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REVIEW

# Bile acid nuclear receptor FXR and digestive system diseases

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**KEY WORDS**

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**Abstract** Bile acids (BAs) are not only digestive surfactants but also important cell signaling molecules, which stimulate several signaling pathways to regulate some important biological processes. The bile-acid-activated nuclear receptor, farnesoid X receptor (FXR), plays a pivotal role in regulating bile acid, lipid and glucose homeostasis as well as in regulating the inflammatory responses, barrier function and prevention of bacterial translocation in the intestinal tract. As expected, FXR is involved in the pathophysiology of a wide range of diseases of gastrointestinal tract, including inflammatory bowel disease, colorectal cancer and type 2 diabetes. In this review, we discuss current knowledge of the roles of FXR in physiology of the digestive system and the related diseases. Better understanding of the roles of

*Abbreviations:* 6-ECDCA, 6$\alpha$-ethyl-chenodeoxycholic acid; AF2, activation domain; ANGTPL3, angiopoietin-like protein 3; AOM, azoxymethane; AP-1, activator protein-1; Apo, apolipoprotein; ASBT, apical sodium-dependent bile salt transporter; BAAT, bile acid-CoA amino acid N-acetyltransferase; BACS, bile acid-CoA synthetase; BAs, bile acids; BMI, body mass index; BSEP, bile salt export pump; CA, cholic acid; CD, Crohn's disease; CDCA, chenodeoxycholic acid; CREB, cAMP regulatory element-binding protein; CYP7A1, cholesterol 7$\alpha$-hydroxylase; *db/db*, diabetic mice; DBD, DNA binding domain; DCA, deoxycholic acid; DSS, dextrane sodium sulfate; ERK, extracellular signal-regulated kinase; FABP6, fatty acid-binding protein subclass 6; FFAs, free fatty acids; FGF19, fibroblast growth factor 19; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; FXRE, farnesoid X receptor response element; G6Pase, glucose-6-phosphatase; GLP-1, glucagon-like peptide 1; GLUT2, glucose transporter type 2; GPBAR, G protein-coupled BA receptor; GPCRs, G protein-coupled receptors; GSK3, glycogen synthase kinase 3; HDL-C, high density lipoprotein cholesterol; HNF4$\alpha$, hepatic nuclear factor 4$\alpha$; I-BABP, intestinal bile acid-binding protein; IBD, inflammatory bowel disease; IL-1, interleukin 1; KLF11, Krüppel-like factor 11; KRAS, Kirsten rat sarcoma viral oncogene homolog; LBD, ligand binding domain; LCA, lithocholic acid; LRH-1, liver receptor homolog-1; LPL, lipoprotein lipase; MCA, muricholicacid; MRP2, multidrug resistance-associated protein 2; NF-$\kappa$B, nuclear factor-kappa B; NOD, non-obese diabetic; NRs, nuclear receptors; OST$\alpha$, organic solute transporter alpha; OST$\beta$, organic solute transporter beta; PEPCK, phosphoenol pyruvate carboxykinase; PGC-1$\alpha$, peroxisome proliferators-activated receptor $\gamma$ coactivator protein-1$\alpha$; SHP, small heterodimer partner; SREBP-1c, sterol regulatory element-binding protein 1c; STAT3, signal transducers and activators of transcription 3; T2D, type 2 diabetes; TLCA, taurolithocholic acid; TNBS, trinitrobenzensulfonic acid; TNF$\alpha$, tumor necrosis factors $\alpha$; UC, ulcerative colitis; UDCA, ursodeoxycholic acid; VSG, vertical sleeve gastrectomy

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FXR in digestive system will accelerate the development of FXR ligands/modulators for the treatment of digestive system diseases.



## 1. Introduction

Bile acids (BAs) are amphipathic molecules synthesized from cholesterol in the liver. They are physiological detergents that play important roles in facilitating hepatobiliary secretion of endobiotic and xenobiotic metabolites. In the intestines, BAs help intestinal absorption of dietary fats, fat-soluble vitamins, and other nutritions[1]. Over the past decade, BAs change beyond digestive surfactants to signaling molecules in a wide range of biological functions, including glucose and lipid metabolism, energy homeostasis, and the modulation of immune response[1–3]. The regulatory functions of BAs are mainly the result of activation of intracellular ligand-activated nuclear receptors (NRs), such as the farnesoid X receptor (FXR, NR1H4)[4–6] and cell surface G protein-coupled receptors (GPCRs), specifically the G protein-coupled BA receptor (TGR5 or GPBAR-1)[7,8]. Chenodeoxycholic acid (CDCA) is the most potent BA for FXR[9–11]. In contrast, lithocholic acid (LCA) and taurolithocholic acid (TLCA) are most potent endogenous ligands for TGR5 with an $EC_{50}$ of ~600 and 300 nmol/L, respectively[12–14]. FXR has been considered as a master regulator of BA synthesis and secretion, lipid and glucose metabolism in the liver and intestine[15,16]. In contrast, activation of TGR5 by BAs stimulated adenylate cyclase, rapid intracellular cAMP production, and protein kinase A activation. Such regulatory function of TGR5 plays important roles in regulating energy metabolism in brown adipose tissue, relaxing and refilling gallbladder, secreting glucagon-like peptide 1 (GLP-1) in intestinal endocrine cells and controlling gastrointestinal motility to help maintain BA, lipid and glucose homeostasis[2,17].

