Effect of different bile acids on the intestine through enterohepatic circulation based on FXR

Junwei Xiang, Zhengyan Zhang, Hongyi Xie, Chengcheng Zhang, Yan Bai, Hua Cao, Qishi Che, Jiao Guo, and Zhengquan Su

ABSTRACT
Farnesoid X receptor (FXR) is a nuclear receptor for bile acids (BAs) that is widely expressed in the intestine, liver, and kidney. FXR has important regulatory impacts on a wide variety of metabolic pathways (such as glucose, lipid, and sterol metabolism) and has been recognized to ameliorate obesity, liver damage, cholestasis and chronic inflammatory diseases. The types of BAs are complex and diverse. BAs link the intestine with the liver through the enterohepatic circulation. BAs derivatives have entered clinical trials for liver disease. In addition to the liver, the intestine is also targeted by BAs. This article reviews the effects of different BAs on the intestinal tract through the enterohepatic circulation from the perspective of FXR, aiming to elucidate the effects of different BAs on the intestinal tract and lay a foundation for new treatment methods.

Introduction
Bile acids (BAs) are important signaling molecules involved in glucose metabolism, lipid metabolism and energy consumption.1–3 BAs dysregulation and impaired BAs receptor transduction are associated with liver and intestinal diseases, such as steatohepatitis, hepatocellular carcinoma, enteritis and colorectal cancer.4–6 In 1999, BAs were discovered to be endogenous ligands of farnesoid X receptor (FXR),7,8 which is widely expressed in the intestine, liver, and kidney.9,10 BAs are generated in the liver and stored in the gallbladder. Postprandially, BAs are secreted into the intestine and metabolized by the intestinal flora. However, 95% of the BAs are reabsorbed in the ileum and returns to the liver for entry into the enterohepatic circulation. Another 5% of BAs are excreted in feces.11,12 BAs can maintain their own synthesis, metabolism and homeostasis by regulating FXR and related pathways.13

BAs have different chemical structures, and the conversion between these chemical structures are mediated primarily by the conjugation of amino acids and the metabolism by microorganisms. The four known mechanisms of microbial BA metabolism are dehydroxylation, dehydration and epimerization of cholesterol, and deconjugation of amino acids.14,15 A recently published study systematically analyzed the effects of microorganisms on the mouse metabolome using mass spectrometry analysis and data visualization methods. Researchers have discovered a new type of amino acid-conjugated BA, which represents a fifth and completely different mechanism of microbial-mediated BA transformation: amide conjugation of the cholate backbone with amino acids phenylalanine, tyrosine and leucine. Moreover, researchers confirmed that the resulting BAs are also present in humans and are more common in patients with inflammatory bowel disease and cystic fibrosis. Cells and mouse experiments have shown that these BAs may affect host physiology by acting on the FXR pathway.16 The latest research has revealed the signaling pathway of gut microbe-mediated cholic acid (CA) dehydroxylation. CA can be used to
induce of 7α-dehydroxylation, through which it can be converted into deoxycholic acid (DCA) over time in the presence of a mixture of 8 Bai enzymes, β-nicotinamide adenine dinucleotide (NAD+), coenzyme A and ATP, without the requirement for additional enzymes. This process provides possible opportunities for controlling BA metabolism and synthesizing related metabolic molecules. Studies have shown that the BA composition varies across species. The main BAs in human bile are CA (30%-40%), DCA (20%-30%) and chenodeoxycholic acid (CDCA) (30%-40%). In mice, the main BAs are CA and MCA. In rodents, DCA produced by dehydroxylation in the intestine can be rehydroxylated to generate CA. However, rehydroxylate does not occur in humans; therefore, humans have higher levels of secondary BAs such as DCA. BAs are not present in invertebrates but are present in all vertebrates. The conjugation of BAs varies greatly among species. BAs in mice are mainly conjugated with taurine, while those in humans are conjugated with glycine and taurine at a ratio of 5:1.

