Emerging roles of bile acids in control of intestinal functions

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Emerging roles of bile acids in control of intestinal functions

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Purpose of review
Bile acids and their signalling pathways are increasingly recognized as potential therapeutic targets for several diseases. This review summarizes new insights in bile acid physiology, focussing on regulatory roles of bile acids in intestinal functions.

Recent findings
Recent studies have highlighted the interactions between bile acids and gut microbiome: interfering with microbiome composition may be beneficial in treatment of liver and metabolic diseases by modulating bile acid composition, as different bile acid species have different signalling functions. In the intestine, bile acid receptors FXR, VDR and TGR5 are involved in control of barrier function, paracellular ion transport and hormone release. Specific microbial bile acid metabolites modulate immune responses of the host. In addition, new functions of bile acids in regulation of gastric emptying and satiation via brain–gut–liver axis have been discovered. Identification of Cyp2c70 as the enzyme responsible for generation of hydrophilic mouse/rat-specific muricholic acids has allowed the generation of murine models with a human-like bile acid composition.

Summary
Specific bile acids act as important signalling molecules affecting whole body metabolism, specific transport processes and immunity in different segments of the intestinal tract. Their relevance for human (patho)physiology is emerging. Novel mouse models with human-like bile acid composition will aid to accelerate translational research.

Keywords
bile acid signalling, bile acids, immunity, intestinal integrity, microbiome

INTRODUCTION

Bile acids are amphipathic steroid molecules acting as 'intestinal soaps' to facilitate intestinal absorption of fat-soluble nutrients. Beyond their well established role in lipid absorption, bile acids also exert hormone-like functions by signalling *via* nuclear and membrane-bound receptors that are involved in regulation of lipid, glucose and energy metabolism [1]. This knowledge has led to the design of pharmacological modulators of bile acid signalling pathways for treatment of cholestatic and metabolic liver diseases that are currently already in clinical use [2,3] or in advanced stages of development [4]. In the past 2 years, a number of intriguing novel functions of bile acids have been discovered, particularly in association with the expanding insights into the role of the microbiome in health and disease. The multiple signalling functions of bile acids are mediated by bile acid receptors that are expressed in liver, gut as well as in several peripheral organs and tissues. Established bile acid receptors include farnesoid X receptor (FXR), G protein-coupled bile acid receptor (TGR5), pregnane X receptor (PXR), constitutive androstane receptor (CAR), vitamin D receptor (VDR), sphingosine-1-phosphate receptor-2 (S1P2R) and muscarinic acetylcholine receptor M3 (M3R) [1]. These receptors bind different bile acid species with different affinities, implying that the composition of the bile acid pool and the concentrations of specific bile acid species at specific locations are of (patho)physiological importance. In this review, we focus on newly

