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Modulating Bile Acid Pathways and TGR5 Receptors for Treating Liver and GI Diseases

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Abstract

Bile acids are central signals in enterohepatic communication and also integrate microbiota-derived signals into this signaling axis. Discovery of the tissue distribution and signaling pathways activated by the natural receptors for bile acids, farnesoid X receptor and G protein-coupled bile acid receptor 1 (GPBAR1) also known as TGR5, and bile acid transporters has led to the development of therapeutic agents that target these molecules. Obeticholic acid, a selective FXR agonist, and NGM282, a non-mitogenic FGF-19 analog, are two of the agents in this pipeline. Obeticholic acid has been approved by regulatory agencies for use in patients with primary biliary cholangitis.

INTRODUCTION

Enterohepatic Circulation of Bile Acids: The Gut-Liver-Microbiome Axis

The rate limiting enzyme in the classical pathway of bile acid synthesis from cholesterol in the liver is 7α-hydroxylase (cytochrome P450 7A1, CYP7A1). The primary bile acids produced in the liver are cholic acid (CA) and chenodeoxycholic acid (CDCA), which are conjugated with taurine and glycine and are excreted into bile and stored in the gallbladder (Figure 1) (1).

After food ingestion, the gallbladder contracts, delivering bile acids into the small bowel and facilitating digestion and absorption of fat. Most of the conjugated bile acids (~95%) are absorbed in the terminal ileum by active transporters [apical sodium bile acid transporter (ASBT) also called ileal BA transporter (IBAT)] and transported via the portal circulation to the liver to be recycled. The unabsorbed (~5%) CA and CDCA reaching the colon are deconjugated by bacterial bile salt hydrolases and 7α-dehydroxylated by bacteria to secondary bile acids, predominantly deoxycholic acid (DCA) and lithocholic acid (LCA).

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Thus, colonic microbiota are an integral part of the enterohepatic bile acid axis. In the colon, CDCA and DCA stimulate fluid secretion (2), increase mucosal permeability, and induce high amplitude propagated contractions (3,4). The colon reabsorbs, by diffusion, ~75% of the bile acids reaching the colon.

Farnesoid X Receptor

The farnesoid X receptor (FXR) is highly expressed in the intestine and liver. It is a natural receptor for bile acids. Of the natural bile acids, it is most potently activated by CDCA. The bile acids absorbed by the ileal enterocytes bind to the nuclear farnesoid X-receptor (FXR) which stimulates synthesis of the hormone, fibroblast growth factor-19, FGF-19, which enters the hepatocyte through fibroblast growth factor-receptor 4 (FGF-R4) with interaction with a surface protein, klotho β. In the hepatocytes, FGF-19 inhibits bile acid synthesis through inhibition of CYP7A1. Direct bile acid activation of hepatocyte FXR leads to the induction of small heterodimer protein (SHP) which inhibits the transcription of CYP7A1. These two pathways constitute the major negative regulators of bile acid synthesis (Figure 2).

G-Protein Coupled Bile Acid Target Receptor

This receptor, also called Takeda G-coupled receptor 5 (TGR5), is located on cholangiocytes, the epithelial surface of gallbladder and intestinal cells, the basolateral surface of smooth muscle, neural cells, brown adipose tissue, immune cells including dendritic cells and macrophages, and enteroendocrine cells that produce glucagon-like peptide 1 (GLP-1) (5). Of the natural bile acids, TGR5 is most potently activated by LCA, and is an important receptor for mediating effects of bile acids on motility, directly by action on neurons and indirectly by stimulating serotonin release (1).

PHARMACOTHERAPEUTICS OF BILE ACIDS AND RECEPTORS

I. Intestinal Tract

A. Treatment options for constipation—When used for gallstone dissolution and cholestatic liver disease, CDCA was associated with diarrhea and, in patients with chronic constipation, it increased stool frequency and loosened stool consistency compared with placebo (6). On the other hand, ursodeoxycholic acid (UDCA) did not cause diarrhea, consistent with studies of bile acids on epithelial functions in animal models and in vitro (7,8). Fluid secretion results from stimulation of intracellular messengers (e.g. cAMP and calcium) and activation of chloride secretion through the cystic fibrosis transmembrane regulator (9–11). Bile acids also induce high amplitude propagated contractions of the colon (4), at least partly mediated through TGR5 receptors on enteric cholinergic and nitrergic neurons and smooth muscle cells (12) and resulting in prokinetic effects (13).