Currently, some BAs have been used in clinical treatment, usually for hepatobiliary diseases. A highly effective FXR agonist, 6-ethylchenedoxycholic acid (6-ECDCA), was recently highlighted for the treatment of primary biliary cholangitis (PBC), and is in late-stage clinical trials for non-alcoholic steatohepatitis (NASH). Obeticholic acid (OCA) is an agonist of FXR. Clinical trials have shown that OCA can improve the characteristics of liver tissue, and OCA is the only investigational drug for NASH that has been awarded the designation of breakthrough treatment. But the long-term efficacy and safety still need to be further confirmed. OCA is still approved to treat PBC that does not respond to UDCA. Itching has also been observed in some patients with PBC under treatment with OCA, although the mechanism is unclear. In some PBC patients with obvious liver damage, taking OCA that exceeds the prescription can cause further deterioration of liver function and death, suggesting that the liver toxicity of FXR agonists should not be ignored. Some researchers have speculated whether targeted intestinal transport of BAs or FXR antagonism could improve the therapeutic. Recently, some researchers have discovered a new mechanism for OCA to treat NASH by inhibiting the activity of NLRP3 inflammasome in macrophage. These findings indicated that liver FXR is a viable therapeutic target for the development of drugs to treat human liver diseases; however, the potential of FXR as a drug target for intestinal diseases remains to be explored, although its prospects are bright. The intestine is a complex ecosystem and intestinal dysfunction is a serious threat to the health of the host. Generally, intestinal dysfunction is related to inflammatory bowel disease, irritable bowel syndrome, necrotizing enterocolitis, and even intestinal cancer. BAs are important emulsifiers that facilitate the absorption of fats and fat-soluble vitamins. Therefore, they are called “cleanser” of the intestine. Studies have demonstrated that FXR is a nuclear receptor that plays an important role in maintaining BA metabolism and lipid and sugar homeostasis. Moreover, FXR is an important target for treatments related to BA homeostasis. Recently, new functions of FXR have been discovered, including intestinal barrier protection, regulation of innate immunity and regulation of tumorigenesis. Thus, BAs is not only based on FXR acting on the liver and gallbladder through enterohepatic circulation, but also may be based on FXR acting on related molecules to treat intestinal diseases.

The mechanism of action between BAs and intestinal diseases still needs in-depth study. Current research indicates that modulating interaction among the microbiota, BAs and FXR is a promising therapeutic approach for the treatment of metabolic diseases. Therefore, this article reviews the effects of different BAs on the intestinal tract through the enterohepatic circulation via FXR to improve the treatment of intestinal diseases in the future.

**BAs and enterohepatic circulation**

**Classification of BAs**

As an endogenous signaling molecules regulating lipid, sterol, glucose and energy metabolism, BAs play important roles in many pathological and physiological activities. BAs have different chemical
structures (Figure 1), which are complex and diverse. These complex structures of BAs are the key to their different physiological functions.

Based on whether they are conjugated with glycine or taurine, BAs are classified as conjugated BAs and unconjugated BAs. Notably, human BAs are conjugated with glycine and taurine, while rodent BAs are conjugated with taurine. 7

BAs are also classified as primary BAs and secondary BAs based on their source. 17 The primary BAs synthesized in the human liver are CA and CDCA. Notably, CA, CDCA, UDCA, α-MCA and β-MCA are synthesized in mice. 38 Primary conjugated BAs are first hydrolyzed by bile salt hydrolase (BSH) to generate unconjugated BAs; UDCA is then generated through epimerization, and secondary BAs are then generated through dehydroxylation catalyzed by 7α-dehydroxylase. In humans, secondary BAs include DCA and LCA. However, in rodents, hyocholic acid (HCA), murideoxycholic acid (MDCA), ω-MCA, hyodeoxycholic acid (HDCA), DCA and LCA can be produced.