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KEY POINTS

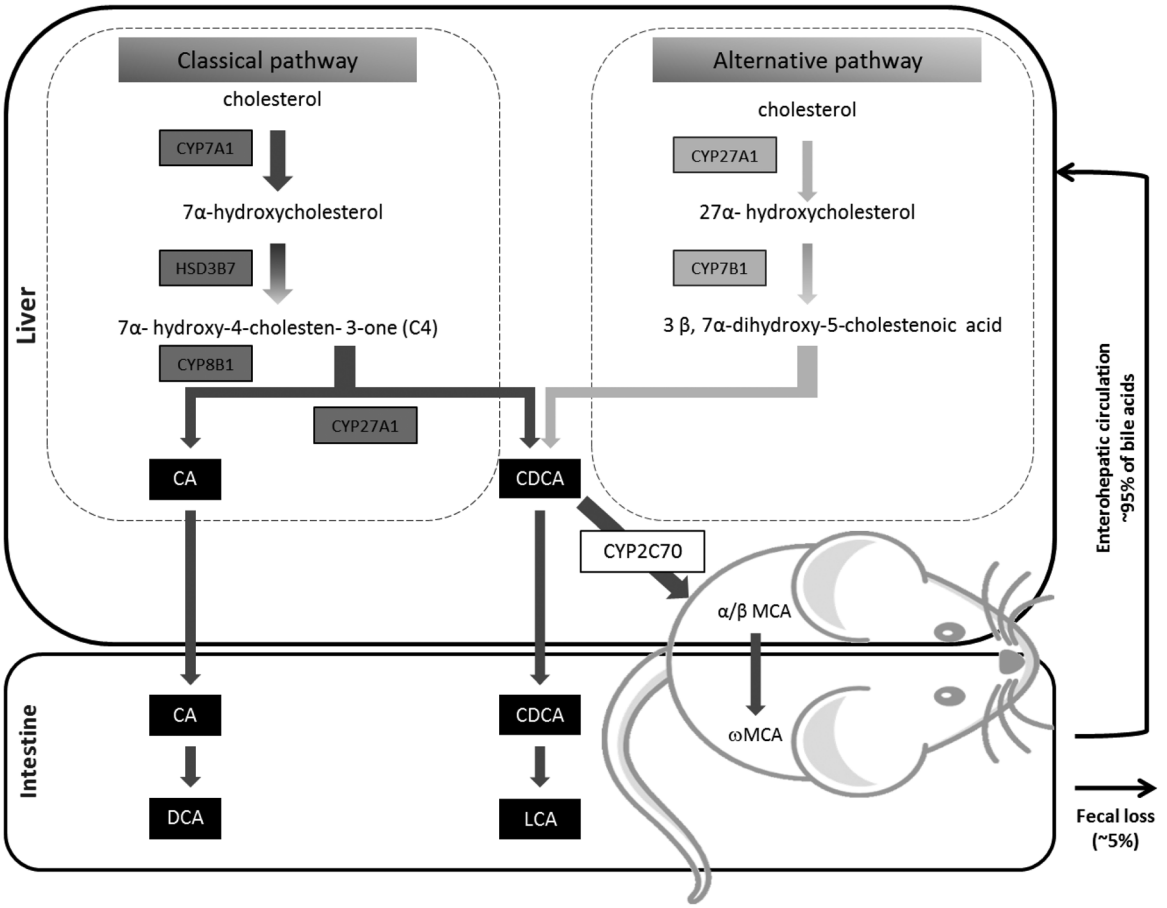
- Different bile acid species, which can originate from microbial metabolism, have different signalling properties through activation of receptors such as FXR, VDR and TGR5, which are expressed in various tissues and organs within but also outside the gastrointestinal system.
- Mouse model with humanized bile acid metabolism (Cyp2c70KO mice) have been developed to allow more accurate translation of bile acid related aspects of metabolism.
- Bile acids regulate the integrity of intestinal barrier and specific secondary bile acids modulate adaptive immunity.
- Composition of the murine bile acid pool modulates intestinal lipid sensing and thereby gastric emptying and satiation through gut hormones GLP-1 and PYY.
- Gut microbes influence bile acid composition and bile acids modulate the gut microbial community structure.

identified functions of BAs in the intestine, a major limb of the enterohepatic circulation and the site of intensive bile acid structure modulation.

BILE ACID BIOSYNTHESIS, TRANSPORT AND METABOLISM

BAs are synthesized from cholesterol in the liver *via* now well defined pathways. Human livers produce cholic acid (CA) and chenodeoxycholic (CDCA) acids as primary bile acid s, whereas murine livers primarily synthesize CA and α and β-muricholic acids (MCAs) [5]. These primary bile acids are conjugated to glycine or taurine, actively secreted into the bile, stored in the gallbladder and, after meal ingestion, released into the small intestine to facilitate the absorption of dietary lipids and fat-soluble vitamins. The majority of these bile acids will be actively reabsorbed by the ileal bile acid transporting machinery, but a small part will enter the colon to interact with the microbiome that is able to modify bile acid structures, leading to formation of so-called secondary bile acids, of which deoxycholic acid (DCA) and lithocholic acid (LCA) are most prominent. Part of the secondary bile acid species will be passively absorbed from the colon and, together with bile acids absorbed from the ileum, transported to the liver via the portal venous circulation, to be taken up and resecreted into the bile (Fig. 1). Consequently, the bile acid pool consists of a mixture of primary and secondary species that cycle between liver and the intestine within the enterohepatic circulation. The relatively small fraction of bile acids that escapes intestinal absorption and is lost *via* faeces is compensated for by hepatic bile acid synthesis to maintain bile acid pool size. Various transporters involved in enterohepatic cycling of bile acid have been identified over the years and insight in their regulation, in several cases by the actions of bile acid activated nuclear receptors, has greatly expanded [1]. Some of these transporters have been identified as potential drug targets. In the ileum, the majority of bile acids is actively reabsorbed by the apical sodium-dependent bile acid transporter (ASBT, SLC10A2). Pharmacological inhibition of ASBT has been shown to effectively reduce bile acid pool and bile acid content in liver and systemic circulation and several ASBT inhibitors have already been tested in clinical trials to treat cholestatic liver diseases such as biliary atresia, progressive familial intrahepatic cholestasis and Alagille syndrome as well as chronic constipation and NASH [6,7]. The high expression and high uptake capacity of ASBT in ileum makes this transporter also a promising target for delivery of prodrugs [8]. Basolateral uptake of bile acids from portal blood into the hepatocytes is mainly mediated by Na^+-taurocholic acid cotransporting polypeptide (NTCP, SLC10A1). Donkers *et al.* [9] recently demonstrated that NTCP-deficiency in mice, which leads to elevated systemic bile acid concentrations, is associated with increased energy expenditure. These authors also propose that pharmacological inhibition of NTCP-mediated bile acid uptake by Myrcludex B might represent a novel therapeutic approach for treatment obesity and hepatic steatosis [10].