Abnormal BA metabolism has been associated with liver injury, metabolic disorders, cardiovascular diseases and digestive system diseases such as inflammation bowel disease (IBD) and colorectal cancer[18–21]. FXR has been suggested to counteract pro-inflammatory and pro-atherogenic responses in cardiovascular diseases[22]. Moreover, FXR plays a pivotal role in regulating liver inflammation and regeneration as well as in regulating the extent of inflammatory responses, barrier function and prevention of bacterial translocation in the intestinal tract[23–25]. Direct modulation of BA receptor activities by synthetic and natural FXR agonists or antagonists has shown promise in treating human diseases related to metabolic perturbations and inflammation[23,26–29]. Here, we will focus on the current understanding of the functions of BAs and FXR in enterohepatic circulation, with special emphasis on their roles in pathophysiology of the gastrointestinal tract.

## 2. Bile acid nuclear receptor FXR

FXR belongs to a subclass of metabolic receptors within the NR-family and is identified as an NR for BAs[4–6]. It is expressed in several tissues, including liver, intestine, adipose tissue, the vascular wall, pancreas and kidney[30]. Four FXR splice variants have been identified, *i.e.* FXR$\alpha$1–4. These isoforms show difference in spatial and temporal expression patterns as well as in transcriptional activities[31]. The general structure of FXR consists of an N-terminal DNA binding domain (DBD), a unique ligand binding domain (LBD) allowing receptor dimerization, and a C-terminal activation domain (AF2) for co-regulator interactions[32]. FXR binds to an FXR response element (FXRE) as a heterodimer with RXR or as monomer to regulate gene expression[32]. A large number of publications have shown that FXR regulates a network of genes in hepatic BA synthesis, biliary BA secretion, intestinal BA absorption, and hepatic BA uptake, thereby playing a key role in the regulation of BA homeostasis[33–35].

BAs were identified as endogenous FXR ligands with high affinity. FXR can be activated by both free and conjugated BAs. The hydrophobic CDCA is the most efficacious ligand of FXR ($EC_{50}$ = approximately 10 μmol/L). The order of potency of BAs is CDCA > LCA = deoxycholic acid (DCA) > cholic acid (CA), whereas hydrophilic BAs, such as ursodeoxycholic acid (UDCA) and muricholicacid (MCA), cannot activate FXR[36]. These studies have suggested for the first time that BAs are also endocrine hormones[16,32,37]. A number of compounds unrelated to BAs were also found to act as FXR ligands with varying degrees of affinity, including androsterone[38] and the exogenous natural products such as forskolin[39], epigallocatechin-3-gallate[40] and cafestol[41]. In addition, a series of synthetic BA derivatives have been developed as FXR ligands, such as 6$\alpha$-ethylchenodeoxycholic acid (6-ECDCA) and bile alcohols, showing a higher affinity with FXR than the original BAs[42]. Along with the regulation of BA metabolism, accumulated data have demonstrated that FXR is a multipurpose NR that plays an essential role in maintaining lipid and glucose homeostasis[32,37,43]. Thus, activation or repression of FXR can have significant influences on metabolic homeostasis. FXR ligands have been proposed for potential treatment of cholestasis[44], liver fibrosis[27], inflammatory bowel disease[23], atherosclerosis[45] and erectile dysfunction[46]. Detailed analysis of the ChIP-seq data indicates that the global binding patterns of FXR in primary human hepatocytes are similar to those in mouse livers. Therefore, in a major extent, mouse model is suitable for studying human FXR functions[47]. Since numerous excellent review articles on FXR are already available, we will focus on the roles of FXR in digestive system diseases and type 2 diabetes (T2D).

