Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.jzus.zju.edu.cn; www.springerlink.com
E-mail: jzus@zju.edu.cn

Review:

Bile-ology: from bench to bedside*

Li-hua JIN[1,2], Zhi-peng FANG[1], Min-jie FAN[3], Wen-dong HUANG[†‡1]

[1]*Department of Diabetes Complications and Metabolism, Beckman Research Institute of City of Hope, Duarte, CA 91010, USA*

[2]*State Key Laboratory of Cellular Stress Biology; Innovation Center for Cell Signaling Network; School of Life Sciences, Xiamen University, Xiamen 361005, China*

[3]*College of Life Science, Zhejiang University, Hangzhou 310058, China*

[†]E-mail: whuang@coh.org

Received Mar. 28, 2019; Revision accepted Apr. 5, 2019; Crosschecked May 14, 2019

Abstract: Bile acids (BAs) are originally known as detergents essential for the digestion and absorption of lipids. In recent years, extensive research has unveiled new functions of BAs as gut hormones that modulate physiological and pathological processes, including glucose and lipid metabolism, energy expenditure, inflammation, tumorigenesis, cardiovascular disease, and even the central nervous system in addition to cholesterol homeostasis, enterohepatic protection and liver regeneration. BAs are closely linked with gut microbiota which might explain some of their crucial roles in organs. The signaling actions of BAs can also be mediated through specific nuclear receptors and membrane-bound G protein-coupled receptors. Several pharmacological agents or bariatric surgeries have demonstrated efficacious therapeutic effects on metabolic diseases through targeting BA signaling. In this mini-review, we summarize recent advances in bile-ology, focusing on its translational studies.

Key words: Bile acid; Gut microbiota; Farnesoid X receptor; G protein-coupled bile acid receptor; Metabolic disease
https://doi.org/10.1631/jzus.B1900158 **CLC number:** Q548+.5

1 Introduction

Bile acids (BAs) are amphipathic molecules synthesized from cholesterol in the liver and efficiently retained within an enterohepatic circulation through a complex biosynthetic pathway, biliary secretion, bacterial modification, ileum reabsorption, and liver reflux (Slijepcevic and van de Graaf, 2017). Because of their unique detergent properties, BAs have long been known to facilitate the absorption, transport, and metabolism of dietary fats and lipid-soluble nutrients. Excitingly, extensive research in the last decade has demonstrated that in addition to the role in cholesterol homeostasis, fat absorption and digestion, BAs play important roles as signaling molecules in regulating physiological and pathological processes including glucose and lipid metabolism, energy expenditure, inflammation, cancer, heart failure, Alzheimer's disease (AD), and aging. In this mini-review, we summarize recent advances in the understanding of BA signaling, gut microbiota, and the related regulatory functions in metabolic diseases (Fig. 1), and discuss the development of new BA-based therapeutics for the treatment of metabolic diseases by targeting nuclear BA receptor farnesoid X receptor (FXR) and membrane Takeda G protein-coupled BA receptor (GPBAR or TGR5).

2 BAs, gut microbiota, and related metabolic diseases

BAs' synthesis and their enterohepatic circulation have been elaborately reviewed previously (Li

‡ Corresponding author
* Project supported by the National Cancer Institute (No. 2R01CA139158) and John Hench Foundation to Wen-dong HUANG, and the National Natural Science Foundation of China (Nos. 81471084 and 81773793) to Li-hua JIN
ORCID: Li-hua JIN, https://orcid.org/0000-0002-2685-6048

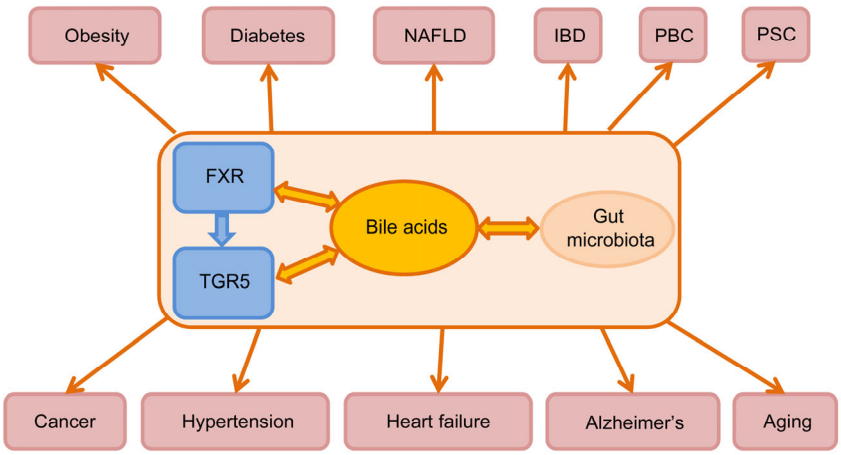

Fig. 1 Bile acid signaling and related diseases

Farnesoid X receptor (FXR) regulates the expression of Takeda G protein-coupled bile acid (BA) receptor (TGR5). Both as BA receptors, FXR and TGR5 are closely involved in BA signaling and the balance of gut microbiota, resulting in the regulation of BA-related diseases. NAFLD, non-alcoholic fatty liver disease; IBD, inflammatory bowel disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis

and Chiang, 2014; Mertens et al., 2017). BAs and gut microbiota are closely linked. Gut microbiota is involved in the biotransformation of BAs through deconjugation, dehydroxylation, and reconjugation of BAs (Ridlon et al., 2006). The gut-to-liver axis of microbiota plays a crucial role in the regulation of BA metabolism, BA pool size, and enterohepatic circulation of BAs (Chiang and Ferrell, 2018). Reciprocally, BAs shape the gut microbiome to regulate host metabolism. BAs have antimicrobial activity by damaging the bacterial cell membrane and thus inhibiting bacteria outgrowth (Inagaki et al., 2006; Kurdi et al., 2006). Importantly, BAs link the gut microbiota to both hepatic and intestinal metabolism, and this tripartite relationship has been implicated in different metabolic diseases, which we will highlight below.

2.1 Obesity

Obesity has become one of the most prevalent public health concerns worldwide. Being overweight is related to the incidence of several comorbidities, including type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD) (Golay and Ybarra, 2005; Esser et al., 2014), cardiovascular disease (Sommer and Twig, 2018), stroke and cancer (Xu and Mishra, 2018). Elevated serum BA levels have been observed a long time ago in overweight subjects as compared to those with an ideal weight (Halmy et al., 1986). Later, many studies have found increased total BA levels in humans with obesity (Prinz et al., 2015; Chávez-Talavera et al., 2017). This evidence indicates that BAs may be closely related to the pathogenesis of obesity.

Bariatric surgery represents a viable clinical intervention to efficaciously remit obesity and its associated complications. Interestingly, it has been reported that bariatric surgeries, including Roux-en-Y gastric bypass (RYGB) and vertical sleeve gastrectomy (VSG), increase circulating BA concentrations (Nakatani et al., 2009; Gerhard et al., 2013). Serum BA levels were higher in obese patients who received RYGB when compared to controls (no RYGB), and elevated levels of BAs were sustained for at least 2 years post-surgery (Nakatani et al., 2009; Patti et al., 2009). Further investigation demonstrated that the mechanism is due to the regulation of specific BAs (Wang et al., 2017; Browning et al., 2019). This might also be explained by the evidence that plasma BAs were negatively correlated with cognitive restraint of eating (Prinz et al., 2015). Obesity is mainly due to a long-term excess energy intake above energy expenditure. Studies using isolated rodent tissues indicated that a BA mixture (cholic acid (CA), deoxycholic acid (DCA), and chenodeoxycholic acid (CDCA) in both un-conjugated and glycine- and taurine-conjugated forms) increased secretion of glucose-dependent insulinotropic peptide, glucagon-like peptide-1 (GLP-1), polypeptide YY and neurotensin through activating TGR5, leading to metabolic improvement (Kuhre et al.,

2018). BAs are also identified as regulators of energy expenditure. In brown adipose tissue (BAT), BAs activate TGR5, resulting in increased concentrations of cyclic adenosine 3',5'-monophosphate (cAMP); cAMP subsequently activates type-2 deiodinase (D2) which induces active triiodothyronine (T3), and this cascade results in enhanced energy expenditure in both murine and human BAT by inducing the expression of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) and uncoupling protein 1 (UCP1) (Watanabe et al., 2006; Broeders et al., 2015).