It is now evident that many of the bile acid mediated signalling cascades are primarily activated by relatively hydrophobic bile acid species, such as CDCA and secondary DCA and LCA, implying an important role of the microbiome in the determining an individual's 'endogenous signalling capacity'. Conversely, relatively hydrophilic bile acid species may actually exert opposing effects: it has been demonstrated that the mouse/rat-specific MCAs [11] as well as tauroursodeoxycholic acid [12] may actually act antagonistic rather than agonistic on the prominent bile acid activated receptor FXR. Our laboratory has very recently demonstrated that fasting plasma bile acid profiles showed a remarkably large inter-individual variability in a cohort of 300 obese individuals [13▪]. A total of 27 independent genetic associations to 23 bile acid entities were identified at genome-wide level, including transcription factor-related genetic variants as potential novel genetic determinates of human bile acid metabolism. Importantly, 439 microbial associations to 45 bile acid entities were



Bile acid composition

Human		**Mouse**	
Cholic acid (3α,7α,12α-OH)[1]	~ 45%	Cholic acid (3α,7α,12α-OH)[1]	~ 56%
Chenodeoxycholic acid (3α,7α-OH)[1]	**~ 28%**	Chenodeoxycholic acid (3α,7α-OH)[1]	**~ 2%**
Deoxycholic acid (3α,12α-OH)[2]	~ 23%	α-Muricholic acid (3α,6β,7α-OH)[1]	~ 5%
Lithocholic acid (3α-OH)[2]	~ 1%	β-Muricholic acid (3α,6β,7β-OH)[1]	~ 25%
Ursodeoxycholic acid (3α, 7β–OH)	~ 3%	ω-Muricholic acid (3α,6α,7β-OH)[2]	~ 5%
		Ursodeoxycholic acid(3α,7β-OH)[1/2]	~ 1%
		Deoxycholic acid (3α,12α-OH)[2]	~ 5%
		Lithocholic acid (3α-OH)[2]	~ 0%
		Others	~ 1%
Taurine/glycine ratio	30/70	*Taurine/glycine ratio*	99/<1
BA synthesis rate (μmol kg^{-1} day^{-1}):	~ 20	*BA synthesis rate (μmol kg^{-1} day^{-1})*:	~ 100

FIGURE 1. Differences in bile acid metabolism between humans and mice: the murine bile acid pool is more heterogeneous in composition and more hydrophilic in nature.

also identified, involving well known bacterial bile acid modifiers as *Eubacterium hallii* as well as new bacterial modifiers like *Ruminococcus sp_5_1_39BFAA*, a species associated with secondary bile acids [13▪]. The metabolic pathway involved in 7α-dehydroxylation of primary cholic acid to secondary DCA has recently been established in detail [14▪]. Using an elegant anaerobic in-vitro reconstitution system, it

was shown that a set of six enzymes is required for the eight-step conversion of cholic acid into DCA. The demonstrated ability to engineer this pathway functionally into a nonproducing commensal opens avenues to modulate human bile acid composition for therapeutic applications. Intriguingly, microbes were also found to be able to produce novel amino acid-bile acid conjugates such as phenylalanocholic and leucocholic acids [15]. These bile acids were found in humans, particularly in patients with inflammatory bowel disease or cystic fibrosis and were shown to activate FXR *in vitro* and to suppress bile acid synthesis *in vivo* when given to mice. Evidently, their potential (patho)physiological roles, if any, remain to be established.