BA molecules contain a hydrophilic pole (hydroxyl and carboxyl groups) and a hydrophobic pole (alkyl group). Due to the different modifications of their surface structure, BAs can have both a hydrophilic surface and a hydrophobic surface; that is, BAs have amphipathic properties. Hydrophilic BAs include UDCA and taurodeoxycholic acid (TDCA); hydrophobic

| Bile acid | R_1 | R_2 | R_3 | R_4 (Conjugation) |
|-----------|-----|-----|-----|-------------------|
| CA        | H   | α-OH| OH  | TCA    | GCA     |
| HCA       | α-OH| α-OH| H   | THCA   | -       |
| αMCA      | β-OH| α-OH| H   | T-αMCA | -       |
| βMCA      | β-OH| β-OH| H   | T-βMCA | -       |
| ωMCA      | α-OH| β-OH| H   | T-ωMCA | -       |
| UDCA      | H   | β-OH| H   | TUDCA  | GUDCA   |
| CDCA      | H   | α-OH| H   | TCDC    | GCDC    |
| DCA       | H   | H   | OH  | TDCA   | GDCD    |
| LCA       | H   | H   | H   | TLCA   | GLCA    |
| MDCA      | β-OH| H   | H   | -      | -       |
| HDCA      | α-OH| H   | H   | -      | -       |

Figure 1. Structure diagram of bile acids. Abbreviations: Cholic acid (CA), Hyodeoxycholic acid (HCA), α-Muricholic acid (α-MCA), β-Muricholic acid (β-MCA), ω-Muricholic acid (ω-MCA), Ursodeoxycholic acid (UDCA), Chenodeoxycholic acid (CDCA), Deoxycholic acid (DCA), Lithocholic acid (LCA), Murideoxycholic acid (MDCA); Hyodeoxycholic acid (HDCA).
BAs include DCA, LCA and CDCA. Generally, different forms of BAs play different roles in organisms.

**FXR**

BAs are produced in the liver through the breakdown of cholesterol and are then further metabolized by the intestinal flora to produce a set of chemically heterogeneous steroids. These steroids bind and activate members of cell surface and nuclear receptor families, collectively referred to as BA-activated receptors. BA-activated receptors include FXR, Takeda G protein-coupled receptor 5 (TGR5), liver X receptor (LXR), pregnane X receptor (PXR), vitamin D receptor (VDR), constitutive androstane receptor (CAR), cholinergic receptor muscarinic 2 (CHRM2), et al. Among these receptors, FXR is the most important receptor that controls the BA, affects the transport of BA, and regulates the homeostasis of BA. FXR is the bridge between the liver and intestines to control the level of BAs and regulate the concentration of BAs in the enterohepatic circulation. FXR regulates the expression of genes involved in BA synthesis and transport in the liver and intestines and is thus the main modulator of BA homeostasis and enterohepatic circulation. FXR affects the concentration of BAs in various ways, mainly to regulate their synthesis, metabolism, recovery and transport of BAs. FXR regulates BAs through the enterohepatic circulation mainly via 3 main pathways: the small heterodimer partner (SHP) pathway, the mouse fibroblast growth factor 15 or fibroblast growth factor 19 (FGF15/FGF19) pathway and the c-Jun N-terminal kinase (JNK) pathway. Liver FXR activation increases the expression of the target gene SHP, which leads to the inhibition of cholesterol 7α-hydroxylase (CYP7A1) and sterol 12α-hydroxylase (CYP8B1). Interestingly, in Shp-null mice, BAs were shown to inhibited the expression of CYP7A1. This finding indicates that transcriptional inhibition of CYP7A1 by BAs involves other pathways that depend on not only SHP. Intestinal FXR activation by BAs can increase the expression of the intestinal FGF15/FGF19, induce these proteins to enter the liver through the enterohepatic circulation, act on fibroblast growth factor receptor 4 (FGFR4), activate the JNK signaling pathway, inhibit the expression of CYP7A1, reduce BA synthesis, and improve cholestasis. However, the expression of CYP7A1 in Fgfr4-null mice was found to be increased, as was the BA pool, further indicating that increased expression of FGF15 and FGFR4 inhibits the synthesis of BAs. Intestinal FXR can also reduce the absorption of BAs by epithelial cells of the small intestinal mucosa and inhibit the enterohepatic circulation of BAs to further reduce the BA toxicity in hepatocytes and maintain BA homeostasis.

