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Pharmacology of Bile Acid Receptors: Evolution of Bile Acids from Simple Detergents to Complex Signaling Molecules

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Abstract

For many years, bile acids were thought to only function as detergents which solubilize fats and facilitate the uptake of fat-soluble vitamins in the intestine. Many early observations, however, demonstrated that bile acids regulate more complex processes, such as bile acids synthesis and immune cell function through activation of signal transduction pathways. These studies were the first to suggest that receptors may exist for bile acids. Ultimately, seminal studies by many investigators led to the discovery of several bile acid-activated receptors including the farnesoid X receptor, the vitamin D receptor, the pregnane X receptor, TGR5, α5 β1 integrin, and sphingosine-1-phosphate receptor 2. Several of these receptors are expressed outside of the gastrointestinal system, indicating that bile acids may have diverse functions throughout the body. Characterization of the functions of these receptors over the last two decades has identified many important roles for these receptors in regulation of bile acid synthesis, transport, and detoxification; regulation of glucose utilization; regulation of fatty acid synthesis and oxidation; regulation of immune cell function; regulation of energy expenditure; and regulation of neural processes such as gastric motility. Through these many functions, bile acids regulate many aspects of digestion ranging from uptake of essential vitamins to proper utilization of nutrients. Accordingly, within a short time period, bile acids moved beyond simple detergents and into the realm of complex signaling molecules. Because of the important processes that bile acids regulate through activation of receptors, drugs that target these receptors are under development for the treatment of several diseases, including cholestatic liver disease and metabolic syndrome. In this review, we will describe the various bile acid receptors, the signal transduction pathways activated by these receptors, and briefly discuss the physiological processes that these receptors regulate.

GRAPHICAL ABSTRACT

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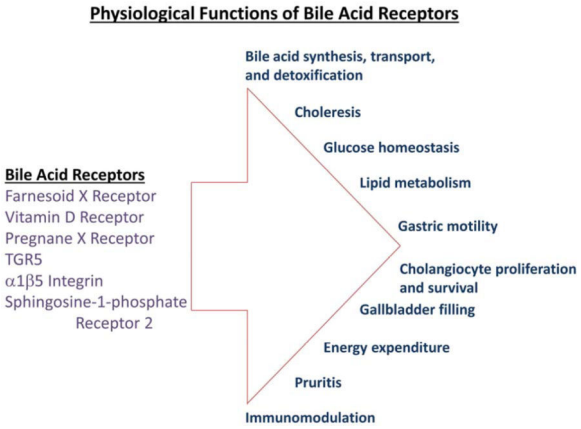

Keywords

Bile Acids; Farnesoid X Receptor; Vitamin D Receptor; Pregnane X Receptor; TGR5; Sphingosine-1-phosphate Receptor 2

1. Introduction

Bile acids are amphipathic molecules synthesized from cholesterol through a series of enzymatic reactions that predominately occur in hepatocytes in the liver (for excellent reviews of bile acid chemistry and metabolism see [1,2]). There are two pathways for the synthesis of bile acids, the classical or neutral pathway and the acidic pathway, which result in the formation of the primary bile acids, cholic acid (CA) and chenodeoxycholic acid (CDCA). These bile acids are further modified by conjugation reactions that add glycine or taurine to the bile acid backbone, which increases their hydrophilicity. In the gut, bile acids can also be modified by the gut flora to produce the secondary bile acids, deoxycholic acid (DCA) and lithocholic acid (LCA). After they are synthesized in hepatocytes, bile acids are secreted at the apical side of the hepatocytes into the bile canaliculi through active transport. Bile acids form mixed micelles with cholesterol and phospholipids and, along with other bile constituents, are stored in the gallbladder and ultimately secreted into the intestine through the bile duct. Approximately 95% of bile acids are reabsorbed by enterocytes in the gut and recycled back to the liver via the portal vein in a process called enterohepatic circulation. Within the liver, bile acids are reabsorbed back into hepatocytes by transporters expressed on the basolateral hepatocyte membrane.