Accumulating evidence indicates that the gut microbiota plays a significant role in the development of obesity and obesity-associated disorders (Shen et al., 2013) by impacting the composition and relative abundance of BA species (Ridaura et al., 2013). Turnbaugh et al. (2006) found that the obese microbiome has an increased capacity to harvest energy from the diet. In this process, the relative abundance of the two dominant bacterial divisions, Bacteroidetes and Firmicutes, contributes to energy homeostasis. Recently, Worthmann et al. (2017) found that BAs are also involved in energy homeostasis regulated by gut microbiota stimulated by cold. They found that cold-induced conversion of cholesterol to BAs in mice shapes the gut microbiome and promotes adaptive thermogenesis. In this process, the crucial enzyme for the alternative BA synthetic pathway, sterol 27-hydroxylase (CYP27A1), is selectively activated in the liver, and thus modulates gut-microbiome composition (Kuipers and Groen, 2017). This research provides a BAT–liver–intestine axis in connecting the BA homeostasis with obesity. Taken together, BAs play dual roles by regulating both energy intake and energy expenditure in balancing body weight.

Interestingly, the obesity-treating strategies by targeting BAs also display some conflicting results. Diet-induced obesity is ameliorated by BA-binding resin (Kobayashi et al., 2007). An additional series of studies demonstrated that BA sequestrants improve metabolic diseases (Beysen et al., 2012; Hansen et al., 2017). The profile of BAs is fluctuated delicately according to many factors, including circumstance temperature (Worthmann et al., 2017), nutrient intake (Matysik et al., 2011; Schmid et al., 2016), drug treatment (Camilleri and Gores, 2015), surgery (Tian et al., 2017), etc. Thus, these reports implicate the sophisticated mechanism of obesity regulated by BA signaling, and pinpoint the importance of analyzing the composition of BAs in different conditions in terms of therapeutic strategies.

2.2 T2D

Changes in circulating BA profile have been implicated in the pathogenesis of insulin resistance and T2D including gestational diabetes mellitus (Haeusler et al., 2013; Maghsoodi et al., 2019). T2D is associated with an increase in the hydrophobicity of the circulating BA pool in humans (Haeusler et al., 2013). Consistent with this, hydrophilic BA subtypes, such as tauroursodeoxycholic acid (TUDCA), have been shown to protect against inflammation and improve insulin sensitivity in rodent models and patients with T2D (Mahmoud and Elshazly, 2014; Shima et al., 2018). The mechanism of metformin also confirms this observation (Sun et al., 2018). Sun et al. (2018) found that metformin acts through lowering levels of *Bacteroides fragilis* in the gut, resulting in a decrease in the enzyme bile salt hydrolase and a subsequent increase of hydrophilic glycoursodeoxycholic acid (GUDCA), which might inhibit intestinal FXR and increase the level of liver BAs, leading to improvement of metabolic dysfunction including hyperglycemia.

T2D is also proposed to be associated with the ratio of 12α-hydroxylated BAs (CA and DCA) to non-12α-hydroxylated BAs (CDCA and lithocholic acid (LCA)). It has been reported that ratios of 12α-hydroxylated/non-12α-hydroxylated BAs were associated with key features of insulin resistance, including higher insulin, proinsulin, glucose, glucagon and triglyceride levels, and lower high-density lipoprotein associated cholesterol by comparing a cohort of 200 healthy subjects and 35 T2D patients (Haeusler et al., 2013). A similar result was also reported that in patients with verified insulin resistance, enhanced BA synthesis and increased ratio of 12α-hydroxylated (CA and DCA) to non-12α-hydroxylated (CDCA, LCA, and ursodeoxycholic acid (UDCA)) BAs were observed (Kaur et al., 2015). Consistently, sterol 12α-hydroxylase knockout (*Cyp8b1*$^{-/-}$) mice with low levels of 12α-hydroxylated BAs showed increased GLP-1 and improved glucose tolerance (Kaur et al., 2015). Non-12α-hydroxylated BAs were also reported to be negatively correlated with fasting glucose in women with previous gestational diabetes mellitus with homeostatic model assessment of insulin

resistance (HOMA-IR) >2.8 (Maghsoodi et al., 2019). These results suggest 12α-hydroxylated BAs as negative regulators of insulin action. However, in a randomized trial of lifestyle-induced weight loss in 74 non-smoking men with metabolic syndrome, data show that individuals with improved metabolic control by lifestyle modifications have lower serum levels of BAs and GLP-1, and changes in serum BA composition towards an increased 12α-hydroxylated/non-12α-hydroxylated ratio (Biemann et al., 2016). Although this might due to the difference in the specific health condition of individuals, nevertheless the conflicting results suggest that metabolism is regulated by a dynamically changing profile of BAs.

2.3 NAFLD

The prevalence of NAFLD that is comprised of non-alcoholic fatty liver (NAFL) and its exacerbated condition non-alcoholic steatohepatitis (NASH) is increasing worldwide, reflecting the current epidemics of obesity, insulin resistance and T2D, and metabolic syndrome (Mullish et al., 2018). The relationship between BAs and NAFLD has been extensively investigated previously (Carr and Reid, 2015; Chávez-Talavera et al., 2017). BAs were found to be significantly increased in NASH patients over that when they were in simple steatosis (Bechmann et al., 2013; Jiao et al., 2018). The ratio of CDCA was lower while DCA was significantly increased in NASH patients, and there was a comparable CA and UDCA ratio, suggesting that the elevated 12α-hydroxylated (CA and DCA)/non-12α-hydroxylated (CDCA and UDCA) ratio may also highly correlate with the progress of NAFLD in addition to T2D. Surprisingly, the fibroblast growth factor 19 (FGF19)-FXR pathway was suppressed in NASH patients, indicating that the 12α-hydroxylated/non-12α-hydroxylated ratio of BAs, but not the BA pool size, could be the major regulatory element for NASH (Jiao et al., 2018).

Recently, Puri et al. (2018) found that the presence and severity of NASH are associated with specific changes in circulating BAs. Increase of key BAs was associated with higher grades of steatosis (taurocholic acid (TCA)), lobular (glycocholic acid (GCA)) and portal inflammation (taurolithocholic acid (TLCA)), and hepatocyte ballooning (TCA). Conjugated CA and TCA directly correlated, while the secondary to primary BA ratio inversely correlated to the NAFLD activity score. A higher ratio of total secondary to primary BA decreased and higher conjugated cholate increased the likelihood of significant fibrosis. These observations further provide evidence to support the idea that specific BAs affect specific aspects of NASH.

Gut microbes produce enzymes that convert primary BAs into secondary BAs in the intestines. Consistently, specific species of gut microbe control a diverse effect on NAFLD. For instance, *Parabacteroides distasonis* is one of the 18 core members in the gut microbiota of humans (Falony et al., 2016). Treatment with live *P. distasonis* dramatically altered the BA profile with elevated LCA and UDCA that reduced hyperlipidemia by activating the FXR pathway and repairing gut barrier integrity (Wang et al., 2019). Actinobacteria and Firmicutes are the gut phyla capable of degrading all conjugated BAs, with Bacteroidetes limited to tauro-conjugation activities, exclusively (Jones et al., 2014). It has also been shown that the gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD (Soderborg et al., 2018). Another example is that *Bilophila wadsworthia* aggravates high-fat diet (HFD)-induced metabolic dysfunctions in mice. *B. wadsworthia* acts on both host and microbiota by worsening HFD-induced intestinal inflammation, inhibiting pathways involved in metabolic homeostasis, favoring increased lipopolysaccharides production and translocation, and decreasing butyrate production by the microbiota (Natividad et al., 2018). In the HFD setting, increased production of taurine-conjugated BAs had been proposed to underlie the expansion of *B. wadsworthia* (Devkota et al., 2012). Many studies have investigated the shift of the gut microbiome in NAFLD (Chen et al., 2019). These results further support the idea that different genera of bacteria exert different functions in gut, suggesting that microbiome restoration could be an alternative approach for the treatment of NAFLD.