Numerous studies in mice have shown that Fxr-null is related to the pathological processes of many serious diseases. Liver Fxr-null mice showed elevated serum cholesterol and triglyceride levels and elevated levels of circulating free fatty acids, leading to abnormal glucose metabolism and severe fatty liver. Studies have indicated that intestinal Fxr-null mice is resistant to HFD-induced obesity, insulin resistance and NAFLD; thus, intestinal FXR has been confirmed to be related to exacerbation metabolic diseases.

FXR has a typical nuclear receptor structure. It consists of an N-terminal ligand-independent transcription activation function 1 (AF1) domain, a DNA binding domain (DBD), a ligand binding domain (LBD), a carboxy-terminal ligand-dependent transcription activation function 2 (AF2) domain, and a hinge region (Figure 2). FXR can bind to many endogenous BAs, including

![Figure 2](image-url)
CDCA, taurocholic acid (TCA), DCA, LCA, CA and polyphenolic acid. However, the pleiotropic downstream effects of FXR vary across BAs, and the metabolic effects of different BA receptors in different organs are also vary. The strength of the natural activators of FXR follows the order of CDCA > DCA > CA > LCA, and the natural inhibitors of FXR are tauro-α-MCA (T-α-MCA), tauro-β-MCA (T-β-MCA) and UDCA. Notably, glycodeoxycholic acid (GCDCA), TCA and TDCA are weak activators of FXR. Compared with conjugated BAs, unconjugated BAs have a stronger ability to activate FXR. These results may be explained by the different structures of BAs or the different mechanisms of binding to FXR; that is, the type and content of BAs produced in the body may regulate the expression of FXR. Therefore, it is important to consider the different mechanisms of different BAs and to link different types of BAs with specific diseases to provide valuable guidance for the diagnosis and clinical treatment of related diseases.

**Enterohepatic circulation of BAs**

BAs are the intermediates between the intestine and liver. BAs are the final product of cholesterol catabolism. Primary BAs are synthesized in hepatocytes through the classical or alternative pathway, conjugated with amino acids and secreted into the bile duct via bile salt export protein (BSEP). Postprandially, BAs are secreted into the duodenum through the biliary tract. Conjugated BAs are dehydroxylated under the action of the intestinal flora and BSH to generate secondary BAs. Approximately 95% of BAs are reabsorbed by intestinal cells in the terminal ileum through the apical sodium-dependent bile acid transporter (ASBT) and are transported to hepatocytes through the portal vein; this route is referred to as the enterohepatic circulation. However, approximately 5% of the remaining BAs content undergoes oxidation by microbes in the colon for side chain modification and is then excreted in the feces. (Figure 3)

Under physiological conditions, the taurine/glycine conjugates in the side chain of BAs can be removed under the action of intestinal microorganisms. Intestinal microorganisms can oxidize or dehydroxylate the hydroxyl groups at C3, C7 and C12 in the BA molecular structure to form unsaturated BAs, and can also convert BAs via carbonyl reduction or epimerization. Approximately 5% of enterically secreted BAs, including polyphenolic acid (PPA), are absorbed at the ileum, and the remaining BAs are absorbed at the colonic mucosa.