## 3. FXR and enterohepatic circulation

FXR plays a key role in regulation of BA levels in enterohepatic circulation. BAs are synthesized in hepatocytes by cholesterol 7$\alpha$-hydroxylase (CYP7A1), conjugated with taurine or glycine *via* bile acid-CoA synthetase (BACS) and bile acid-CoA amino acid N-acetyltransferase (BAAT), and secreted through the bile canalicular membrane by two ABC transporters (bile salt export pump (BSEP) and multidrug resistance-associated protein 2 (MRP2)) into the canalicular lumen[1,33,37]. They are stored in the gallbladder

before being excreted into the intestinal lumen, where they function to emulsify dietary lipids and vitamines. In the liver, BAs bind to FXR, which transcriptionally upregulates a protein called small heterodimer partner (SHP; NR0B2) to inhibit transactivity of hepatic nuclear factor 4$\alpha$ (HNF4$\alpha$) and liver receptor homolog-1 (LRH-1; NR5A2) that bind to the BA response element in the *Cypza1* and *Cyp8b1* gene promoters[48].

Roughly 95% of the BAs re-absorption occurs at the terminal ileum through the apical sodium-dependent bile salt transporter (ASBT; SLC10A2)[49,50]. After transporting inside ileal enterocytes by ASBT, BAs are reversibly bound by the intestinal bile acid-binding protein (I-BABP) (also known as fatty acid-binding protein subclass 6 (FABP6)) expressed in the ileum[49,51]. I-BABP has an important role in enterohepatic circulation by regulating BA trafficking. It shuttles BAs from the apical to basolateral membrane in the enterocytes[52]. Finally, organic solute transporter alpha and beta (OST$\alpha$ and OST$\beta$) move bile salts to blood vessels, in accordance with its location at the basolateral membrane[53]. Mechanistic studies reveal that BAs generate a negative feedback on ASBT expression by FXR-mediated induction of SHP, which binds to and represses the transcriptional activities of LRH-1 for the *Cyp7a1* gene[54]. The negative regulation of ASBT expression was observed in mice. But it was not found in rats due to the absence of an LRH-1 responsive element within the rat *Asbt* promoter[54]. Similar to the effect of FXR activation in the hepatocytes, activation of intestine FXR by BAs limits BA uptake and promotes basolateral BA secretion to decrease intracellular BA concentrations. BAs in the enterocytes bind FXR and increase the expression of IBABP and two transporters, OST$\alpha$ and OST$\beta$, that are responsible for the transport of BAs from the intestine to the portal vein[55,56]. Thus, FXR controls the entire transport of BAs from the intestinal lumen to the enterocytes, within the enterocytes and ultimately to the blood vessel for transportation to the liver.

Interestingly, intestinal FXR activation also generates an endocrine feedback regulation. Fibroblast growth factor 19 (FGF19) in humans, and its mouse homolog FGF15 (sometimes referred to as FGF15/19) are activated by FXR in the ileum[57,58]. FGF15/19 is secreted from the ileum to the bloodstream where it circulates to the liver and suppresses BA synthesis through binding and activation of the FGF receptor 4 (FGFR4) complexed with $\beta$-Klotho located on the surface of hepatocytes and other epithelial cells[59,60]. These effects were not observed in $Shp^{-/-}$ mice, thus suggesting that SHP is required for the suppressive effects of FGF15/19[36]. Binding of FGF15/19 to the FGFR4/$\beta$-Klotho complex strongly suppresses the expression of CYP7A1 through MAPK-dependent pathways, specifically, ERK and JNK pathways[61]. Extracellular signal-regulated kinase (ERK) was markedly elevated by FGF15 administration to mice and deficiency of both JNK and ERK pathways prevented FGF15-mediated suppression of CYP7A1 and CYP8B1 expression. However, deficiency of either pathway alone had minimal effect on FGF15-mediated suppression of these genes[61]. Therefore, intestinal FXR activated by BAs downregulates CYP7A1 expression indirectly through the intestinal FGF15/19 synthesis and secretion. In addition, FGF15/19 was reported to work as a hormone to facilitate gallbladder filling by binding to FGFR3, a receptor that is highly expressed in the gallbladder[62]. These studies indicate that FXR-FGF15-19 signaling contributes to the control of intestinal BA levels. Furthermore, FGF15/19 is also recently reported to activate hepatic glycogen synthesis through elevating the activities of glycogen synthase kinase 3 (GSK3)[63] and to inhibit hepatic gluconeogenesis by inhibiting the cAMP regulatory element-binding protein (CREB)–peroxisome proliferators-activated receptor $\gamma$ coactivator protein-1$\alpha$ (PGC-1$\alpha$) pathway[64].