A minority of patients with constipation-predominant irritable bowel syndrome (IBS-C) has evidence of bile acid deficiency (14). CDCA accelerates colonic transit, increases stool frequency, loosens stool consistency, and eases passage of stool in patients with IBS-C (15). Similar pharmacodynamics (16) and clinical effects to those of ileocolonic delivery of CDC were observed with an IBAT inhibitor, elobixibat, in chronic idiopathic constipation (17,18).

A preliminary study of NGM282, a non-mitogenic variant of FGF19, reported acceleration of colonic transit and relief of constipation in a single-center, phase 1 trial in patients with functional constipation (19).

B. Treatment options for bile acid diarrhea

Bile acid sequestrants: About 25–33% of patients with diarrhea-predominant irritable bowel syndrome (IBS-D) or functional diarrhea have evidence of bile acid diarrhea (20). Bile acid sequestrants bind bile acids and decrease diarrhea in bile acid diarrhea. There are three currently available bile acid sequestrants: cholestyramine (powder form), colestipol and colesevelam (both available in tablet form).

The only randomized trial of cholestyramine efficacy in bile acid diarrhea showed response rates of 40% and 53.8% in patients with ^{75}SeHCAT (selenium homocholic acid taurine) retention <10% or 20% respectively. Less than 15% retention signifies excessive bile acid loss. In comparison to the effects of cholestyramine, treatment with hydroxypropyl cellulose (which also binds bile salts in the colon without affecting hepatic bile acid synthesis) showed response rates of 25% and 38.5% respectively (no statistical difference between the two treatments) (21). Cholestyramine is unpalatable and associated with bloating; hence, compliance is low (22).

In an open-label trial in patients with bile acid diarrhea with ^{75}SeHCAT retention <20%, colestipol reduced stool frequency and IBS severity score (23).

In another open-label study in patients with high 48-hour stool bile acid excretion, colesevelam, 1875 mg twice daily for 10 days, decreased stool consistency and increased stool excretion of sequestered bile acids (24). Colesevelam also slowed emptying of the ascending colon compared with placebo in IBS-D; the treatment effect was associated with baseline serum C4, which reflects the hepatic bile acid synthesis rate (25).

Further controlled trials are necessary to assess the effects of bile acid sequestrants for diarrhea. Patients will likely need long-term therapy with bile acid sequestrants for symptom relief. In a long-term, follow-up study of patients with a median time from bile acid diarrhea diagnosis of 6.8 years, 38% were still on bile acid sequestrants, with adequate relief of their symptoms, while 24% discontinued therapy, most commonly due to poor tolerability (26).

FXR agonist: Obeticholic acid (OCA), a potent FXR agonist that stimulates FGF-19 production and decreases hepatic bile acid synthesis, was administered at 25 mg orally, daily for two weeks; it decreased stool frequency, improved stool consistency, increased FGF-19 levels, and decreased serum C4 and serum bile acids in patients with primary and secondary bile acid diarrhea, but not in patients with diarrhea and normal ^{75}SeHCAT levels (27).

C. UDCA reduces *Clostridium difficile* sporulation, infection and pouchitis—

It has been suggested that restoration of secondary bile acid metabolism may be a key mechanism for the beneficial effects of fecal microbiota transplantation in treating recurrent *C. difficile* infection. Thus, bile acids at concentrations found in patients after fecal microbiota transplantation did not induce germination of *C. difficile* strains and actually

inhibited vegetative growth (28). Moreover, administration of UDCA eradicated *C. difficile* infection in a patient with recurrent pouchitis (29). Indeed, it has been shown in experimental animal studies that complete microbial engraftment following fecal microbiota transplantation is not required to recover from recurrent *C. difficile* infection, and bile acid metabolism with formation of secondary bile acids (who typically harbored greater relative abundance of members of the *Clostridium* XIVa clade or *Holdemania* in the family *Erysipelotrichaceae*) could potentially provide resistance to the infection (30).