**Effects of different BAs on the intestine**

**Roles of BAs in cells**

The dynamic balance among intestinal epithelial cells, the intestinal flora and the intestinal mucosa is very important for maintaining intestinal permeability and normal tissue function. BAs have amphiphilic properties, and when combined with polar phospholipids, dietary lipids can be incorporated into the mixed solution in the intestinal lumen. This incorporation results in a micellization process, which is essential for fat absorption and systemic energy balance. In cells, BAs can be inserted into cell membranes, including plasma membranes; supraphysiological doses can also damage cell membranes and cause cell lysis. The hydrophobicity of BAs determines their cytotoxicity, which decreases in the following order: UDCA < CA < CDCA < DCA < LCA. Hydrophobic BAs have high affinity for lipids and can damage mitochondria. DCA can colocalize
with the outer mitochondrial membrane and disrupt its structure. Hydrophobic BAs have been shown to cause HepG2 cell apoptosis through endoplasmic reticulum stress. N-acyl phosphatidylethanolamine D (NAPE-PLD), an enzyme expressed in the brain and intestines, can convert membrane lipids into unique active lipids, and hydrophobic substrates can bind and stabilize NAPE-PLD. LCA has been shown to inhibit NAPE-PLD, while CDCA and DCA have been shown to activate NAPE-PLD; these differences may be attributed to the different hydroxyl sites in different BAs.\textsuperscript{7}

Enterocendocrine L cells are chemical sensors located in the intestinal epithelium that can sense BAs, monosaccharides, fatty acids and their microbial metabolites.\textsuperscript{77} L cell hormones are secreted according to changes in the intestinal

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Figure 3. Synthesis and transformation of BAs in liver and intestine. Abbreviations: cholesterol 7α-hydroxylase (CYP7A1); sterol 27-hydroxylase (CYP27A1); oxysterol 7α-hydroxylase (CYP7B1); sterol 12α-hydroxylase (CYP8B1); acyl-CoA oxidase 2(ACOX2); bile acid–CoA: amino acid N-acyltransferase (BAAT); bile salt hydrolase (BSH); 3β-hydroxy-Δ5-C27-steroid dehydrogenase (HSD3B7); D-bifunctional protein (HSD17B4).
microenvironment, and the steady-state regulation of BAs affects the intestinal microenvironment. Niss Kristoffer et al. used proteomic and gene expression data from GLUTag L cells to suggest that FXR is a multifaceted activating factor in L cells, but the mechanism by which FXR regulates intestinal L cell metabolism is unclear.

Hang Saiyu et al. screened nearly 30 primary and secondary BA compounds and found two derivatives of LCA: 3-oxoLCA and isoalloLCA. 3-OxoLCA can differentiate IL-17a-expressing T helper cells (Th17 cells) by directly binding to its key transcription factor retinoid-related orphan receptor γt (RORγt), while isoalloLCA can enhance Treg cell differentiation through the production of mitochondrial reactive oxygen species (mitoROS). This finding suggests that BA metabolites can directly regulate the balance of Th17 and Treg cells, thereby regulating host immunity. Soon afterward, a new study showed that BA metabolites generated by the intestinal flora can induce the production of Treg cells and that these two components form a complex regulatory network to maintain the balance of the intestinal mucosal immune response. This study showed that in the presence of dendritic cells (DCs), 3-oxoDCA is less effective than isoDCA in promoting Treg cell proliferation and that 6-oxo-MCA is less successful than ω-MCA in promoting Treg cell proliferation. This pattern indicates that epimerization may play an important role in the biotransformation of BAs in the presence of bacterial flora. Ultimately, this study further revealed the effect of secondary BA metabolites of intestinal microorganisms on Treg cells and proved that isoDCA limits the activity of FXR in DCs and exerts an anti-inflammatory effect. In addition, intestinal Paneth cells modulate innate immunity. Studies have found that Western diets rely on Clostridium-mediated increase in DCA levels in the ileum, as well as excessive transduction of FXR and type I interferon signals in intestinal epithelial cells, which leads to Paneth cell dysfunction in humans and mice. This study reveals the link between poor diet and innate immunity in the gut. These studies clearly reveal the importance of BAs in shaping the host immune system.