For decades, bile acids were mainly thought to function in the gut where they solubilize fats and facilitate uptake of fat-soluble vitamins. Studies in the last two decades, however, have made it clear that bile acids are not only detergents, but important signaling molecules that signal throughout the body by activating various receptors, including nuclear receptors and G protein-coupled receptors. Through activation of these receptors, bile acids affect a number of important processes, including bile acid metabolism, glucose homeostasis, lipid metabolism, energy expenditure, gut motility, and immune cell function. Because of the wide distribution of bile acid receptors in the body, the list of functions of these “simple detergents” will most likely continue to grow. In this review, we will describe the various

receptors activated by bile acids; the signal transduction pathways down-stream of these receptors; and briefly discuss the physiological effects of activation of these receptors.

2. Activation of Nuclear Receptors by Bile Acids

Nuclear receptors are a group of ligand-activated transcription factors that play important roles in various aspects of development, physiology, and pathophysiology [3–5]. A typical nuclear receptor consists of an N-terminal DNA binding domain (DBD) that recognizes the consensus DNA response element in the target genes, and a highly conserved C-terminal ligand-binding domain (LBD) that usually binds hydrophobic small molecule ligands. Most nuclear receptors recognize two tandem AGGTCA-like consensus sequences and bind to DNA as either homodimers (e.g. glucocorticoid receptor) or heterodimers with the nuclear receptor retinoid X receptor (RXR) (e.g. Thyroid hormone receptor). A few nuclear receptors such as hepatocyte nuclear factor 4α (HNF4α) and liver receptor homologue-1 (LRH-1) bind DNA as a monomer. Ligand binding causes the LBD to undergo conformational changes that allow the nuclear receptor to recruit co-activators via the LXXLL motif-containing NR box on the co-activators which also displaces the co-repressor complex. Once recruited to the target gene promoter, the co-activator complex can function through chromatin remodeling to facilitate the assembly of the general transcriptional complex that eventually leads to transcriptional activation. Forty-eight nuclear receptor genes have been identified in the human genome and 49 nuclear receptors have been identified in the mouse genome [5]. Studies thus far have shown that bile acids directly bind and activate three nuclear receptors, the farnesoid X receptor (FXR) [6–8], the pregnane X receptor (PXR) [9], and the vitamin D receptor (VDR) [10]. These bile acid-activated nuclear receptors are highly expressed in the liver and/or the intestine which are routinely exposed to bile acids at relatively high concentrations [11,12]. In these tissues, these nuclear receptors act as sensors for bile acid levels in the enterohepatic circulation and in turn help to maintain bile acid homeostasis by regulating genes involved in bile acid synthesis, transport and detoxification. Furthermore, studies in recent years have further established key roles for these bile acid receptors in mediating bile acid regulation of nutrient metabolism, immune responses, and drug metabolism. Because of the pleiotropic effects of bile acid-activated nuclear receptors, these receptors are promising therapeutic targets for the treatment of several human diseases.

2.1 Farnesoid X Receptor

FXR, which is highly expressed in hepatocytes and enterocytes, was identified as a nuclear receptor that formed a heterodimer with RXR and was activated by farnesol in cell-based reporter assays [12]. Further studies determined, however, that farnesol did not directly bind to FXR, suggesting that other ligands activate this receptor. A few years later, several independent studies reported that both the free and conjugated primary bile acids, CDCA and CA, and to a lesser extent the secondary bile acids, DCA and LCA, activated FXR [6–8]. These studies not only identified the true ligand for FXR, but also identified the first bile acid receptor, which set into motion years of research aimed at discovering the many physiological functions of bile acids. Among all bile acids tested, CDCA was the most potent ligand of FXR with an EC_{50} = ~10 μM for human FXR and an EC_{50} = ~50 μM for

murine FXR. The more hydrophilic bile acids, UDCA and muricholic acid (MCA), do not activate FXR.