## 4. FXR and inflammatory bowel disease

IBD, which primarily includes ulcerative colitis (UC) and Crohn's disease (CD), represents a group of chronic disorders characterized by gastrointestinal tract inflammation[65]. Although many details of IBD have been explored, the exact pathogenetic mechanisms of IBD have not been fully elucidated. At present, IBD is generally believed to result from imbalance of gut microbiota, epithelial dysfunction, and aberrant mucosal immune response[66].

Recently, FXR has been implicated to participate in immune modulation and barrier function in the intestine. FXR alleviates inflammation and preserves the integrity of the intestinal epithelial barrier in many ways by regulating the extent of the inflammatory response, maintaining the integrity and function of the intestinal barrier, and preventing bacterial translocation in the intestinal tract[67].

First, FXR plays an important role in the mucosal immune response, thereby exerting strong influence on immunoregulation[68]. Vavassori et al.[69] notice that $Fxr^{-/-}$ mice display significantly elevated pro-inflammatory cytokine mRNA expression in the colon. In two complementary murine models (intrarectal administration of trinitrobenzensulfonic acid (TNBS) and oral administration of dextrane sodium sulfate (DSS)), concurrent administration of the potent synthetic FXR ligand 6-ECDCA represses the expression of various proinflammatory cytokines, chemokines and their receptors in wild type, but not $Fxr^{-/-}$ mice. In addition, Raybould et al.[73] show that FXR activation by INT-747 prevents DSS- and TNBS-induced intestinal inflammation, with improvement of colitis symptoms, inhibition of epithelial permeability, and reduced goblet cell loss. Furthermore, FXR activation inhibits proinflammatory cytokine production *in vivo* in the mouse colonic mucosa, and *ex vivo* in different immune cell populations[23]. These results provide strong support for the involvement of FXR in IBD due to counter-regulatory effects on cells of innate immunity[23,69]. FXR ligands exert anti-inflammatory activities by antagonizing other signaling pathways, in part through the interaction with other transcription factors, including activator protein-1 (AP-1), and signal transducers and activators of transcription 3 (STAT3)[70]. Several of the intestinal macrophage genes inhibited by FXR agonists are established targets for nuclear factor-kappa B (NF-$\kappa$B) (tumor necrosis factors $\alpha$ (TNF$\alpha$), interleukin 1 (IL-1), IL-6, cyclooxygenase-1, cyclooxygenase-2) and AP-1, two most important transcriptional regulators of innate and adaptive immunity in cells[71] (Fig. 1).

Second, FXR has been implicated in barrier function by regulating intestinal antibacterial growth. Gut microbiota play important roles in pathogen defense, immunity, and nutrient harvest. Recent evidence suggests that there is a regulatory relationship between the development of IBD and altered gut microbiota[72–74]. It has been demonstrated that BAs and gut microbiota are closely related to each other. Gut microbiota are involved in the biotransformation of BAs through deconjugation, dehydroxylation, and reconjugation of BAs[75]. BAs have antimicrobial activities by damaging the bacterial cell membrane, thus inhibiting bacterial outgrowth[76].

The administration of bile or conjugated BAs to ascitic cirrhotic rats or obstructive jaundice rats eliminates intestinal bacterial

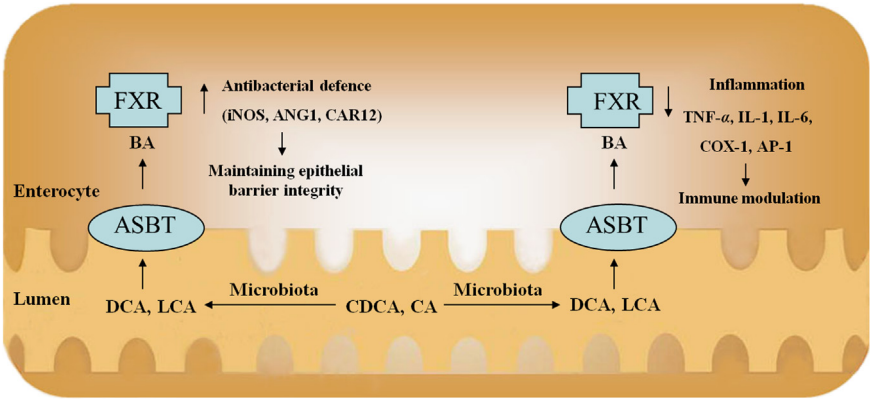


**Figure 1** The roles of FXR in the IBD. FXR activation increases mRNA expression of *iNOs, ANG1 and CAR12*, which are involved in antibacterial defense by producing antimicrobial peptides (iNOs and ANG1) or maintaining appropriate intestinal pH (CAR12). This is important for the homeostasis of intestinal luminal contents and epithelial barrier integrity. Moreover, FXR activation induces the repression of inflammatory genes (*IL-1, IL-6* and *MCP-1*) and promotes antimicrobial actions.