2.4 Inflammatory bowel disease (IBD)

BAs significantly affect gastrointestinal motor, sensory and secretory functions, intestinal barrier permeability and regulation of the inflammatory response (Panek-Jeziorna and Mulak, 2017). In the healthy gut, these primary BAs aid in the digestion of lipids and are deconjugated by microbes to secondary

BAs, while the primary BAs including CA and CDCA were enriched in IBD (Franzosa et al., 2019). The relative overabundance of primary BAs in the guts of IBD patients is consistent with the disruption of BA transformation activities in the IBD microbiome (Duboc et al., 2013). High-level fecal DCA may act as an endogenous danger signal to activate nod-like receptor protein 3 (NLRP3) inflammasome and contribute to HFD-related colonic inflammation (Zhao et al., 2016). It has also been reported that LCA specifically inhibits NLRP3 inflammasome activation via activating TGR5–cAMP–protein kinase A (PKA) axis (Guo CS et al., 2016). The anti-inflammatory function of TGR5 in protection against IBD is also mediated by inhibition of nuclear factor κB (NF-κB)-dependent proinflammatory cytokine production (Yoneno et al., 2013). Although there has been an increasing number of studies on the role of BAs in IBD (Hegyi et al., 2018; Tiratterra et al., 2018), no cure has been found for treating IBD. Further understanding of the pathogenic mechanisms underlying IBD is still urgently needed.

2.5 Other diseases

BAs, especially secondary BAs, have been well known as strong carcinogens or promoters of colon cancers (Nguyen et al., 2018). The BA receptors FXR and TGR5 not only play key roles in regulating BA homeostasis but also are essential in suppressing BAs' carcinogenic effects (Modica et al., 2008; Wang et al., 2013). This is supported by the facts that FXR-null mice have increased BA pool and spontaneous hepatocarcinogenesis (Kim et al., 2007; Yang et al., 2007; Wang et al., 2008), and deficiency of TGR5 enhances chemically induced liver carcinogenesis (Chen et al., 2013). Additionally, Lee et al. (2019) recently reported that BAs activate yes-associated protein (YAP) through the nuclear vitamin D receptor, resulting in tumor metastasis to lymph nodes. On the other hand, BA metabolism is also involved in antitumor immunosurveillance. Ma et al. (2018) found that gut microbiome-mediated primary-to-secondary BA conversion provides BA messengers to control a chemokine-dependent accumulation of hepatic natural killer T (NKT) cells, leading to selective antitumor in the liver. Therefore, the hypothesis of treating cancer by targeting BAs still needs further detailed investigation. In addition to the above described metabolic diseases, BAs also participate in the development and progression of cardiovascular diseases, including heart failure. This has been extensively reviewed recently (Tang et al., 2019). BA receptors FXR and TGR5 are expressed in endothelial cells, and a variety of FXR ligands show efficacious antihypertensive effects (He et al., 2006; Verbeke et al., 2014; Schwabl et al., 2017), implying the involvement of BA signaling in hypertension. Recent work suggests that microbial disturbances linked to BA profiles are implicated in neurodegenerative disorders. Because of their involvement in immune, neuroendocrine, and neural pathways, gut microbiota has been shown to regulate microglial maturation and function, and may contribute to AD (Nho et al., 2019). Interestingly, BAs might also be closely related to aging because diet enriched in CA enhances health span and lifespan of progeria mice (Bárcena et al., 2018). All of these results demonstrate the importance of maintaining the homeostasis of BAs as well as gut microbiota. The BA/gut microbiome axis might be a promising therapeutic target for the treatment of these diseases (Fig. 1).

3 Therapeutic strategies by targeting BA signaling

3.1 Drug discovery by targeting BA receptors

BAs are metabolic regulators that act as signaling molecules through receptor-dependent and -independent pathways. The most prominent signaling molecules mediating BA signaling are the nuclear receptor FXR and the membrane receptor TGR5. Both are implicated in the regulation of lipid, glucose, energy metabolism, and inflammation. Dysregulation of these pathways might contribute to the development of the diseases summarized above.

3.1.1 Drug discovery by targeting FXR

FXR is expressed in various tissues but its roles in BA signaling have mostly been studied in the liver and the intestine. FXR regulates a network of genes in hepatic BA synthesis, biliary BA secretion, intestinal BA absorption, and hepatic BA uptake, and thus plays a key role in the regulation of BA homeostasis and related gut microbiota composition that has been extensively reviewed (Li and Chiang, 2014). Extensive research has been undertaken to elucidate the molecular mechanism of BA signaling-related diseases

regulated by FXR, including nuclear translocation (Liu et al., 2015; Thompson et al., 2018), post translational modifications (Kemper et al., 2009; Byun et al., 2018; Blokker et al., 2019), and the transcription activity of FXR (Li and Chiang, 2014). FXR is a promising drug target for metabolic diseases.

As a transcriptional factor, the activity of FXR is mediated by ligand binding and regulates BA signaling-related diseases (Jin and Li, 2010; Ding et al., 2015). Several BAs regulate FXR activity as ligands, for example, CDCA, DCA, LCA, and CA may activate FXR, while UDCA, tauro-α-muricholic acid (T-α-MCA) and T-β-MCA may antagonize FXR. Dozens of FXR ligands, including agonists, antagonists, and selective modulators, have been identified to bind FXR and regulate metabolism by modulating BA homeostasis. The FXR agonists include steroid compounds such as BAs and their derivatives, 17β-(4-hydroxybenzoyl) androsta-3,5-diene-3-carboxylic acid (MFA-1), and non-steroid ligands including isoxazole GW4064 and derivatives (Feng et al., 2009), benzopyran fexaramine and derivatives (Downes et al., 2003), azapyrene WAY-362450 and derivatives (Flatt et al., 2009), benzimidazolyl amide compounds (Richter et al., 2011), etc. Additionally, some drugs on the market are identified as novel FXR modulators and have been repurposed to show promising potential in treating BA-mediated diseases by targeting FXR, such as the anti-parasitic drug ivermectin and its analogues (Jin et al., 2013, 2015), and anti-hypertension drugs 1,4-dihydropyridines (DHPs) (Wei et al., 2018). There are also many natural products identified as FXR ligands. Many of them have been in clinical trial for treating FXR-mediated diseases such as primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), NASH, duodenal polyps, etc. (Jia et al., 2018). Among them, obeticholic acid (OCA, a derivative of CDCA) and UDCA have been approved by the US Food and Drug Administration (FDA) in treating PBC. OCA is currently the only FDA-designated breakthrough therapy in development for NASH with compensated cirrhosis. The FXR ligands in clinical trials are summarized in Table 1. The development of these candidates strongly supports the feasibility and value of FXR as a target for metabolic diseases.

3.1.2 Drug discovery by targeting TGR5

TGR5 is widely expressed in the intestine, gall bladder, adipose tissue, skeletal muscle, pancreas, and the hepatic sinusoidal endothelial cells and Kupffer cells but is not expressed in hepatocytes (Maruyama et al., 2002; Keitel and Häussinger, 2011). Among all BAs, TLCA is the most potent TGR5 agonist, followed by taurodeoxycholic acid (TDCA), taurochenodeoxycholic acid (TCDCA), and TCA (Li and Chiang, 2014). Both as BA receptors, interestingly, the transcription of TGR5 is directly regulated by FXR through binding to the promoter of *Tgr5* (Pathak et al., 2017). The molecular signaling pathways regulated by TGR5 have been extensively reviewed (Guo C et al., 2016). As a metabolic regulator, TGR5 is involved in energy homeostasis, BA homeostasis, as well as glucose metabolism and has been extensively investigated in the current decade (Duboc et al., 2014; Velazquez-Villegas et al., 2018; Donkers et al., 2019; Ferrell et al., 2019; Schmid et al., 2019). Thus, in recent years, TGR5 has been the target of drug discovery efforts in the hope of identifying effective treatments for metabolic diseases including T2D, obesity, atherosclerosis, fatty liver disease, and cancer (Hodge and Nunez, 2016; Tian et al., 2017).