II. Liver

In the liver, FXR is predominantly expressed on hepatocytes and cholangiocytes, whereas TGR5 is expressed on non-parenchymal cells including hepatic macrophages (Kupffer cells), sinusoidal endothelial cells, and on the apical surface and primary cilium of cholangiocytes (31). In contrast, both receptors are poorly expressed on hepatic stellate cells. The importance of FXR and TGR5 in hepatic pathophysiology has led to the development of potent steroidal and non-steroidal agonists, with variable specificity for each of these receptors. These pharmacological agents are being tested for their anti-inflammatory and anti-fibrotic actions in diverse liver diseases including nonalcoholic steatohepatitis (NASH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and portal hypertension.

A. Primary Biliary Cholangitis

A (i). OCA: The POISE trial was a 12-month, double-blind, phase 3 trial followed by a 12-month, open-label extension examining the efficacy of 5 mg and 10 mg OCA, a selective FXR agonist, in PBC patients with inadequate response or intolerance to ursodeoxycholic acid (UDCA) (32). The trial met its primary endpoint, which was biochemical, and was approved for marketing; the long-term efficacy of OCA on patient survival and disease-related outcomes such as the need for liver transplantation is unknown, though improved outcome would be predicted based on previous studies that have associated improved prognosis in PBC patients with normalization of serum alkaline phosphatase (33). This study has entered a 5-year extension phase that will provide information on long-term outcomes. Pruritus, a significant symptom in PBC patients, is also the most common and dose-dependent adverse effect of OCA. In the POISE trial, only 4% of patients discontinued OCA due to pruritus, most in the 10 mg dosage group.

(Aii). IBAT inhibitors: In a Phase 2a, 14-day trial in PBC patients, the IBAT inhibitor, GSK2330672, reduced pruritus and the serum total bile acid by 50%s and increased serum C4 about 3-fold, consistent with impaired reabsorption and increased fecal bile acid losses. The most common and predictable adverse effect was diarrhea, which might limit its use (34).

The IBAT inhibitor, LUM001 (maralixibat), has been tested in combination with UDCA for treating pruritus in 66 patients with PBC (NCT01904058); the study results presented in Clinical Trials.gov show that changes from baseline in pruritus weekly sum score or serum alkaline phosphatase after 4, 8 or 13 weeks' treatment were not significant compared to UDCA alone.

(Aiii) FGF19 analog: NGM282 was tested in PBC patients with incomplete response to UDCA, and showed significant biochemical responses: reduced alkaline phosphatase and serum C4. The most common adverse effect was diarrhea (3–4 fold that of placebo), which might limit its long-term use (35).

B. Primary Sclerosing Cholangitis—In a preclinical mouse model of PSC, the dual FXR and TGR5 agonist, **INT-767**, improved liver injury, inflammation and fibrosis (36).

Based on the results of OCA observed in other liver diseases, OCA is being tested in PSC patients (NCT02177136) in a Phase 2 trial expected to be completed in November 2018. Similarly, **NGM282** is being tested in a phase 2 trial (NCT02704364).

An open-label, dose-finding, Phase 2 study of **LUM001 (maralixibat)** (NCT02061540) has been completed in 27 PSC patients, and there was significant reduction in fasting serum bile acids and numerical reduction (nonsignificant) in circulating liver enzymes, and no effect on pruritus after 14 weeks' treatment. A larger, randomized, placebo-controlled, double-blind trial is ongoing.

C. Nonalcoholic Steatohepatitis—Glucose homoeostasis, lipid and lipoprotein metabolism, inflammatory responses and intestinal dysbiosis are all components of the pathogenesis of NASH that are benefited by bile acid signaling (Figure 3). TGR5 activation is anti-inflammatory and increases energy expenditure in brown adipose tissue. Furthermore, it induces secretion of GLP-1 from enteroendocrine L cells. However, the wide tissue distribution of TGR5 limits the use of systemic agonists which can increase gallbladder volume and pruritus.