Current knowledge of molecular mechanisms by which bile acids exert their metabolic effects mainly derives from studies in (genetically engineered) mice. However, fundamental differences in bile acid composition between humans and mice, particularly the presence of hydrophilic MCAs in the latter (Fig. 1), hamper translation of preclinical outcomes to the human situation. The identification of Cyp2c70 as the enzyme responsible for the production of MCAs in mice [16] has allowed for the generation of novel mouse models with a 'humanized' bile acid metabolism [17,18,19▪]. De Boer *et al.* [19▪] established a mouse model in which Cyp2c70 can be inactivated in adult mouse livers through CRISPR/Cas9 technology (Cyp2c70AKO). Cyp2c70AKO mice showed a strong reduction in mouse-specific β- and ω-MCAs, the expected increase of CDCA and an augmented amount of UDCA in their bile acid pool and, accordingly, a more human-like and hydrophobic plasma bile acid profile [17,19▪]. It was demonstrated that Cyp2c70 is responsible for hydroxylation as well as epimerization the hydroxyl group at the C6 position to produce β-MCA. The hydrophobic bile acid pool of Cyp2c70AKO mice clearly affected the response to pharmacological FXR activation with PX20606 on transintestinal intestinal cholesterol excretion, underscoring the translational relevance of this model. Honda *et al.* [18] evaluated the joint roles of Cyp2c70 and Cyp2a12 in murine livers by generating Cyp2c70KO and Cyp2c70/Cyp2a12 doubleKO mice. Their results confirm that Cyp2c70 is responsible for CDCA hydroxylation to MCAs and demonstrate that Cyp2a12 mediates rehydroxylation of DCA and LCA [17,18]. The latter reaction does not occur in human liver. Straniero *et al.* [20] also evaluated the effects of deletion of the Cyp2c70 gene and confirmed that plasma of Cyp2c70KO mice was completely devoid of MCAs; Cyp2c70KO mice showed more than 50% reductions in bile acid and cholesterol synthesis and in hepatic LDL receptors and, consequently, a significant increase in serum LDL cholesterol.

BILE ACID SIGNALLING AND ADAPTIVE IMMUNITY

In the past year, a remarkable series of observations also revealed an important link between microbial bile acid metabolism and *adaptive* immunity [21▪,22,23,24▪▪]. By screening a library of bile acid metabolites, Hang *et al.* [23] identified two distinct metabolites of LCA, 3-oxoLCA and isoalloLCA, as T cell regulators. Interestingly, 3-oxoLCA suppressed differentiation of T helper (T_H17) cells by direct binding to the transcription factor RORγt, while isoalloLCA promoted differentiation of regulatory T (Treg) cells by stimulation of mitochondrial ROS production leading to increased expression of FOXP3. Importantly, feeding of mice with either 3-oxoLCA or isoalloLCA indeed reduced T_h17 cell differentiation and increased T_{reg} differentiation, respectively, in the ileal lamina propria. Song *et al.* [24▪▪] searched for the mediators of the diet-dependent induction of a distinct population of $FOXP3^+$ T_{reg} cells that express RORγ, that is $ROR\gamma^{+-}$ T_{reg} cells, that are critical in the maintenance of immune homeostasis in the colon: convential mice fed a nutrient-rich diet showed much higher numbers of these cells than convential mice fed a minimal diet and than germ-free mice fed the rich diet, the latter implying a role for the microbiome. Colonic concentrations of bile acid were higher in both convential (primary and secondary bile acid) and germ-free (primary bile acid only) mice fed the rich diet, suggesting a role for secondary bile acid formed by the microbiome in $ROR\gamma^+T_{reg}$ cell induction. The latter was confirmed by bile acid feeding experiments and bioengineering experiments in which it was shown that bacterial species capable of inducing $ROR\gamma^+T_{reg}$ cells induction lost this ability after genetic deletion of the enzyme bile acid hydrolase that catalyzes the obligatory first step in secondary bile acid formation. Studies employing several bile acid receptor deficient mice revealed that VDR mediates $ROR\gamma^+T_{reg}$ cell after its activation by secondary bile acids, whose identities were not revealed in this study. Indeed, VDR is highly expressed in the $ROR\gamma^+T_{reg}$ population and LCA and 3-oxoLCA are potent bile acid activators of VDR. The pathophysiological relevance of this bile acid-VDR signalling axis was demonstrated by showing that mice fed the minimal diet were more vulnerable to DSS-induced colitis than mice fed the rich diet and that lack of VDR worsened DSS-induced colitis. Finally, Campbell *et al.* [21▪] reported that particularly 3β-hydroxydeoxycholic