Recently, Finn et al. (2019) identified an orally administered TGR5 agonist RXD8940 that can induce incretin (GLP-1, GLP-2, and peptide YY) secretion which improves liver steatosis and insulin sensitivity in NASH and NAFLD. Berberine exerts powerful renoprotective effects on diabetic nephropathy by activating TGR5 and inhibiting sphingosine 1-phosphate receptor 2 (S1P2)/mitogen-activated protein kinase (MAPK) signaling (Yang et al., 2016). A selective TGR5 agonist SB756050 in clinical trial phase I showed good tolerance and safety, but without therapeutic effects on T2D (Hodge et al., 2013). There are also several dual TGR5/FXR agonists in trial (Table 1), but tolerance and side effects are still critical obstacles for their development. Aside from BAs, a class of plant natural triterpenes, including betulinic acid, oleanolic acid, and ursolic acid, were identified as selective TGR5 agonists with physiologic functions (Sato et al., 2007; Genet et al., 2010; Lo et al., 2017; Chianese et al., 2019). These natural oleanane-type triterpenes have been non-BA drug templates for target TGR5 (Castellano et al., 2013) but not for FXR even though FXR and GPBAR1 have similar binding pockets for BAs. Lu et al. (2018) found that a structurally similar triterpene, hedragonic acid, selectively activates FXR. These results suggest the oleanane-type triterpene may be a novel structure template

Table 1 Clinical trial of compounds for metabolic diseases by targeting FXR and TGR5

Drug candidate	Disease	Type of study	Status	Clinical phase	Reference
FXR agonist					
OCA	Liver cirrhosis, biliary	Double-blind, randomized, placebo-controlled study	Recruiting	Phase IV	US National Library of Medicine. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT02308111
	NASH	Double-blind, randomized, long-term, placebo-controlled study	Recruiting	Phase III	US National Library of Medicine. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT02548351
	NAFLD with raised ALT	Open label	Recruiting		US National Library of Medicine. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03836937
	PSC	Randomized, double-blind, placebo-controlled study	Completed	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT02177136
	PBC	Open label	Completed	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT01865812
	Obesity	Randomized study	Recruiting	Phase I	US National Library of Medicine. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT02532335
	Alcoholic hepatitis	Double-blind, placebo-controlled study	Completed	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT02039219
Cilofexor (GS-9674)	NASH	Randomized, double-blind, placebo-controlled study	Active, not recruiting	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT03449446; Trauner et al., 2019
Tropifexor (LJN452)	NASH	Randomized, double-blind, placebo-controlled study	Recruiting	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT02855164
	PBC	Randomized, double-blind, placebo-controlled study	Completed	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT02516605
Px-104	NAFLD	Open label	Completed	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2016. https://clinicaltrials.gov/ct2/show/NCT01999101
LMB763	NASH	Randomized, patient and investigator blinded, placebo-controlled study	Active, not recruiting	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT02913105; Laffitte et al., 2017
	Diabetic nephropathy	Randomized, patient and investigator blinded, placebo-controlled study	Recruiting	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2019. https://clinicaltrials.gov/ct2/show/NCT03804879
TGR5 agonist					
SB756050	T2D	Single-blinded randomized, placebo-controlled, staggered-parallel, escalating-dose study	Completed	Phase I	US National Library of Medicine. ClinicalTrials.gov. 2017. https://clinicaltrials.gov/ct2/show/NCT00733577; Hodge et al., 2013
Ursolic acid	Metabolic syndrome X	Randomized, double-blind, placebo-controlled study	Completed	Phase II	US National Library of Medicine. ClinicalTrials.gov. 2015. https://clinicaltrials.gov/ct2/show/NCT02337933
Dual FXR/TGR5 agonist					
INT-767	PSC			Phase I	Intercept Pharmaceuticals Initiates Phase 1 Study of INT-767, a Dual FXR and TGR5 Agonist. 2015. http://ir.interceptpharma.com/news-releases/news-release-details/intercept-pharmaceuticals-initiates-phase-1-study-int-767-dual
UDCA	T2D and chronic liver diseases	Open label	Recruiting	Phase IV	US National Library of Medicine. ClinicalTrials.gov. 2011. https://clinicaltrials.gov/ct2/show/NCT01337440
CDCA	Severe obesity	Open label	Recruiting	Phase IV	US National Library of Medicine. ClinicalTrials.gov. 2016. https://clinicaltrials.gov/ct2/show/NCT02876484

FXR: farnesoid X receptor; OCA: obeticholic acid; TGR5: G protein-coupled BA receptor; UDCA: ursodeoxycholic acid; CDCA: chenodeoxycholic acid; NASH: non-alcoholic steatohepatitis; NAFLD: non-alcoholic fatty liver disease; ALT: alanine transaminase; PSC: primary sclerosing cholangitis; PBC: primary biliary cirrhosis; T2D: type 2 diabetes

for drug design of a selective modulator for FXR or TGR5, or dual FXR/TGR5 agonist with pharmaceutical value.

3.2 Bariatric surgeries

In addition to pharmacological agents, there are other therapies which target BA signaling. Bariatric surgery is the most effective strategy, to date, for the treatment of obesity and its comorbidities. The outcomes and mechanisms for bariatric surgery are under extensive investigation (Tian et al., 2017; Sandoval, 2019). The BA receptors FXR and TGR5 are shown as two potential targets for bariatric surgery VSG (Ryan et al., 2014; Ding et al., 2016; McGavigan et al., 2017). The mRNA expression of FXR, small heterodimer partner (SHP), and peroxisome proliferator-activated receptor α (PPARα) in the liver was significantly higher in the laparoscopic sleeve gastrectomy (SG) group than in the Sham-operated group (Watanabe et al., 2018), further supporting the idea that the therapeutic effect of SG on NAFLD may also be by targeting the FXR signaling pathway. Duodenal-jejunal bypass surgery has a direct effect on NASH improvement. The increase of plasma BA level followed by the stimulation of FXR signaling may contribute to this phenomenon (Tsuchiya et al., 2018).

CYP8B1 is a BA synthetic enzyme expressed primarily in hepatocytes (Wang et al., 2005, 2007). CYP8B1 is required for the synthesis of 12α-hydroxylated BAs and thereby determines the ratio of 12α-hydroxylated to non-12α-hydroxylated BAs (Li and Chiang, 2014). The BA profile hydrophobicity plays a crucial role in intestinal fat absorption, and *Cyp8b1* ablation prevents Western diet-induced weight gain and hepatic steatosis because of impaired fat absorption (Bertaggia et al., 2017). Genetic ablation of *Cyp8b1* decreases BA profile hydrophobicity and protects against several metabolic diseases, including obesity and T2D, in mice (Zaborska and Cummings, 2018). Of note, the percentage of 12α-hydroxylated BAs was reduced after SG, associated with overexpression of V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog G (MAFG) and lower mRNA and protein levels of CYP8B1 (Wang et al., 2017). Interestingly, MAFG is an FXR target gene that transcriptionally represses CYP8B1 expression (de Aguiar Vallim et al., 2015); these results suggest that in addition to FXR and TGR5, the downstream CYP8B1 may present an alternative target for bariatric surgery.

4 Future perspectives

Although there are some conflicting reports about the BA level in metabolic diseases, as mentioned in this review, there is increasing evidence that the BA composition plays a more important role than the total BA level in regulating gut microbiome and metabolism. One important example is the BA hydrophobicity modulated by the ratio of 12α-hydroxylated to non-12α-hydroxylated BAs that is switched by the activity of CYP8B1. However, FXR suppresses expression of both CYP7A1 and CYP8B1, implying a possible mechanism for the side effects of FXR agonists. Selective regulation of CYP8B1 expression may lead to the development of BA-based therapeutics with fewer adverse side effects. TGR5 has been shown to reduce hepatic CYP8B1 protein expression with no effect on hepatic CYP7A1 expression (McGavigan et al., 2017), whereas drug development by targeting TGR5 shows other side effects beyond BA signaling. Thus, specific genetic modulation or inhibition by directly targeting CYP8B1 may be a promising therapeutic modality for metabolic diseases.

There is also a conundrum on whether activating or inhibiting FXR will be beneficial for maintaining the homeostasis of metabolism. Numerous data demonstrate that FXR agonists exert efficacious therapeutic effects on metabolic diseases. This can be supported by the drug development processes mentioned in Table 1. However, there is increasing evidence that FXR antagonists ameliorate the disease condition by inhibiting the activity of FXR, especially in the intestine. HFD-fed intestine-specific FXR-null mice show lower diet-induced obesity; tempol improves obesity via inhibition of intestinal FXR by T-β-MCA (Li et al., 2013). It is well known that throughout the gastroenteric tract the most crucial role of FXR is to maintain the BA homeostasis, associated with the homeostasis of gut microbiota, resulting in the final metabolic homeostasis. The regulation of FXR activity by the BAs in the intestine may mainly be the intermediate steps involved in this homeostasis maintenance. With the slow process of drug development targeting BA receptors including FXR and

TGR5, side effects are the most difficult obstacles, suggesting over activating of the BA receptors might cause side effects because of the interruption of this homeostasis, and fine tuning by modulators might be more feasible. Furthermore, directly modulating the downstream enzymes included in BA synthesis might be an alternative strategy for BA-related diseases.

In a similar way, it will be necessary to identify which gut microbes are beneficial and feasible. Careful selection of commensal bacteria for probiotics may lead to an effective therapy for metabolic diseases. Therefore, with an increasing understanding of the complicated interaction between the gut microbiota and host, studies on single gut symbioses are urgently required to define the exact functions of a given bacterium in causing disease or maintaining health.