The FXR agonist, OCA, has shown clinical efficacy in the treatment of NASH. In the NIH-sponsored FLINT trial (37), OCA was evaluated in patients with biopsy-proven NASH. OCA, 25 mg, showed histologic improvement as assessed by the NAFLD activity score and alanine aminotransferase (ALT). This was associated with a modest weight loss, an increase in plasma low density lipoprotein (LDL) cholesterol, and a decrease in plasma high density lipoprotein cholesterol which reversed upon discontinuation of drug at study completion.

Results from a Phase 2a trial of the FGF19 analog, NGM282, in NASH patients showed significant reduction in liver fat, ALT and serum C4, and increase in serum LDL (38).

Accumulated empirical data have shown that loss of intestinal FXR protected high fat-fed mice from hepatic steatosis (39). Inhibition of the IBAT (ASBT) led to increased fecal bile acid loss and altered the bile acid pool to increase bile acids, which are agonists to FXR and enhance resistance to high fat diet-induced hepatic steatosis and glucose intolerance (40). Conversely, fexaramine, an intestinal FXR agonist, also ameliorated high fat diet-induced weight gain, insulin resistance and hepatic steatosis (41). Fexaramine treatment induced expression of intestinal Fgf15 (murine equivalent of human FGF19) with changes in bile acid composition. Therefore, larger and longer comparative studies will be needed to determine which of these approaches is efficacious in the long term. It is likely that both approaches, i.e., intestinal FXR agonism and antagonism, will ameliorate fatty liver, albeit

via different signaling pathways; one of these involves enteric FGF19 (agonist), whereas the antagonist may lead to primary changes in bile acid composition and the microbiome.

D. Pruritus, Diarrhea and Dyslipidemia—Pruritus (itch) is the most common symptom in PBC and is frequent in PSC and other cholestatic diseases such as intrahepatic cholestasis of pregnancy. Recent advances have identified bile acid activated neuronal TGR5 as one mechanism of cholestasis-induced pruritus (42,43). Though complete understanding of endogenous pruritogens remains obscure, pruritus is a frequent (~60% prevalence on OCA compared to 38% on placebo in 12-month trial in PBC patients) and dose-related adverse effect of OCA and may potentially be observed with TGR5 agonists (32,37,44). Bile acid diarrhea remains a potential side effect of intestinal FXR antagonists and IBAT antagonists. Lastly, increase in plasma LDL has been observed with the FXR agonist, OCA, and the FGF19 agonist, NGM282. Given the high prevalence of cardiovascular disease in obese patients, either a more selective agent without this adverse effect, or concurrent pharmacotherapy to lower LDL cholesterol may be necessary.

III. Conclusions

Bile acid signaling is the endogenous circuit for communication between the microbiome, intestine, liver and also other organ systems such as adipose tissue. Therapeutic manipulation of bile acid signaling has proven to be efficacious in several intestinal and hepatic diseases. This field has seen rapid advances, including the identification of receptors, FXR and TGR5, the development of candidate drugs, and the FDA approval of OCA for PBC patients.

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HIGHLIGHTS

- Bile acids are central signals in enterohepatic communication.
- The natural receptors for bile acids [farnesoid X receptor and G protein-coupled bile acid receptor 1 (GPBAR1) also known as TGR5] and transporters are therapeutic targets.
- Obeticholic acid (a selective FXR agonist) and NGM282 (a non-mitogenic FGF-19 analog) are two of the agents in this pipeline.