acid (isoDCA), a relatively low abundant secondary bile acid, has a strong ability to potentiate the differentiation of peripherally-induced T_{reg} (pT_{reg}) cells. IsoDCA increased FOXP3 induction through its action on dendritic cells to diminish their immune-stimulatory properties, with involvement of isoDCA-FXR signalling in this process. Using a synthetic biology approach, it was shown that isoDCA-producing microbial consortia increased the numbers of $ROR\gamma^{+}T_{reg}$ cells in the colon. Overall, these studies underscore the (patho)physiological importance of microbiome-derived bile acids as signalling molecules, now also in control of adaptive immunity. LCA may also exert protective effects on the intestinal epithelial barrier function mediated *via* VDR [25], while Song *et al.* [26]. showed that bile acid improves ileal tight junction via an FXR–MLCK signalling pathway. FXR also controls proliferation of Lgr5+ intestinal stem cells: Fu *et al.* [27▪▪] showed that an intestine-specific FXR agonist restricts abnormal Lgr5+ cell growth in jejunum and ileum and prevents colorectal cancer progression induced by high intestinal bile acid levels (Fig. 2). It will be of interest to assess whether the large inter-individual variations in human bile acid pool size and composition [13▪] translate into inter-individual differences in immunity and whether engineering of microbial activities may be useful for the treatment of inflammatory disorders such as colitis.