overgrowth, and decreases bacterial translocation and endotoxemia[77,78]. Inagaki et al.[79] provide an explanation for this protective effect of BAs by demonstrating that intestinal FXR has a crucial role in limiting bacterial overgrowth and thus protecting the intestine from bacterial-induced damage. They show that mice lacking FXR experience bacterial overgrowth, increase intestinal permeability and contain large amounts of bacteria in mesenteric lymph nodes, as well as inflammation of the intestinal walls. However, activation of intestinal FXR by GW4064 leads to the identification of several novel intestinal FXR target genes, including those encoding angiogenin, carbonic anhydrase 12 and inducible nitric oxide synthase, which have been reported to have antibacterial properties[79]. The cytokine IL-18 is also induced by FXR stimulation. IL-18 stimulates resistance to an array of pathogens, including intracellular and extracellular bacteria and mycobacteria, and appears to have a protective role during the early, acute phase of mucosal immune response[79,80]. These results are consistent with the idea that FXR is critical for controlling intestinal bacterial growth, which has significant implications for maintaining a competent barrier, thereby contributing to the prevention of intestinal inflammation.

## 5. FXR and colorectal cancer

Colorectal cancer is considered as the third most common form of cancer and the second most common cause of cancer-related death worldwide, leading to an incidence of 1.36 million cases estimated in 2012 (19.2% of total cancer cases) as attending to incidence and mortality statistics[81]. In addition to inherited mutations, lifestyle, diet and nutritional habits are closely related to the development of colorectal cancer. Recently, there is increasing evidence that a fat-rich diet is positively associated with colon cancer incidence[82–84]. Consumption of high-fat diet has been correlated with elevated levels of BAs in the colonic lumen as a consequence of increased fecal excretion of BAs, which at last promote elevated incidence of colorectal cancer[85,86]. In addition, population-based studies have shown that subjects who consume a western diet display elevated levels of fecal secondary BAs, mostly DCA and LCA, as do patients diagnosed with colonic carcinomas[87,88]. Elevated secondary BA concentrations have detrimental effects on colonic epithelium architecture and function through multiple mechanisms, such as DNA oxidative damage, inflammation, NF-κB activation and enhanced cell proliferation[89]. Therefore, BAs can be considered as tumor-promoting factors in colorectal cancer development[82,90,91].

So far, there is considerable evidence for a role of FXR in modulating intestinal tumorigenesis. Given the crucial roles of FXR in maintaining BA concentrations within a physiological range, thereby preventing BA-induced cytotoxicity, the loss of FXR would contribute to tumorigenesis of colorectal cancer. De Gottardi et al.[92] first suggest that *FXR* mRNA expression is decreased in colonic polyps, and even more pronounced, in colonic adenocarcinoma. These results indicate that FXR expression levels may positively correlated to the degree of malignancy of colon cancer and there is a causal link between FXR and colon carcinogenesis in humans. It is indeed further demonstrated by that FXR deficiency leads to significantly increased sizes and numbers of the tumors in two common murine intestine tumorigenesis models: $APC^{min}$ mice and azoxymethane (AOM)-induced colon cancer[93]. Modica et al.[94] consider that FXR activity is relevant to the pathogenesis of intestinal cancer. On one hand, when FXR is absent, there is an upregulation of Wnt signaling *via* increased infiltrating neutrophils and TNFα production with expansion of the basal proliferative compartment both in the ileum and in the colon, and a concomitant reduction in the apical, differentiated apoptosis competent compartment. This scenario leads to increased tumor progression and early mortality in mice. On the other hand, when FXR is activated in the differentiated normal enterocytes and in colon cancer cells, there is an induction of apoptosis and removal of genetically altered cells, which may otherwise progress to complete transformation. Thus, up-regulation of FXR expression in colon tumors might be useful in the treatment of colon cancer. Further studies on a larger collection of human frozen colon carcinomas tissues and human cell lines show that FXR expression may be linked to the development of colorectal carcinomas and indicate that altered *FXR* signaling in neoplastic cells offers novel pathogenetic, prognostic and, in particular, therapeutic insights and perspectives[95]. Bailey et al.[96] investigate the regulation of FXR during the development of human colon cancer. The results showed that FXR is downregulated very early in human colon cancer development, which is partly due to DNA methylation of the *FXR* promoter and increased V-Kiras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) signaling. Silencing of *FXR* alone is not sufficient to initiate colon cancer development, but

activation of remnant FXR in healthy tissues may prevent and inhibit the promotion of colon cancer[93,94,97]. Restoration of basal FXR expression through inhibition of DNA methylation or KRAS signaling, or through activation of residual FXR, might slow or prevent the progression of colorectal cancer[96].