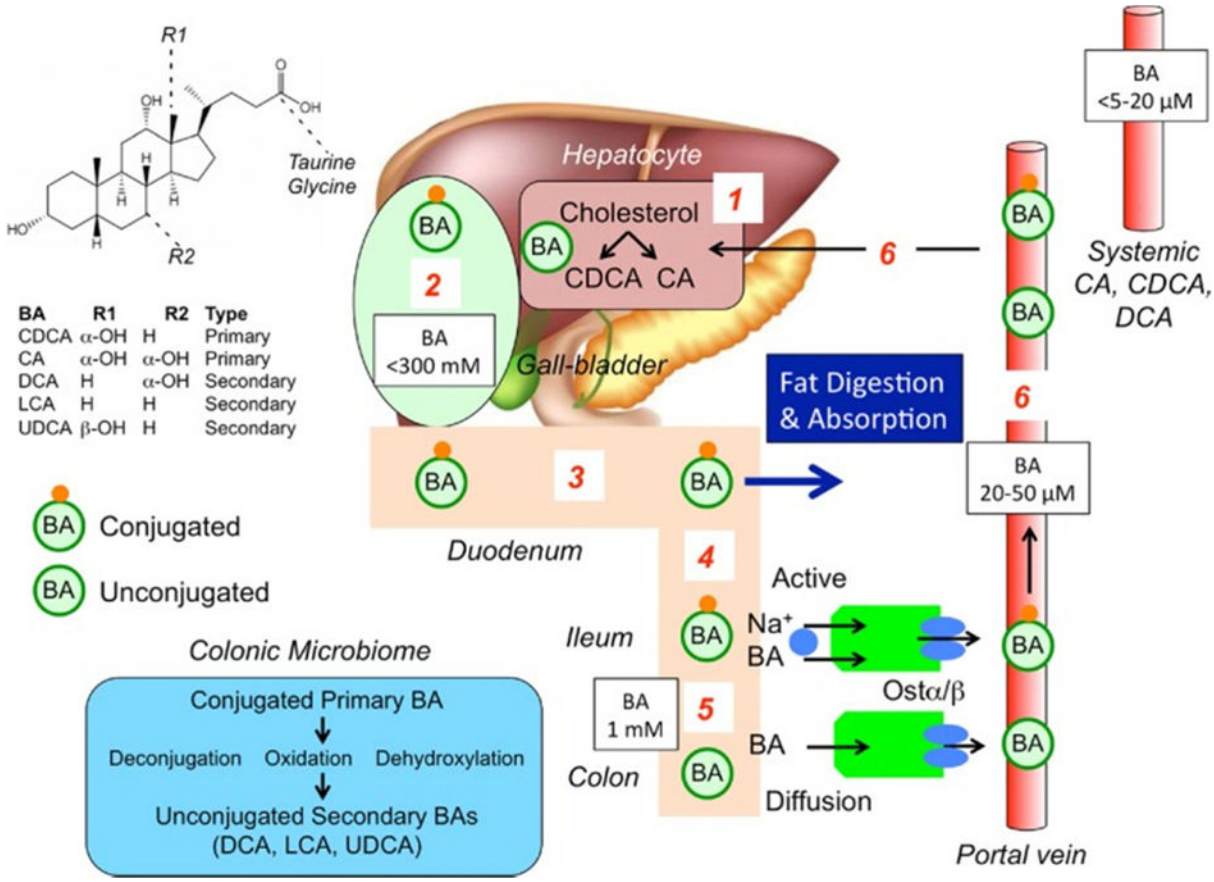

Figure 1. Synthesis, secretion and enterohepatic circulation of bile acids in humans

(1) Primary bile acids (BAs) are synthesized in hepatocytes from cholesterol. (2) BAs are conjugated to glycine and taurine and are stored in the gallbladder at high concentrations. (3) After feeding, conjugated BAs are secreted in the intestine where they emulsify dietary fats and form mixed micelles that facilitate digestion and absorption of the products of triglyceride digestion. (4) Conjugated BAs are actively absorbed by the apical sodium BA co-transporter (ASBT [IBAT]) at the apical membrane of enterocytes of the terminal ileum. (5) In the colon, bacteria deconjugate and dehydroxylate primary BAs to form secondary BAs, which are passively absorbed. (6) Conjugated and unconjugated BAs enter the portal vein and recirculate to the liver for re-use.