It is important to note that, to date, most findings on the crosstalk among BAs, gut microbiota and metabolic diseases are from rodent models. However, the BA composition of rodents and humans is different. In mice, the majority of CDCA is converted to α-muricholic acid (MCA) and β-MCA, and accordingly, CA and MCAs are the major primary BAs in the mouse BA pool. Therefore, it is not well known whether alterations of BAs in mice also occur in humans. It is noteworthy that inconsistent results have been seen in a few human studies. Thus the differences in BA composition between humans and mice need to be considered when interpreting data from mice studies. Additionally, it is of particular importance to elucidate how a human gut microbiota influences BA composition. To improve the clinical trial of drug candidates, testing on large animals such as monkeys in preclinical trial might be helpful for the medical translation.

Contributors

Li-hua JIN drafted and revised the manuscript. Zhi-peng FANG and Min-jie FAN drafted the manuscript. Wen-dong HUANG revised the manuscript. All authors approved the final manuscript.

Acknowledgments

We have to apologize that we are not able to include all relevant publications in this review because of space limitation.

Compliance with ethics guidelines

Li-hua JIN, Zhi-peng FANG, Min-jie FAN, and Wen-dong HUANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Bárcena C, Quirós PM, Durand S, et al., 2018. Methionine restriction extends lifespan in progeroid mice and alters lipid and bile acid metabolism. *Cell Rep*, 24(9):2392-2403. https://doi.org/10.1016/j.celrep.2018.07.089

Bechmann LP, Kocabayoglu P, Sowa JP, et al., 2013. Free fatty acids repress small heterodimer partner (SHP) activation and adiponectin counteracts bile acid-induced liver injury in superobese patients with nonalcoholic steatohepatitis. *Hepatology*, 57(4):1394-1406. https://doi.org/10.1002/hep.26225

Bertaggia E, Jensen KK, Castro-Perez J, et al., 2017. *Cyp8b1* ablation prevents Western diet-induced weight gain and hepatic steatosis because of impaired fat absorption. *Am J Physiol Endocrinol Metab*, 313(2):E121-E133. https://doi.org/10.1152/ajpendo.00409.2016

Beysen C, Murphy EJ, Deines K, et al., 2012. Effect of bile acid sequestrants on glucose metabolism, hepatic de novo lipogenesis, and cholesterol and bile acid kinetics in type 2 diabetes: a randomised controlled study. *Diabetologia*, 55(2):432-442. https://doi.org/10.1007/s00125-011-2382-3

Biemann R, Penner M, Borucki K, et al., 2016. Serum bile acids and GLP-1 decrease following telemetric induced weight loss: results of a randomized controlled trial. *Sci Rep*, 6:30173. https://doi.org/10.1038/srep30173

Blokker BA, Maijo M, Echeandia M, et al., 2019. Fine-tuning of sirtuin 1 expression is essential to protect the liver from cholestatic liver disease. *Hepatology*, 69(2):699-716. https://doi.org/10.1002/hep.30275

Broeders EPM, Nascimento EBM, Havekes B, et al., 2015. The bile acid chenodeoxycholic acid increases human brown adipose tissue activity. *Cell Metab*, 22(3):418-426. https://doi.org/10.1016/j.cmet.2015.07.002

Browning MG, Pessoa BM, Khoraki J, et al., 2019. Changes in bile acid metabolism, transport, and signaling as central drivers for metabolic improvements after bariatric surgery. *Curr Obes Rep*, Epub ahead of print. https://doi.org/10.1007/s13679-019-00334-4

Byun S, Kim DH, Ryerson D, et al., 2018. Postprandial FGF19-induced phosphorylation by Src is critical for FXR function in bile acid homeostasis. *Nat Commun*, 9(1):2590. https://doi.org/10.1038/s41467-018-04697-5

Camilleri M, Gores GJ, 2015. Therapeutic targeting of bile acids. *Am J Physiol Gastrointest Liver Physiol*, 309(4): G209-G215. https://doi.org/10.1152/ajpgi.00121.2015

Carr RM, Reid AE, 2015. FXR agonists as therapeutic agents for non-alcoholic fatty liver disease. *Curr Atheroscler Rep*, 17(4):16. https://doi.org/10.1007/s11883-015-0500-2

Castellano JM, Guinda A, Delgado T, et al., 2013. Biochemical basis of the antidiabetic activity of oleanolic acid and related pentacyclic triterpenes. *Diabetes*, 62(6):1791-1799. https://doi.org/10.2337/db12-1215

Chávez-Talavera O, Tailleux A, Lefebvre P, et al., 2017. Bile acid control of metabolism and inflammation in obesity, type 2 diabetes, dyslipidemia, and nonalcoholic fatty liver disease. *Gastroenterology*, 152(7):1679-1694.e3. https://doi.org/10.1053/j.gastro.2017.01.055

Chen JZ, Thomsen M, Vitetta L, 2019. Interaction of gut microbiota with dysregulation of bile acids in the pathogenesis of nonalcoholic fatty liver disease and potential therapeutic implications of probiotics. *J Cell Biochem*, 120(3):2713-2720. https://doi.org/10.1002/jcb.27635

Chen WD, Yu D, Forman BM, et al., 2013. Deficiency of G-protein-coupled bile acid receptor Gpbar1 (TGR5) enhances chemically induced liver carcinogenesis. *Hepatology*, 57(2):656-666. https://doi.org/10.1002/hep.26019

Chianese G, Golin-Pacheco SD, Taglialatela-Scafati O, et al., 2019. Bioactive triterpenoids from the caffeine-rich plants guayusa and maté. *Food Res Int*, 115:504-510. https://doi.org/10.1016/j.foodres.2018.10.005

Chiang JYL, Ferrell JM, 2018. Bile acid metabolism in liver pathobiology. *Gene Expr*, 18(2):71-87. https://doi.org/10.3727/105221618X15156018385515

de Aguiar Vallim TQ, Tarling EJ, Ahn H, et al., 2015. MAFG is a transcriptional repressor of bile acid synthesis and metabolism. *Cell Metab*, 21(2):298-310. https://doi.org/10.1016/j.cmet.2015.01.007

Devkota S, Wang YW, Musch MW, et al., 2012. Dietary-fat-induced taurocholic acid promotes pathobiont expansion and colitis in *il*10$^{-/-}$ mice. *Nature*, 487(7405):104-108. https://doi.org/10.1038/nature11225

Ding LL, Yang L, Wang ZT, et al., 2015. Bile acid nuclear receptor FXR and digestive system diseases. *Acta Pharm Sin B*, 5(2):135-144. https://doi.org/10.1016/j.apsb.2015.01.004

Ding LL, Sousa KM, Jin LH, et al., 2016. Vertical sleeve gastrectomy activates GPBAR-1/TGR5 to sustain weight loss, improve fatty liver, and remit insulin resistance in mice. *Hepatology*, 64(3):760-773. https://doi.org/10.1002/hep.28689

Donkers JM, Roscam Abbing RLP, van de Graaf SFJ, 2019. Developments in bile salt based therapies: a critical overview. *Biochem Pharmacol*, 161:1-13. https://doi.org/10.1016/j.bcp.2018.12.018

Downes M, Verdecia MA, Roecker AJ, et al., 2003. A chemical, genetic, and structural analysis of the nuclear bile acid receptor FXR. *Mol Cell*, 11(4):1079-1092. https://doi.org/10.1016/S1097-2765(03)00104-7

Duboc H, Rajca S, Rainteau D, et al., 2013. Connecting dysbiosis, bile-acid dysmetabolism and gut inflammation in inflammatory bowel diseases. *Gut*, 62(4):531-539. https://doi.org/10.1136/gutjnl-2012-302578

Duboc H, Taché Y, Hofmann AF, 2014. The bile acid TGR5 membrane receptor: from basic research to clinical application. *Dig Liver Dis*, 46(4):302-312. https://doi.org/10.1016/j.dld.2013.10.021

Esser N, Legrand-Poels S, Piette J, et al., 2014. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res Clin Pract*, 105(2):141-150. https://doi.org/10.1016/j.diabres.2014.04.006

Falony G, Joossens M, Vieira-Silva S, et al., 2016. Population-level analysis of gut microbiome variation. *Science*, 352(6285):560-564. https://doi.org/10.1126/science.aad3503