2.1.1 FXR regulation of bile acid homeostasis—Since the identification of FXR as the physiological bile acid receptor, extensive studies have been conducted to elucidate the roles of FXR in the regulation of bile acid homeostasis and in experimental cholestasis. Numerous studies have demonstrated increased susceptibility of *fxr* knockout mice to bile acid toxicity upon bile duct ligation (BDL), bile acid feeding or drug-induced intrahepatic cholestasis [13–15]. Furthermore, activation of FXR protects against liver injury in experimental models of cholestasis [16–18]. It is now established that the protective role of FXR against bile acid toxicity can be largely attributed to its function as a bile acid sensor in the enterohepatic system where it regulates bile acid synthesis, transport and excretion. Bile acid feedback inhibition of *CYP7A1*, which encodes the rate-limiting enzyme in the classic bile acid synthetic pathway, and other bile acid synthesis genes including *CYP8B1* and *CYP27A1*, are well-recognized mechanisms to decrease bile acid synthesis in response to an expanded bile acid pool or in cholestasis where bile acid concentrations are greatly elevated [19]. Sinal and colleagues demonstrated that bile acid inhibition of *CYP7A1* was defective in mice lacking FXR, which established a central role of FXR in regulating bile acid synthesis [20]. It is now clear that FXR can repress *CYP7A1* gene expression in the liver by sensing elevated bile acid concentrations in both the liver and the intestine. In the liver, FXR induces a nuclear receptor called small heterodimer partner (SHP), which acts as a co-repressor by interacting with and inhibiting the transcriptional activity of liver receptor homologue-1 (LRH-1) and its target gene *CYP7A1* [21,22]. In the intestine, FXR induces fibroblast growth factor 15 (FGF15) which acts in an endocrine manner to repress hepatic *CYP7A1* via binding to the FGF receptor 4 (FGFR4) on the hepatocytes [23,24]. Mice lacking either FGF15 or FGFR4 show elevated hepatic CYP7A1 mRNA and an enlarged bile acid pool size, while mice expressing a constitutively active FGFR4 show reduced hepatic CYP7A1 mRNA and a smaller bile acid pool [25,26]. The intracellular signaling mechanism that results in *CYP7A1* inhibition following FGFR4 activation has not been fully elucidated, however Erk1/2 signaling has been suggested by several independent studies [23,27,28]. In addition, the β-Klotho [29], cytoplasmic tyrosine phosphatase SHP-2 [30] and FGF receptor substrate 2 (FSR2) [31] have been identified as key components of the FGFR4 signaling complex at the plasma membrane. Deletion of any of these genes results in the loss of FGF15-mediated repression of the hepatic *CYP7A1* gene and an enlarged bile acid pool in mice. Human FGF19 shares ~51% amino acid sequence identity with mouse FGF15, and is considered to be the mouse FGF15 orthologue. FGF19 has also been shown to repress *CYP7A1* in human hepatocytes [27,32]. In contrast to mice where FGF15 is not expressed in hepatocytes, FGF19 mRNA is detectable not only in human ileum but also in human livers and human hepatocytes where it is induced by FXR [27,33,34]. Furthermore, circulating FGF19 levels are elevated in patients with obstructive cholestasis, where bile acid concentrations in the intestine are reduced, indicating that human hepatocytes produce FGF19 [33]. Finally, it is worth mentioning that the hepatic FXR/SHP cascade, but not the intestinal FXR/FGF15 axis, inhibit the *CYP8B1* gene which is involved in CA synthesis [28]. A more recent report identified MAFG as an FXR-induced liver transcriptional

repressor that inhibited *CYP8B1*, but not *CYP7A1*, and altered bile acid composition in mice [35].