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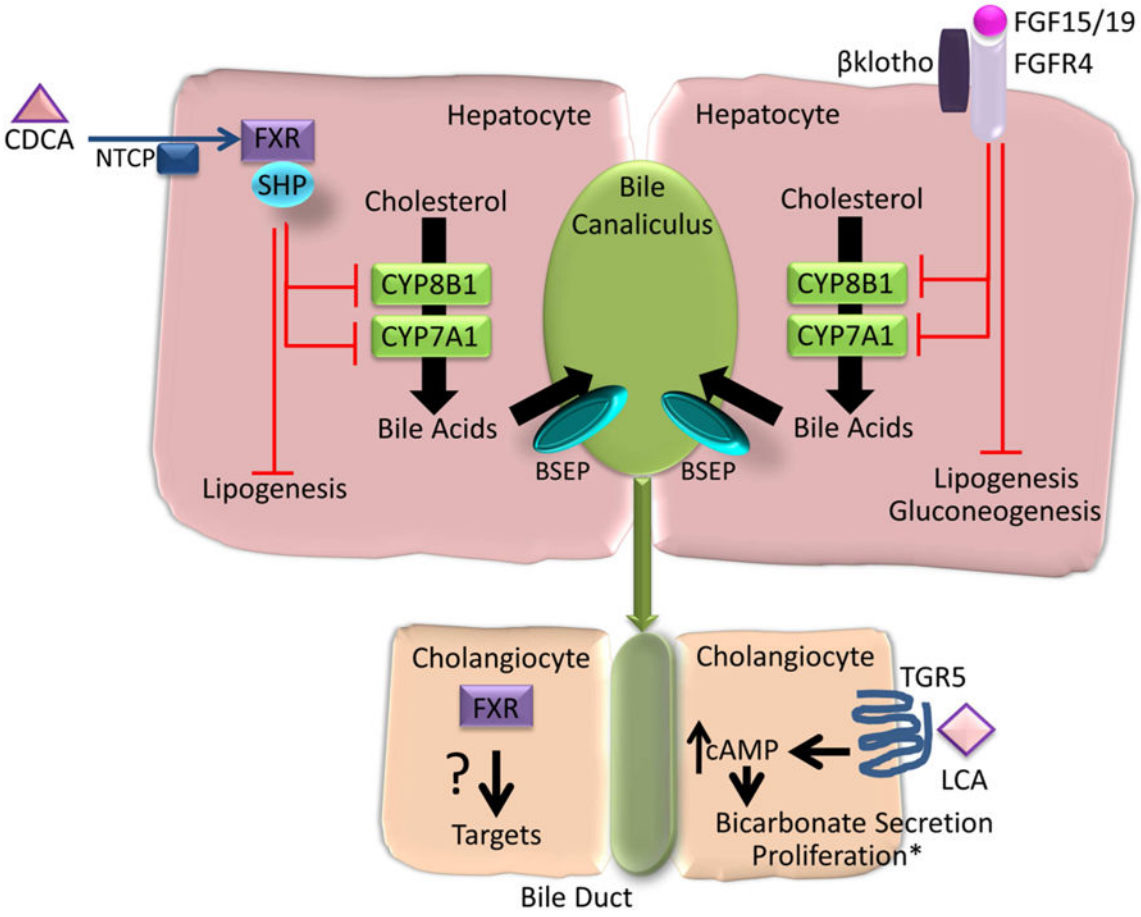

Figure 2. Bile acid induced FXR and TGR5 signaling in hepatocytes and cholangiocytes

The farnesoid X receptor (FXR) is expressed in hepatocytes and cholangiocytes. Of the natural bile acids, chenodeoxycholic acid (CDCA), most potently activates FXR leading to the induction of small heterodimer protein (SHP) and inhibition of cytochrome P450 (CYP) 7A1 and CYP8B1 and negative feedback regulation of bile acid synthesis from cholesterol. FXR stimulated FGF-19 (Fgf15 in mice) from enterocytes activates fibroblast growth factor 4 (FGFR4) and β klotho leading to inhibition of CYP7A1 and CYP8B1. Bile acids activation of FXR also inhibits lipogenesis and FGF19 inhibits lipogenesis and gluconeogenesis. Though FXR is expressed on cholangiocytes its biologic relevance is less well defined. Lithocholic acid (LCA) activates TGR5 which is expressed on cholangiocytes, and not on hepatocytes. TGR5 activation leads to an increase in intracellular cyclic AMP (cAMP) and bicarbonate secretion. *TGR5 activation leads to cholangiocyte proliferation, except in the case of ciliated cholangiocytes, where proliferation is inhibited. NTCP, sodium taurocholate cotransporting polypeptide. BSEP, bile salt export pump.