**Effects of BAs on the intestinal mucosa**

The destruction of BA homeostasis plays a key role in intestinal inflammation. Indeed, accumulating evidence indicates that BA metabolism disorders are related to malnutrition and mucosal inflammation. In addition, studies have shown that a lack of intestinal FXR leads to increased intestinal permeability and decreased intestinal mucosal integrity. The enterohepatic circulation regulates BA synthesis and the BA pool size through the joint action of FXR and FGF19. In the ileum, BA-dependent FXR activation induces the expression of the intestinal factor FGF19. The first study revealing that FGF19-M52 can protect mice with FXR function against colitis proved that the FXR-FGF19-M52 axis plays a role in regulating the relative content of CDCA and CA by reducing BA synthesis. However, interestingly, systemic and local anti-inflammatory activity was abolished in *Fxr-null* mice, emphasizing the necessity of FXR. These results also showed that FXR is closely related to the integrity of the intestinal epithelial barrier and the suppression of inflammatory immune responses. This study assessed preclinical treatment of experimental colitis with FXR-FGF19 and BAs.

Regarding DCA, studies have shown that long-term excessive supplementation with DCA will inhibit the expression of organic solute transporter-β (OST-β) in the ileum, significantly increases expression of CYP7A1 and CYP27A, and affects the intestinal FXR-FGF15 signaling pathway. Therefore, the negative feedback on BA synthesis is abolished, leading to dysregulation of BAs in the small intestine and an excess concentration of BAs in feces, thereby promoting intestinal inflammation.

Barrier dysfunction can increase intestinal microbial abundance and barrier permeability. Destruction of the intestinal vascular barrier causes the translocation of bacteria or bacterial products. The key to barrier maintenance is proper regulation of epithelial cell turnover through apoptosis. OCA can activate FXR to control intestinal permeability and play a role in intestinal barrier dysfunction and bacterial translocation. In contrast, UDCA is an FXR antagonist, but it can inhibit small intestinal inflammation by inducing immunosuppression,
reducing bacterial translocation, increasing mucin production, inhibiting lipopolysaccharide production, and inducing intestinal cell apoptosis. Some studies have suggested that UDCA and LCA can prevent intestinal inflammation in mouse models of colitis. UDCA and LCA may inhibit the lysis of colonic epithelial cells and expression of caspase-3 through FXR or TGR5 to resis t apoptosis. Current clinical studies have reported that UDCA and TUDCA can prevent or treat chronic inflammation of the small intestine. UDCA has been proven to inhibit the expression of mucosal factors and reduce the severity of disease. CDCA is an effective inducer of epithelial permeability, increasing epithelial damage, while CA does not induce epithelial permeability but is highly cytotoxic to intestinal epithelial cells. Autophagy and inflammation are regulated bidirectionally. Gupta Biki et al. showed that both the cecal CDCA content in mice and cell permeability were increased and that sevelamer hydrochloride prevented the loss of barrier function induced by CDCA. CDCA and OCA inhibit autophagy via a mechanism dependent on FXR. UDCA can induce the formation of autophagosomes independent of FXR and enhance autophagic flux.