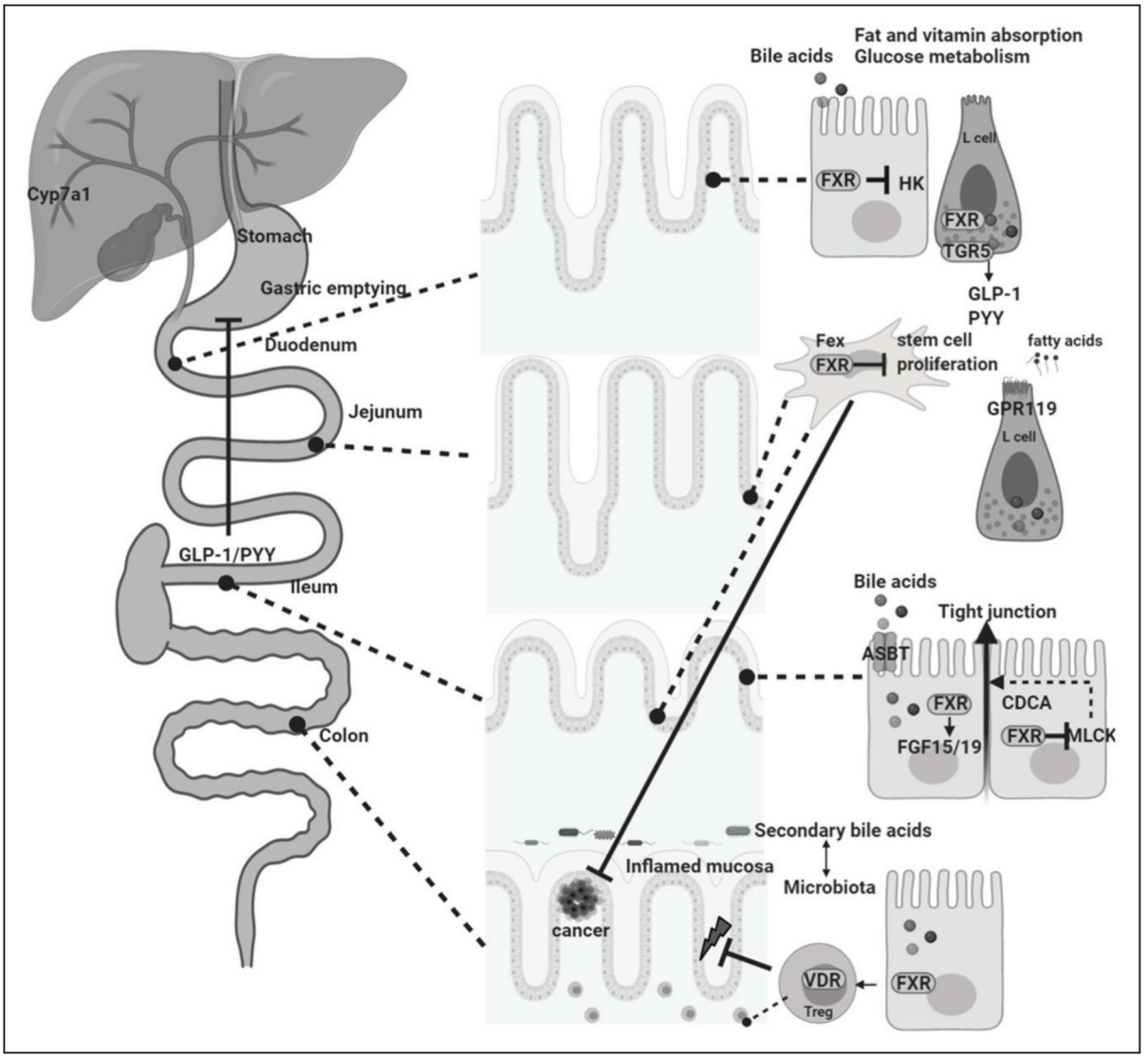


FIGURE 2. Roles of bile acids in different segments of the intestinal tract. ASBT, apical sodium dependent bile acid transporter; Cyp7a1, cholesterol 7 alpha-hydroxylase; Fex, fexaramine; FGF15/19, fibroblast growth factor 15/19; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide 1; MLCK, myosin light-chain kinase; PYY, peptide tyrosine tyrosine; TGR5, G protein-coupled bile acid receptor; VDR, vitamin D receptor.

NEW ROLES OF INTESTINAL BILE ACIDS IN METABOLIC CONTROL

Several segments of the intestine contribute to energy homeostasis by production of gut hormones such as CCK and GLP-1 to modulate gastric emptying, food intake and insulin actions, amongst others. It is now evident that bile acids are *directly* involved in control of these crucial intestinal functions, for example, by TGR5 and FXR-mediated regulation of GLP-1 secretion [28] (Fig. 2). Recent work indicates that bile acid may also *indirectly* regulate food intake and satiety by modulating small intestinal lipid sensing. Higuchi *et al.* [29▪▪] demonstrated the impact of *Cyp8b1*-depletion on intestinal lipid sensing and diet-induced obesity in mice. *Cyp8b1*-deletion translates into a bile acid pool enriched in hydrophilic, mouse-specific MCAs. Due to this hydrophilic bile acid composition, inefficient fat absorption caused more free fatty acids and 2-monoacylglycerol to reach the distal intestine wherein they activated G-protein coupled receptor (GPR)119, leading to increased GLP-1 and PYY secretion, impaired gastric emptying and reduced appetite in *Cyp8b1*KO mice. Due to impaired fat absorption and lower food consumption, *Cyp8b1*-deficient mice were protected against high-fat diet-induced weight gain and insulin resistance. Intriguingly, a similar phenotype with impaired fat absorption, increased incretin secretion and reduced food intake was recently described in intestine-specific CTα-deficient mice with impaired intestinal phosphatidylcholine synthesis [30], delineating the (patho)physiological relevance of (in)efficient intestinal fat absorption. It should be realized that in humans, a reduction of CYP8B1 activity would translate into a more *hydrophobic* bile acid pool with a higher lipid-solubilizing capacity and with substantially different signalling characteristics compared to Cyp8b1-deficient mice.

Recent studies have demonstrated mutual interactions between bile acids and microbiome: gut microbes influence bile acid composition and, in turn, bile acid modulate the gut microbial community structure [31,32,33▪]. Adjusting composition and functionality of the intestinal microbiome has becomes an attractive target for therapeutic interventions. Faecal transplantation clearly modulates plasma bile acid profiles [34]. Faecal transplantation was also shown to largely restore the antibiotics-associated disruption of bile acid metabolism [35]. The clinical use of FXR agonist OCA and secondary bile acid UDCA for the treatment of liver diseases modulates intestinal microbiome [32,36]. Interestingly, UDCA has sex-specific effects on stool microbial community composition [36]. Sex difference should be considered as an important factor in future studies related to gut microbiome and bile acids.

CONCLUSION

In this review, we have provided recent advances in our knowledge of the diverse physiological roles of bile acids, especially those exerted in the intestine with respect to immunity, intestinal barrier integrity, gastric emptying and satiation, and gut microbiome composition. It is anticipated that additional roles of specific bile acids will be identified in the coming years and that interference with bile acid signalling pathways will provide new avenues of treatment for a variety of disorders.

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Conflicts of interest

The authors declare no conflicts of interest.

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