one key research and development project for young scientists in the 14th Five-Year Plan, and presided/participated in 6 national/provincial natural science funds, and participated in a major innovation project in Hubei Province. She has published 30 SCI papers in J Hepatol, Gut, Gut Microbes, Nat Commun, Transl Res, Hepatol Commun and other magazines.

Bernd Schnabl. Dr. Schnabl is Professor of Medicine in Gastroenterology at UCSD School of Medicine. He is the Director of the San Diego Digestive Diseases Research Center (SDDRC). His main interest as a physician scientist is the pathogenesis of chronic liver disease.

Yixiong Chen. Division of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. Yixiong, Chen presided over and participated in the research work of several NSFC projects, and published several papers in domestic and foreign medical journals. He has accumulated rich clinical experience in the diagnosis and treatment of chronic gastrointestinal diseases, viral hepatitis, cirrhosis and complications, and unexplained liver dysfunction.

Zilu Cheng, Postgraduate. Division of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.