Regulation of the intestinal flora

A complex metabolic network connects the intestinal flora and BAs. BAs are important metabolites that not only can regulate but also are modified by the intestinal flora. On the one hand, BAs can shape the microbiome through direct antibacterial effects and antimicrobial peptides produced by FXR, which can inhibit the bacteria in the intestinal tract and limit excessive proliferation of the flora. On the other hand, the intestinal flora converts conjugated BAs into unconjugated BAs by encoding and expressing related enzymes (Figure 4); primary BAs are thus transformed into secondary BAs, resulting in changes in the composition and concentration of the bile pool. For example, BSH metabolizes TCA into CA, and CA is metabolized into DCA by Clostridiumscindens 7α-dehydroxylation through the Bai operon. Recently, some researchers have successfully transferred the plasmid related to Bai enzyme into C. sporogenes to produce the MF001 strain. After the MF001 strain is incubated with CA, DCA can be produced with the incubation time. Therefore, the researchers successfully constructed a strain with the core Bai gene family and sufficient to promote the dehydroxylation of CA. Chen Ming-liang et al. proved that resveratrol can regulate the intestinal flora and reduce atherosclerosis. Specifically, resveratrol can increase the abundances of Lactobacillus and Bifidobacterium by inhibiting the ileal FXR-FGF15 axis, thereby increasing the activity of BSH, promoting the deconjugation of conjugated BAs, increasing the excretion of BAs in feces, and finally reducing the content of BAs in the ileum. BAs not only inhibit the overproduction and harmful colonization of the intestinal flora but also rely on the numerous species of symbiotic bacteria to assist in digestion. FXR can regulate the entry point of bacterial translocation to regulate the intestinal vascular barrier. Therefore, the toxic changes in BAs are closely associated with the intestinal flora, and the intestinal flora is reciprocally involved in the production of BAs. Studies have shown that OCA activates the FXR receptor, which can inhibit the synthesis of endogenous BAs, reduce the proliferation of bacteria, and thereby affect the composition of the small intestinal flora. FXR-dependent inhibition of endogenous BA secretion alters the intestinal flora instead of exerting a direct effect on OCA.

DCA affects the relative abundances of intestinal flora. This molecule is positively correlated with the Clostridium and Eubacteriaceae abundances and negatively correlated with the Bacteroides abundances. Recent studies have shown that chokeberry polyphenols can reduce the relative contents of CA and DCA by extending the treatment time to alter the composition of the intestinal flora and can increase the relative content of CDCA. These changes were found to be positively related to the Bacillus abundance and negatively related to the Clostridium abundance. This research led to the conclusion that treatment with chokeberry polyphenols is likely to activate FXR or TGR5.

Unconjugated BAs have stronger antibacterial activity than conjugated BAs, and gram-positive bacteria are more sensitive to BAs than gram-negative bacteria. OCA stimulates FXR, inhibits BA synthesis, and reversibly induces the proliferation of gram-positive bacteria in the small intestine. Clostridium difficile is a gram-positive spore-forming bacillus that can damage
Figure 4. Conversion of bile acids in the intestine. (a). Conjugated BAs: T/GCA structural transformation in the intestine. (b). Conjugated BAs: T/GCDDA structural transformation in the intestine. Abbreviations: 7β-hydroxysteroid dehydrogenase (7β-HSDH); (3α-HSDH) 3α-hydroxysteroid dehydrogenase; sterol 6β-hydroxylase (Cyp2c70); bile salt hydrolase (BSH).
the intestinal epithelium and cause a strong inflammatory response, which can lead to diarrhea. Clostridium difficile is a gram-positive spore-forming bacillus that damages the intestinal epithelium and causes a strong inflammatory response, which can lead to diarrhea. Studies have found that OCA regulates liver BA synthesis through feedback inhibition of intestinal FXR, thereby improving the severity of Clostridium difficile infection in obese mice induced by a high-fat diet (HFD). An increase in LCA can reduce the toxicity to the cecal microbiota and increase the abundance of Clostridia. Clostridia can synthesize DCA and LCA, which can improve metabolism of the host. UDCA can inhibit harmful bacteria, increase the proportion of Bacteroides, and play an important role in intestinal bacterial homeostasis. CDCA and DCA can reduce sodium reabsorption and increase chloride ion secretion in the human ileum and colon, while CA cannot. However, through the action of intestinal bacteria, nonsecreted CA can be transformed into DCA, which is secreted in feces. Therefore, supplementation with DCA may be able to alleviate the symptoms of constipation. Many studies have shown that the intestinal flora is related to various metabolic diseases, including obesity, nonalcoholic fatty liver and insulin resistance. In the future, it may be possible to regulate BA metabolism by identifying specific flora to control and treat corresponding intestinal diseases.