## 6. FXR, obesity and T2D

The global prevalence of diabetes in 2010 was 280 million people worldwide (around 6.2% of the world's total population), and it has been predicted that in 2030 the prevalence will reach more than 7.5% of the world's total population, paralleling the aging and body mass index (BMI) of the population. Obesity is a leading risk factor for impaired glucose tolerance and T2D. Overweight and obesity lead to adverse metabolic effects on blood pressure, cholesterol levels, triglycerides levels and insulin resistance[98].

In recent years, a body of evidence has surfaced indicating that FXR plays an important role not only in BA but also in lipid and glucose homeostasis[99–101]. Specific targeting of FXR may be an effective way to treat obesity-induced metabolic diseases.

Studies in mice with FXR gene ablation or administering FXR agonists provided key information demonstrating a central role of FXR in lipid homeostasis. $Fxr^{-/-}$ mice display elevated serum cholesterol and triglyceride levels and excessive accumulation of fat in the liver[99,100]. A more detailed study reveals an increased hepatic synthesis of apolipoprotein B-containing lipoproteins (mainly VLDL) and a reduced clearance rate of HDL cholesteryl esters, both of which have theoretically pro-atherogenic effects in $Fxr^{-/-}$ mice[98]. Activation of FXR by BAs or synthetic agonists lowers plasma triglyceride levels[101,102] by a mechanism that involves the repression of hepatic transcription factor sterol regulatory element-binding protein 1c (SREBP-1c) expression and its lipogenic target genes in mouse primary hepatocytes and liver[103,104]. The suppression effect of FXR on SREBP-1c expression is thought to be mediated by a signaling cascade that involves SHP[104]. In addition, activation of FXR facilitates the clearance of VLDL and chylomicrons *via* repressing the expression of microsomal triglyceride transfer protein and apolipoprotein B[103]. FXR activation also results in the induction of peroxisome proliferator-activated receptor $\alpha$, which promotes fatty acid $\beta$-oxidation[105] (Fig. 2). Yet, different FXR isoforms display differential effects. For example, FXR$\alpha$2 is more effective in reducing elevated HDL levels and transrepressing hepatic expression of CYP8B1, which is the regulator of cholate synthesis. In contrast, FXR$\alpha$4 is involved in a switch to regulate the hydrophobicity of the bile salt pool[31].

In addition, FXR activation also directly increases the expression of apolipoprotein Apo CII and AIV[102,106,107], which are activators of lipoprotein lipase (LPL) activity, and decreases the expression of both ApoCIII[108] and ANGTPL3[104], which are LPL inhibitors. However, FXR appears to suppress apolipoprotein A-I expression[100,109,110], the primary protein constituent of high-density lipoprotein defining its size and shape. FXR also regulates the expression of phospholipid transfer protein[111] that is responsible for the transfer of phospholipids and cholesterol from low to high-density lipoprotein and suppresses 3-hydroxy-3-methyl-glutaryl-CoA reductase, likely involving sterol regulatory element-binding protein 2[112]. Another target of FXR is paraoxonase 1, a protein produced in the liver with phospholipase A2 activity that may be important for inactivation of proatherogenic lipids produced by oxidative modification of low-density lipoprotein. FXR mediated repression of paraoxonase 1 involves the induction of fibroblast growth factor 19, its subsequent binding to the fibroblast growth factor receptor 4, and activation of the c-Jun N-terminal kinase pathway[113,114]. Finally, FXR represses proprotein convertase subtilisin/kexin 9[115], a protein that promotes the intracellular degradation of the low-density lipoprotein receptor by interfering with its recycling to the plasma membrane. Collectively, these findings support the concept that FXR activation decreases plasma lipid levels by suppressing hepatic lipogenesis and lipid secretion and increasing the clearance of lipoproteins from blood (Fig. 2).