Feng S, Yang MM, Zhang ZS, et al., 2009. Identification of an N-oxide pyridine GW4064 analog as a potent FXR agonist. *Bioorg Med Chem Lett*, 19(9):2595-2598. https://doi.org/10.1016/j.bmcl.2009.03.008

Ferrell JM, Pathak P, Boehme S, et al., 2019. Deficiency of both farnesoid X receptor and Takeda G protein-coupled receptor 5 exacerbated liver fibrosis in mice. *Hepatology*, https://doi.org/10.1002/hep.30513

Finn PD, Rodriguez D, Kohler J, et al., 2019. Intestinal TGR5 agonism improves hepatic steatosis and insulin sensitivity in Western diet-fed mice. *Am J Physiol Gastrointest Liver Physiol*, 316(3):G412-G424. https://doi.org/10.1152/ajpgi.00300.2018

Flatt B, Martin R, Wang TL, et al., 2009. Discovery of XL335 (WAY-362450), a highly potent, selective, and orally active agonist of the farnesoid X receptor (FXR). *J Med Chem*, 52(4):904-907. https://doi.org/10.1021/jm8014124

Franzosa EA, Sirota-Madi A, Avila-Pacheco J, et al., 2019. Gut microbiome structure and metabolic activity in inflammatory bowel disease. *Nat Microbiol*, 4(2):293-305. https://doi.org/10.1038/s41564-018-0306-4

Genet C, Strehle A, Schmidt C, et al., 2010. Structure-activity relationship study of betulinic acid, a novel and selective TGR5 agonist, and its synthetic derivatives: potential impact in diabetes. *J Med Chem*, 53(1):178-190. https://doi.org/10.1021/jm900872z

Gerhard GS, Styer AM, Wood GC, et al., 2013. A role for fibroblast growth factor 19 and bile acids in diabetes remission after Roux-en-Y gastric bypass. *Diabetes Care*, 36(7):1859-1864. https://doi.org/10.2337/dc12-2255

Golay A, Ybarra J, 2005. Link between obesity and type 2 diabetes. *Best Pract Res Clin Endocrinol Metab*, 19(4):649-663. https://doi.org/10.1016/j.beem.2005.07.010

Guo C, Chen WD, Wang YD, 2016. TGR5, not only a metabolic regulator. *Front Physiol*, 7:646. https://doi.org/10.3389/fphys.2016.00646

Guo CS, Xie SJ, Chi ZX, et al., 2016. Bile acids control inflammation and metabolic disorder through inhibition of NLRP3 inflammasome. *Immunity*, 45(4):802-816. https://doi.org/10.1016/j.immuni.2016.09.008

Haeusler RA, Astiarraga B, Camastra S, et al., 2013. Human insulin resistance is associated with increased plasma levels of 12α-hydroxylated bile acids. *Diabetes*, 62(12):4184-4191. https://doi.org/10.2337/db13-0639

Halmy L, Fehér T, Steczek K, et al., 1986. High serum bile acid level in obesity: its decrease during and after total fasting. *Acta Med Hung*, 43(1):55-58.

Hansen M, Sonne DP, Mikkelsen KH, et al., 2017. Bile acid sequestrants for glycemic control in patients with type 2 diabetes: a systematic review with meta-analysis of randomized controlled trials. *J Diabetes Complications*, 31(5): 918-927.
https://doi.org/10.1016/j.jdiacomp.2017.01.011

He FT, Li J, Mu Y, et al., 2006. Downregulation of endothelin-1 by farnesoid X receptor in vascular endothelial cells. *Circ Res*, 98(2):192-199.
https://doi.org/10.1161/01.RES.0000200400.55539.85

Hegyi P, Maléth J, Walters JR, et al., 2018. Guts and gall: bile acids in regulation of intestinal epithelial function in health and disease. *Physiol Rev*, 98(4):1983-2023.
https://doi.org/10.1152/physrev.00054.2017

Hodge RJ, Nunez DJ, 2016. Therapeutic potential of Takeda-G-protein-receptor-5 (TGR5) agonists. Hope or hype? *Diabetes Obes Metab*, 18(5):439-443.
https://doi.org/10.1111/dom.12636

Hodge RJ, Lin J, Vasist Johnson LS, et al., 2013. Safety, pharmacokinetics, and pharmacodynamic effects of a selective TGR5 agonist, SB-756050, in type 2 diabetes. *Clin Pharmacol Drug Dev*, 2(3):213-222.
https://doi.org/10.1002/cpdd.34

Inagaki T, Moschetta A, Lee YK, et al., 2006. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. *Proc Natl Acad Sci USA*, 103(10): 3920-3925.
https://doi.org/10.1073/pnas.0509592103

Jia W, Xie GX, Jia WP, 2018. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. *Nat Rev Gastroenterol Hepatol*, 15(2):111-128.
https://doi.org/10.1038/nrgastro.2017.119

Jiao N, Baker SS, Chapa-Rodriguez A, et al., 2018. Suppressed hepatic bile acid signalling despite elevated production of primary and secondary bile acids in NAFLD. *Gut*, 67(10): 1881-1891.
https://doi.org/10.1136/gutjnl-2017-314307

Jin LH, Li Y, 2010. Structural and functional insights into nuclear receptor signaling. *Adv Drug Deliv Rev*, 62(13): 1218-1226.
https://doi.org/10.1016/j.addr.2010.08.007

Jin LH, Feng XH, Rong H, et al., 2013. The antiparasitic drug ivermectin is a novel FXR ligand that regulates metabolism. *Nat Commun*, 4:1937.
https://doi.org/10.1038/ncomms2924

Jin LH, Wang R, Zhu YL, et al., 2015. Selective targeting of nuclear receptor FXR by avermectin analogues with therapeutic effects on nonalcoholic fatty liver disease. *Sci Rep*, 5:17288.
https://doi.org/10.1038/srep17288

Jones ML, Martoni CJ, Ganopolsky JG, et al., 2014. The human microbiome and bile acid metabolism: dysbiosis, dysmetabolism, disease and intervention. *Expert Opin Biol Ther*, 14(4):467-482.
https://doi.org/10.1517/14712598.2014.880420

Kaur A, Patankar JV, de Haan W, et al., 2015. Loss of *Cyp8b1* improves glucose homeostasis by increasing GLP-1. *Diabetes*, 64(4):1168-1179.
https://doi.org/10.2337/db14-0716

Keitel V, Häussinger D, 2011. TGR5 in the biliary tree. *Dig Dis*, 29(1):45-47.
https://doi.org/10.1159/000324127

Kemper JK, Xiao Z, Ponugoti B, et al., 2009. FXR acetylation is normally dynamically regulated by p300 and SIRT1 but constitutively elevated in metabolic disease states. *Cell Metab*, 10(5):392-404.
https://doi.org/10.1016/j.cmet.2009.09.009

Kim I, Morimura K, Shah Y, et al., 2007. Spontaneous hepatocarcinogenesis in farnesoid X receptor-null mice. *Carcinogenesis*, 28(5):940-946.
https://doi.org/10.1093/carcin/bgl249

Kobayashi M, Ikegami H, Fujisawa T, et al., 2007. Prevention and treatment of obesity, insulin resistance, and diabetes by bile acid-binding resin. *Diabetes*, 56(1):239-247.
https://doi.org/10.2337/db06-0353

Kuhre RE, Wewer Albrechtsen NJ, Larsen O, et al., 2018. Bile acids are important direct and indirect regulators of the secretion of appetite- and metabolism-regulating hormones from the gut and pancreas. *Mol Metab*, 11:84-95.
https://doi.org/10.1016/j.molmet.2018.03.007

Kuipers F, Groen AK, 2017. An unexpected role for bile acid synthesis in adaptation to low temperature. *Nat Med*, 23(7): 800-802.
https://doi.org/10.1038/nm.4365

Kurdi P, Kawanishi K, Mizutani K, et al., 2006. Mechanism of growth inhibition by free bile acids in lactobacilli and bifidobacteria. *J Bacteriol*, 188(5):1979-1986.
https://doi.org/10.1128/JB.188.5.1979-1986.2006

Laffitte B, Liu B, Kim Y, et al., 2017. Development of LMB763, a novel, orally bioavailable, clinical farnesoid X receptor agonist for the treatment of non-alcoholic steatohepatitis and hepatobiliary disorders. *J Hepatol*, 66(S1):S166.
https://doi.org/10.1016/S0168-8278(17)30609-8