**Regulation of tumors**

The diversity of BA is receiving more and more attention because it not only affects host metabolism and innate immunity, but also has tumor-promoting properties. Suppression or induction of FXR expression can cause various diseases, such as gastrointestinal diseases, liver hypertrophy, cirrhosis, cholestasis, atherosclerosis, inflammation and cancer. Whole-body *Fxr-null* mice spontaneously developed liver tumors, but the lack of mouse hepatocyte-specific FXR did not promote the occurrence of spontaneous liver tumors. Absil et al. pointed out that the high expression of FXR in breast cancer cells promotes bone metastasis of tumor cells. In addition, overexpression of FXR may cause small cell lung cancer (NSCLC) and esophageal adenocarcinoma. Among the various nuclear receptors, FXR is considered to be a tumor suppressor that can block the initiation of colorectal cancer (CRC) through metabolic or epigenetic mechanisms. FXR can regulate BAM metabolism and exhibit a tumor-suppressive effect in the colon. Intestinal inflammation is a contributing factor to the development of CRC in patients with Irritable bowel disease (IBD). Enteral malnutrition is one of the most likely predisposing factors for IBD. However, intestinal malnutrition leads to a decrease in microbial diversity and a decrease in Firmicutes bacteria, resulting in decrease in intestinal secondary BAs levels and increase in conjugated BAs level. Hydrophobicity increases the levels of BAs in tumors, while hydrophilicity has the opposite effect. The hydrophobicity of BA is determined by cytotoxicity. DCA, LCA, CDCA and TCDCA have been individually proven to have cytotoxic and cancer-promoting properties. Among them, DCA affects the signal transduction pathway of epithelial cells, leading to the development of CRC. In addition, studies of CRC mouse models have shown that elevated levels of fecal BAs lead to an increase in the incidence of CRC. In studies of obesity-related CRC, HFD increases the risk of CRC in humans, which may be due to the excretion of CA into the intestine and increase the production of secondary BAs. Studies have revealed that the convergence of HFD and dysregulated WNT signals changes the BA profile to drive the malignant transformation of Lgr5 expression (Lgr5 +) cancer stem cells and promote the progression of adenoma-adenocarcinoma. In mechanism, FXR controls the proliferation of Lgr5+ intestinal stem cells. In CRC, dietary and genetic risk factors are shown to converge to drive FXR-dependent Lgr5 + CSC proliferation and disease progression. Conversely, the activation of FXR in the intestine reduces the severity of the disease, thereby significantly improving survival. Inflammation of the intestine reduces FXR activation. Therefore, FXR can not only inhibit the inflammatory response, but also can be targeted by the inflammatory response itself. This may lead to a vicious circle. Decreased FXR activity...
leads to decreased inhibition of inflammation, which leads to the occurrence of chronic intestinal inflammation, and may lead to the occurrence of inflammation-induced colorectal cancer. FXR maintains the BA concentration in the physiological concentration range, thereby preventing the cytotoxicity induced by BAs. FXR is the main regulator of BA homeostasis. In view of the relationship between abnormal levels of BA and CRC, researchers have presented a large amount of evidence that FXR plays a role in intestinal tumorigenesis. In view of the key role of FXR in maintaining the concentration of BAs within the physiological range, thereby preventing BAs-induced cytotoxicity.

Conclusion and future perspectives
As a signaling molecules regulating glucose, sterol and lipid metabolism, BAs has attracted widespread attention. This article reviews the latest research on different types of BAs on the intestinal tract from the perspective of FXR and will provide a reference for subsequent basic and clinical research. Different BAs have different effects on the intestine and liver, but few clinical studies have focused on the intestine. Thus, the regulation of intestinal microbial metabolism and intestinal mucosal inflammation by BAs needs further research. Different BAs have different structures, act on different regions, and activate different receptors and downstream signal transduction pathways, which may lead to various effects. The final outcome may be the result of competition among several different signaling pathways under the influence of specific environmental factors. In this review, the role of BA-FXR receptor signaling in intestinal regulation and the effects of changes in the BA composition on host metabolism are discussed. BAs may be a new targeted treatment method for metabolic syndrome.

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ORCID
Zhengquan Su http://orcid.org/0000-0001-6324-6620

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