In addition to its pleiotropic effects on lipid metabolism, FXR plays a critical role in glucose homeostasis. The generation and phenotypic characterization of $Fxr^{-/-}$ mice confirm this vital role in the regulation of lipid metabolism and glucose homeostasis. $Fxr^{-/-}$ mice not only display elevated serum levels of free fatty acids (FFAs), triglycerides and high density lipoprotein cholesterol (HDL-C)[99,100], but also develop signs of insulin resistance as shown by hyperglycemia, impaired glucose tolerance, and severely blunted insulin signaling in both liver and muscle[28,116]. High glucose concentrations increased FXR O-GlcNAcylation, thereby enhancing its protein stability and transcriptional activity. The fasting–refeeding experiments show that FXR undergoes O-GlcNAcylation in fed conditions, which is accompanied with increased FXR target gene expression and decreased liver bile acid content[117]. Activation of FXR by synthetic agonists or hepatic overexpression of a constitutively active FXR by adenovirus-mediated gene transfer reduces blood glucose levels in obese *fa/fa* rats, diabetic, leptin deficient, diabetic (*db/db*) mice and wild type mice[28,118]. This decrease in plasma glucose levels in *db/db* mice was associated with decreased glucose-6-phosphatase expression, increased glycogen levels and synthesis in the liver, providing evidence that activation of FXR lowers plasma glucose levels by sensitizing to insulin action[26,116]. Pharmacological treatments with BAs or GW4064, both *in vitro* in human hepatoma cell lines and *in vivo* in mice, decrease the expression of the gene encoding phosphoenol pyruvate carboxykinase (*Pepck*) and other gluconeogenic genes such as those encoding glucose-6-phosphatase (*G6Pase*) and fructose 1,6-bis-phosphatase[119,120]. Consistent with these results, CA treatment for five days decreased *Pepck* and *G6Pase* mRNA levels in wild-type, but not in $Fxr^{-/-}$ mice[121]. This was associated with a decrease in levels of fasting blood glucose only in wild-type mice, indicating that FXR negatively regulates gluconeogenesis[121] (Fig. 2). Moreover, *in vivo* GW4064 treatment reduces PEPCK and G6Pase expression in *db/db* mice[28]. Paradoxically, some studies[28,116], but not all[122], report that FXR activation by GW4064 induces PEPCK expression, leading to an increased glucose output in rodent primary hepatocytes *in vitro*[116].

Recently, there are independent studies identifying a role for FXR in the regulation of insulin sensitivity[29,104,121]. $Fxr^{-/-}$ mice are associated with impaired glucose tolerance and insulin resistance. Moreover, whole-body glucose disposal during a hyperinsulinemic euglycemic clamp is decreased in $Fxr^{-/-}$ mice. Consistent with these observations, insulin signaling is impaired in peripheral insulin-sensitive tissues, including skeletal muscle and white adipose tissue[29,122]. Interestingly, treatment with GW4064 significantly improved insulin sensitivity in both *db/db*[28] and *ob/ob*[29] mice. Similar results are obtained when a constitutively active FXR is over-expressed in *db/db* mice[28]. In contrast, FXR deficiency was also shown to be associated with normal hepatic insulin sensitivity and signaling[121,122]. The reason for this