Lee CK, Jeong SH, Jang C, et al., 2019. Tumor metastasis to lymph nodes requires YAP-dependent metabolic adaptation. *Science*, 363(6427):644-649.
https://doi.org/10.1126/science.aav0173

Li F, Jiang CT, Krausz KW, et al., 2013. Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity. *Nat Commun*, 4:2384.
https://doi.org/10.1038/ncomms3384

Li TG, Chiang JY, 2014. Bile acid signaling in metabolic disease and drug therapy. *Pharmacol Rev*, 66(4):948-983.
https://doi.org/10.1124/pr.113.008201

Liu XJ, Zhang XW, Ji LL, et al., 2015. Farnesoid X receptor associates with β-catenin and inhibits its activity in hepatocellular carcinoma. *Oncotarget*, 6(6):4226-4238.
https://doi.org/10.18632/oncotarget.2899

Lo SH, Li YX, Cheng KC, et al., 2017. Ursolic acid activates the TGR5 receptor to enhance GLP-1 secretion in type 1-like diabetic rats. *Naunyn Schmiedebergs Arch Pharmacol*, 390(11):1097-1104. https://doi.org/10.1007/s00210-017-1409-9

Lu Y, Zheng WL, Lin SC, et al., 2018. Identification of an oleanane-type triterpene hedragonic acid as a novel farnesoid X receptor ligand with liver protective effects and anti-inflammatory activity. *Mol Pharmacol*, 93(2):63-72. https://doi.org/10.1124/mol.117.109900

Ma C, Han MJ, Heinrich B, et al., 2018. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science*, 360(6391):eaan5931. https://doi.org/10.1126/science.aan5931

Maghsoodi N, Shaw N, Cross GF, et al., 2019. Bile acid metabolism is altered in those with insulin resistance after gestational diabetes mellitus. *Clin Biochem*, 64:12-17. https://doi.org/10.1016/j.clinbiochem.2018.11.016

Mahmoud AA, Elshazly SM, 2014. Ursodeoxycholic acid ameliorates fructose-induced metabolic syndrome in rats. *PLoS ONE*, 9(9):e106993. https://doi.org/10.1371/journal.pone.0106993

Maruyama T, Miyamoto Y, Nakamura T, et al., 2002. Identification of membrane-type receptor for bile acids (M-BAR). *Biochem Biophys Res Commun*, 298(5):714-719. https://doi.org/10.1016/S0006-291x(02)02550-0

Matysik S, Martin J, Bala M, et al., 2011. Bile acid signaling after an oral glucose tolerance test. *Chem Phys Lipids*, 164(6):525-529. https://doi.org/10.1016/j.chemphyslip.2011.05.003

McGavigan AK, Garibay D, Henseler ZM, et al., 2017. TGR5 contributes to glucoregulatory improvements after vertical sleeve gastrectomy in mice. *Gut*, 66(2):226-234. https://doi.org/10.1136/gutjnl-2015-309871

Mertens KL, Kalsbeek A, Soeters MR, et al., 2017. Bile acid signaling pathways from the enterohepatic circulation to the central nervous system. *Front Neurosci*, 11:617. https://doi.org/10.3389/fnins.2017.00617

Modica S, Murzilli S, Salvatore L, et al., 2008. Nuclear bile acid receptor FXR protects against intestinal tumorigenesis. *Cancer Res*, 68(23):9589-9594. https://doi.org/10.1158/0008-5472.CAN-08-1791

Mullish BH, Forlano R, Manousou P, et al., 2018. Non-alcoholic fatty liver disease and cardiovascular risk: an update. *Expert Rev Gastroenterol Hepatol*, 12(12):1175-1177. https://doi.org/10.1080/17474124.2018.1533117

Nakatani H, Kasama K, Oshiro T, et al., 2009. Serum bile acid along with plasma incretins and serum high-molecular weight adiponectin levels are increased after bariatric surgery. *Metabolism*, 58(10):1400-1407. https://doi.org/10.1016/j.metabol.2009.05.006

Natividad JM, Lamas B, Pham HP, et al., 2018. *Bilophila wadsworthia* aggravates high fat diet induced metabolic dysfunctions in mice. *Nat Commun*, 9(1):2802. https://doi.org/10.1038/s41467-018-05249-7

Nguyen TT, Ung TT, Kim NH, et al., 2018. Role of bile acids in colon carcinogenesis. *World J Clin Cases*, 6(13):577-588. https://doi.org/10.12998/wjcc.v6.i13.577

Nho K, Kueider-Paisley A, Mahmoudiandehkordi S, et al., 2019. Altered bile acid profile in mild cognitive impairment and Alzheimer's disease: relationship to neuroimaging and CSF biomarkers. *Alzheimer's Dement*, 15(2):232-244. https://doi.org/10.1016/j.jalz.2018.08.012

Panek-Jeziorna M, Mulak A, 2017. The role of bile acids in the pathogenesis of bowel diseases. *Postepy Hig Med Dosw (Online)*, 71(1):737-746.

Pathak P, Liu HL, Boehme S, et al., 2017. Farnesoid X receptor induces Takeda G-protein receptor 5 cross-talk to regulate bile acid synthesis and hepatic metabolism. *J Biol Chem*, 292(26):11055-11069. https://doi.org/10.1074/jbc.M117.784322

Patti ME, Houten SM, Bianco AC, et al., 2009. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. *Obesity (Silver Spring)*, 17(9):1671-1677. https://doi.org/10.1038/oby.2009.102

Prinz P, Hofmann T, Ahnis A, et al., 2015. Plasma bile acids show a positive correlation with body mass index and are negatively associated with cognitive restraint of eating in obese patients. *Front Neurosci*, 9:199. https://doi.org/10.3389/fnins.2015.00199

Puri P, Daita K, Joyce A, et al., 2018. The presence and severity of nonalcoholic steatohepatitis is associated with specific changes in circulating bile acids. *Hepatology*, 67(2):534-548. https://doi.org/10.1002/hep.29359

Richter HGF, Benson GM, Blum D, et al., 2011. Discovery of novel and orally active FXR agonists for the potential treatment of dyslipidemia & diabetes. *Bioorg Med Chem Lett*, 21(1):191-194. https://doi.org/10.1016/j.bmcl.2010.11.039

Ridaura VK, Faith JJ, Rey FE, et al., 2013. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science*, 341(6150):1241214. https://doi.org/10.1126/science.1241214

Ridlon JM, Kang DJ, Hylemon PB, 2006. Bile salt biotransformations by human intestinal bacteria. *J Lipid Res*, 47(2):241-259. https://doi.org/10.1194/jlr.R500013-JLR200

Ryan KK, Tremaroli V, Clemmensen C, et al., 2014. FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature*, 509(7499):183-188. https://doi.org/10.1038/nature13135

Sandoval DA, 2019. Mechanisms for the metabolic success of bariatric surgery. *J Neuroendocrinol*, e12708. https://doi.org/10.1111/jne.12708

Sato H, Genet C, Strehle A, et al., 2007. Anti-hyperglycemic activity of a TGR5 agonist isolated from *Olea europaea*. *Biochem Biophys Res Commun*, 362(4):793-798.

https://doi.org/10.1016/j.bbrc.2007.06.130

Schmid A, Neumann H, Karrasch T, et al., 2016. Bile acid metabolome after an oral lipid tolerance test by liquid chromatography-tandem mass spectrometry (LC-MS/MS). *PLoS ONE*, 11(2):e0148869. https://doi.org/10.1371/journal.pone.0148869

Schmid A, Schlegel J, Thomalla M, et al., 2019. Evidence of functional bile acid signaling pathways in adipocytes. *Mol Cell Endocrinol*, 483:1-10. https://doi.org/10.1016/j.mce.2018.12.006

Schwabl P, Hambruch E, Seeland BA, et al., 2017. The FXR agonist PX20606 ameliorates portal hypertension by targeting vascular remodelling and sinusoidal dysfunction. *J Hepatol*, 66(4):724-733. https://doi.org/10.1016/j.jhep.2016.12.005

Shen J, Obin MS, Zhao LP, 2013. The gut microbiota, obesity and insulin resistance. *Mol Aspects Med*, 34(1):39-58. https://doi.org/10.1016/j.mam.2012.11.001

Shima KR, Ota T, Kato KI, et al., 2018. Ursodeoxycholic acid potentiates dipeptidyl peptidase-4 inhibitor sitagliptin by enhancing glucagon-like peptide-1 secretion in patients with type 2 diabetes and chronic liver disease: a pilot randomized controlled and add-on study. *BMJ Open Diabetes Res Care*, 6(1):e000469. https://doi.org/10.1136/bmjdrc-2017-000469