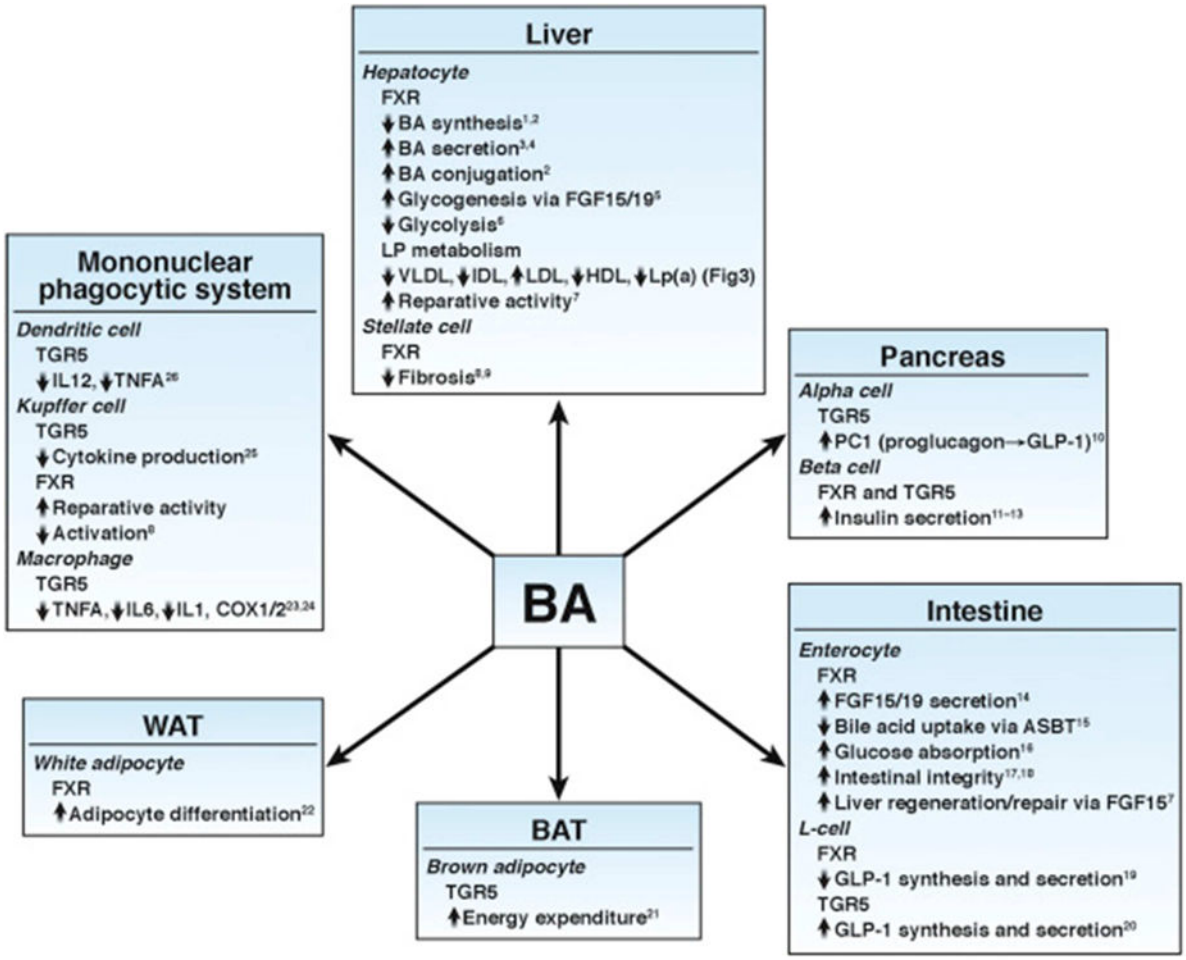

Figure 3. Role of BAs in the control of metabolic and immune homeostasis via activation of their receptors FXR and TGR5

COX, cyclooxygenase; IDL, intermediary density lipoprotein; IL, interleukin; Lp, lipoprotein; Lp(a), lipoprotein (a); VLDL, very-low-density lipoprotein.

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