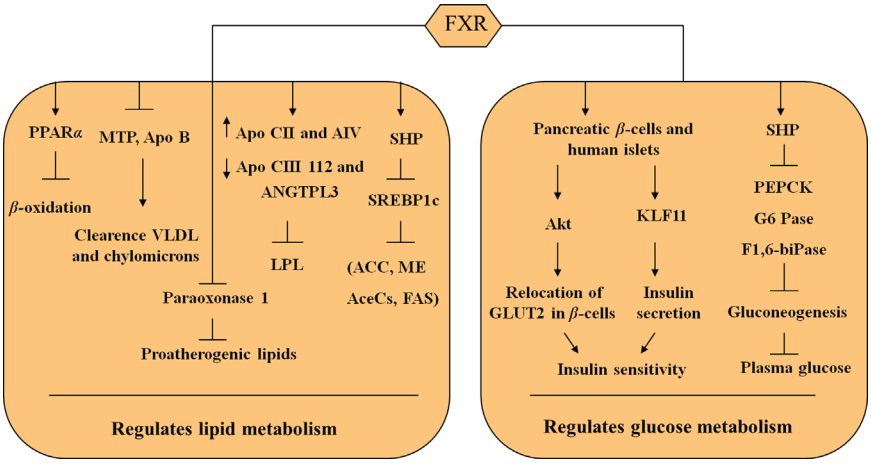


**Figure 2** The roles of FXR in regulating lipid and glucose metabolism. On one hand, FXR plays an important role in regulating lipid metabolism. Activation of FXR by BAs or synthetic agonists lowers plasma triglyceride levels by a mechanism that involves the repression of hepatic transcription factor SREBP-1c expression and its lipogenic target genes in mouse primary hepatocytes and liver. FXR activation also increases the expression of apolipoprotein Apo CII and AIV and decreases the expression of both Apo CIII 112 and ANGTPL3 to stimulate LPL activity. In addition, FXR mediates the repression of paraoxonase 1 to inactivate pro-atherogenic lipids produced by oxidative modification of low-density lipoprotein. Furthermore, FXR activation promotes fatty acid $\beta$-oxidation by inducing the expression of PPAR$\alpha$. Finally, activation of FXR facilitates the clearance of very low-density lipoproteins and chylomicrons *via* repressing the expression of microsomal triglyceride transfer protein and apolipoprotein B (Apo B). On the other hand, FXR exerts a critical role in regulating glucose homeostasis. Activation of FXR in $\beta$TC6 cells increases Akt phosphorylation and translocation of the glucose transporter GLUT2 at plasma membrane, increasing the glucose uptake by these cells. FXR-KLF11 regulated pathway has an essential role in the regulation of insulin transcription and secretion induced by glucose. Furthermore, FXR-SHP negative regulatory cascade can regulate gluconeogenesis in the liver.

discrepancy is unclear, but may be linked to different genetic backgrounds (C57Bl6/J[28,121] *vs.* C75Bl6/N[121,122]) of the mice and/or the insulin dose used during the clamp. The molecular mechanisms behind the insulin-sensitizing effect of FXR remain poorly defined. Since FXR is not expressed in skeletal muscle, it is conceivable that FXR deficiency alters indirectly insulin signaling in this tissue. Recent studies indicated that FXR is expressed by pancreatic $\beta$-cells and human islets and regulates the insulin signaling by genomic and non-genomic effects. Genomic effects include Krüppel-like factor 11 (KLF11)-mediated stimulation of insulin gene expression. Non-genomic effects include an Akt-mediated stimulation of glucose induced relocation of glucose transporter type 2 (GLUT2) in $\beta$-cells. Finally, these effects are reproduced *in vivo* in a rodent model of insulin-deficient diabetes developing in non-obese diabetic (NOD) mice[123].

In humans, pharmacological approaches to induce persistent weight loss and improve glucose level of obesity-induced T2D have so far shown limited effectiveness. However, bariatric surgery has become an effective therapeutic option for morbid obesity, surpassing drug therapies and lifestyle interventions[124]. Vertical sleeve gastrectomy (VSG) is a bariatric procedure that involves the removal of up to 80% of the stomach along the greater curvature, creating a gastric "sleeve" in continuity with the esophagus and pylorus[125]. VSG induces loss of body weight and fat mass and improves glucose tolerance in humans and in rodent models[126–131]. The study of Ryan et al.[132] suggests that FXR is required for the sustained maintenance of weight loss and improved glycemic control after VSG. Furthermore, by identifying a model resistant to the effects of bariatric surgery, the authors were able to identify dissect further a role of the microbiota on the positive effects of bariatric surgery. However, the specific mechanisms by which FXR contributes to glucose control by VSG are still unknown. Further investigating the roles of FXR in mediating the anti-obesity and anti-diabetes effect of VSG and other surgeries will be of great interest.

## 7. Conclusions and future perspectives

Research in BA and FXR signaling during the last 20 years has unraveled its important role in regulation of BA, lipid, glucose, and energy metabolism. In this review, we have summarized the roles of FXR in pathophysiology of the digestive system and the related diseases, including IBD, colorectal cancer and T2D. Recent studies have shown that FXR activation by its ligands affects both immune cells and intestinal epithelium, contributing to intestinal immunomodulation at various levels, thus providing a rationale to extend the clinical trials of FXR ligands to patients with IBD. The critical role of FXR in modulating intestinal tumorigenesis is probably due to its regulation of BA metabolism and detoxification, and its activation may confer protection from BA-induced tumor promoting activities. Activation of FXR improves obesity-induced T2D by regulating lipid metabolism and glucose homeostasis. FXR is required for the positive metabolic effect of VSG surgery. Targeting FXR therefore offers an exciting new perspective for the treatment of these digestive system diseases. However, the therapeutic benefits or risks of synthetic FXR ligands require further consideration in light of differences between mice and humans. One particular challenge in designing FXR agonists is to separate the desired therapeutic effects from the unwanted side effects. The design of organ- or gene-specific FXR modulators may improve their specificity and reduce side effects. A better understanding of the cellular and physiological signaling of FXR and its cofactors will help develop more selective modulators and the development of more efficient therapeutics for digestive system diseases.

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