Slijepcevic D, van de Graaf SFJ, 2017. Bile acid uptake transporters as targets for therapy. *Dig Dis*, 35(3):251-258. https://doi.org/10.1159/000450983

Soderborg TK, Clark SE, Mulligan CE, et al., 2018. The gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD. *Nat Commun*, 9(1):4462. https://doi.org/10.1038/s41467-018-06929-0

Sommer A, Twig G, 2018. The impact of childhood and adolescent obesity on cardiovascular risk in adulthood: a systematic review. *Curr Diab Rep*, 18(10):91. https://doi.org/10.1007/s11892-018-1062-9

Sun LL, Xie C, Wang G, et al., 2018. Gut microbiota and intestinal FXR mediate the clinical benefits of metformin. *Nat Med*, 24(12):1919-1929. https://doi.org/10.1038/s41591-018-0222-4

Tang WHW, Li DY, Hazen SL, 2019. Dietary metabolism, the gut microbiome, and heart failure. *Nat Rev Cardiol*, 16(3):137-154. https://doi.org/10.1038/s41569-018-0108-7

Thompson MD, Moghe A, Cornuet P, et al., 2018. β-Catenin regulation of farnesoid X receptor signaling and bile acid metabolism during murine cholestasis. *Hepatology*, 67(3):955-971. https://doi.org/10.1002/hep.29371

Tian JY, Huang S, Sun SM, et al., 2017. Bile acid signaling and bariatric surgery. *Liver Res*, 1(4):208-213. https://doi.org/10.1016/j.livres.2017.12.007

Tiratterra E, Franco P, Porru E, et al., 2018. Role of bile acids in inflammatory bowel disease. *Ann Gastroenterol*, 31(3):266-272. https://doi.org/10.20524/aog.2018.0239

Trauner M, Gulamhusein A, Hameed B, et al., 2019. The nonsteroidal farnesoid X receptor agonist cilofexor (GS-9674) improves markers of cholestasis and liver injury in patients with primary sclerosing cholangitis. *Hepatology*, Epub ahead of print. https://doi.org/10.1002/hep.30509

Tsuchiya T, Naitoh T, Nagao M, et al., 2018. Increased bile acid signals after duodenal-jejunal bypass improve non-alcoholic steatohepatitis (NASH) in a rodent model of diet-induced NASH. *Obes Surg*, 28(6):1643-1652. https://doi.org/10.1007/s11695-017-3065-z

Turnbaugh PJ, Ley RE, Mahowald MA, et al., 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*, 444(7122):1027-1031. https://doi.org/10.1038/nature05414

Velazquez-Villegas LA, Perino A, Lemos V, et al., 2018. TGR5 signalling promotes mitochondrial fission and beige remodelling of white adipose tissue. *Nat Commun*, 9:245. https://doi.org/10.1038/s41467-017-02068-0

Verbeke L, Farre R, Trebicka J, et al., 2014. Obeticholic acid, a farnesoid X receptor agonist, improves portal hypertension by two distinct pathways in cirrhotic rats. *Hepatology*, 59(6):2286-2298. https://doi.org/10.1002/hep.26939

Wang J, Greene S, Eriksson LC, et al., 2005. Human sterol 12α-hydroxylase (*CYP8B1*) is mainly expressed in hepatocytes in a homogenous pattern. *Histochem Cell Biol*, 123(4-5):441-446. https://doi.org/10.1007/s00418-005-0779-0

Wang J, Olin M, Rozell B, et al., 2007. Differential hepatocellular zonation pattern of cholesterol 7α-hydroxylase (*Cyp7a1*) and sterol 12α-hydroxylase (*Cyp8b1*) in the mouse. *Histochem Cell Biol*, 127(3):253-261. https://doi.org/10.1007/s00418-006-0239-5

Wang K, Liao MF, Zhou N, et al., 2019. *Parabacteroides distasonis* alleviates obesity and metabolic dysfunctions via production of succinate and secondary bile acids. *Cell Rep*, 26(1):222-235.e5. https://doi.org/10.1016/j.celrep.2018.12.028

Wang MG, Wu QZ, Xie HB, et al., 2017. Effects of sleeve gastrectomy on serum 12α-hydroxylated bile acids in a diabetic rat model. *Obes Surg*, 27(11):2912-2918. https://doi.org/10.1007/s11695-017-2714-6

Wang XC, Fu XH, van Ness C, et al., 2013. Bile acid receptors and liver cancer. *Curr Pathobiol Rep*, 1(1):29-35. https://doi.org/10.1007/s40139-012-0003-6

Wang YD, Chen WD, Wang MH, et al., 2008. Farnesoid X receptor antagonizes nuclear factor κB in hepatic inflammatory response. *Hepatology*, 48(5):1632-1643. https://doi.org/10.1002/hep.22519

Watanabe K, Ohta M, Takayama H, et al., 2018. Effects of sleeve gastrectomy on nonalcoholic fatty liver disease in an obese rat model. *Obes Surg*, 28(6):1532-1539. https://doi.org/10.1007/s11695-017-3052-4

Watanabe M, Houten SM, Mataki C, et al., 2006. Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature*, 439(7075):484-489. https://doi.org/10.1038/nature04330

Wei YJ, Lu Y, Zhu YL, et al., 2018. Structural basis for the hepatoprotective effects of antihypertensive 1,4-dihydropyridine drugs. *Biochim Biophys Acta Gen Subj*, 1862(10):2261-2270. https://doi.org/10.1016/j.bbagen.2018.07.022

Worthmann A, John C, Rühlemann MC, et al., 2017. Cold-induced conversion of cholesterol to bile acids in mice shapes the gut microbiome and promotes adaptive thermogenesis. *Nat Med*, 23(7):839-849. https://doi.org/10.1038/nm.4357

Xu YXZ, Mishra S, 2018. Obesity-linked cancers: current knowledge, challenges and limitations in mechanistic studies and rodent models. *Cancers*, 10(12):523. https://doi.org/10.3390/cancers10120523

Yang F, Huang XF, Yi TS, et al., 2007. Spontaneous development of liver tumors in the absence of the bile acid receptor farnesoid X receptor. *Cancer Res*, 67(3):863-867. https://doi.org/10.1158/0008-5472.CAN-06-1078

Yang ZY, Li J, Xiong FX, et al., 2016. Berberine attenuates high glucose-induced fibrosis by activating the G protein-coupled bile acid receptor TGR5 and repressing the S1P2/MAPK signaling pathway in glomerular mesangial cells. *Exp Cell Res*, 346(2):241-247. https://doi.org/10.1016/j.yexcr.2016.06.005

Yoneno K, Hisamatsu T, Shimamura K, et al., 2013. TGR5 signalling inhibits the production of pro-inflammatory cytokines by *in vitro* differentiated inflammatory and intestinal macrophages in Crohn's disease. *Immunology*, 139(1):19-29. https://doi.org/10.1111/imm.12045

Zaborska KE, Cummings BP, 2018. Rethinking bile acid metabolism and signaling for type 2 diabetes treatment. *Curr Diab Rep*, 18(11):109. https://doi.org/10.1007/s11892-018-1092-3

Zhao SN, Gong ZZ, Zhou JF, et al., 2016. Deoxycholic acid triggers NLRP3 inflammasome activation and aggravates DSS-induced colitis in mice. *Front Immunol*, 7:536. https://doi.org/10.3389/fimmu.2016.00536

中文概要

题　目：胆汁学：从研究到临床

概　要：胆汁酸广为人知的功能是帮助脂类的消化和吸收。近几年的大量研究表明：胆汁酸除了在胆固醇代谢平衡、肝肠循环以及调节肝脏再生等方面的作用以外，还可以作为一类肠道激素调节机体的生理和病理反应，包括糖脂代谢、能量消耗、炎症、肿瘤、心血管疾病和神经系统疾病等。胆汁酸与肠道菌群关系密切，这可能也是其在各器官中发挥重要功能的原因之一。胆汁酸调节的信号主要通过其特异的胆酸核受体与G蛋白偶联的胆酸膜受体进行调节。研究表明一些药理制剂或者外科减肥手术在代谢性疾病中的疗效也是通过靶向胆汁酸信号实现的。本文主要总结了胆汁学最新的研究进展，重点关注了与胆汁酸信号通路调节相关的转化医学研究进展。

关键词：胆汁酸；肠道菌群；法尼醇受体；G蛋白偶联胆汁酸受体；代谢性疾病