Bile acids are secreted at the apical side of the hepatocytes into the bile via the bile salt export pump (BSEP). This process is highly efficient and helps maintain intracellular bile acid levels at relatively low concentrations. FXR activation not only induces BSEP [36], but also the phosphatidylcholine transporter, multidrug resistance protein 3 (MRP3, ABCB4) [17], and the cholesterol transporters, ATP-binding cassette transporter G5 and G8 (ABCG5 and ABCG8) [37]. Through this mechanism, FXR coordinates the biliary secretion of bile acids, cholesterol and phospholipids to form micelles in the canaliculus. This process increases cholesterol solubility and prevents bile acid toxicity to the bile duct epithelial cells [17,38,39]. Furthermore, this process decreases intracellular concentrations of bile acids in hepatocytes, thereby preventing bile acid toxicity. At the basolateral membrane of the hepatocyte, the sodium-taurocholate co-transporting polypeptide (NTCP) and isoforms of the organic anion-transporting polypeptide (OATPs) mediate the uptake of most bile acids from the portal circulation. In response to intrahepatic bile acid accumulation, FXR inhibits NTCP thereby decreasing bile acid uptake into hepatocytes and preventing toxicity [40]. Several transporters localized at the basolateral membrane of the hepatocytes, including the heteromeric organic solute transporter (OST) OSTα/β and several isoforms of multidrug resistance-associated proteins (MRP), efflux bile acids into the systemic circulation [41–45]. These transporters are induced in cholestasis resulting in elevated plasma bile acid concentrations and increased renal excretion of bile acids. The *OST*α and *OST*β genes are direct FXR targets [41], whereas induction of MRP1, MRP3, and MRP4 in cholestasis appears to be mediated by PXR [46,47].

In the intestine, bile acids are reabsorbed into the enterocytes via the apical sodium dependent bile acid transporter (ASBT). The intestine bile acid binding protein (I-BABP) facilitates intracellular bile acid transport to the basolateral side of the enterocytes where bile acids are secreted into the portal circulation via the OSTα/β heterodimer [48–50]. Activation of FXR increases both *I-BABP* and *OST*α and *OST*β gene transcription [41,51]. In addition, ASBT is inhibited by FXR [48,49]. Therefore, bile acid accumulation in enterocytes activates FXR which decreases bile acid uptake and promotes bile acid efflux. In addition, as discussed above, activation of FXR in the intestine represses hepatic bile acid synthesis via the FGF15/FGF19-FGFR4 signaling axis [23,24]. In mice lacking OSTα, bile acids accumulate in enterocytes resulting in increased FGF15 which represses hepatic bile acid synthesis, thereby decreasing the bile acid pool size [52,53]. In contrast, mice lacking ASBT have reduced intestinal FGF15 and increased hepatic CYP7A1, which protects against hypercholesterolemia and atherosclerosis most likely through increased conversion of cholesterol to bile acids [54]. The major mechanisms of regulation of bile acid synthesis and transport by FXR in hepatocytes and ileal epithelial cells are summarized in Figure 1.

2.1.2. FXR regulation of lipid and glucose metabolism—Bile acid binding resins have been shown to raise plasma triglyceride levels in patients undergoing cholesterol lowering therapies [55–57]. This demonstrated that prevention of bile acid re-absorption in the intestine, which attenuates bile acid signaling in the liver, causes hypertriglyceridemia, suggesting an important role for FXR in regulation of lipid metabolism [55–57]. Consistent

with this finding, mice lacking FXR have increased hepatic lipid levels; elevated circulating total cholesterol and triglycerides; and a pro-atherogenic lipoprotein profile [20]. In contrast, activation of FXR decreases plasma cholesterol and triglycerides in mice [58]. One mechanism by which FXR decreases lipids is via induction of SHP which interacts with and inhibits sterol regulatory element-binding protein-1c (SREBP-1c) and the carbohydrate response element binding protein (ChREBP) [59,60]. SREBP-1c increases expression of a number of genes involved in *de novo* lipogenesis [61–63], whereas ChREBP induces lipogenic genes, such as *liver pyruvate kinase* (*L-PK*) to facilitate the conversion of carbohydrate into fatty acid. In addition to inhibiting lipogenesis by inhibiting SREPB-1c and ChREBP, more recent studies suggest that FXR may also decrease hepatic fat accumulation via promoting fatty acid oxidation. One study showed that FXR induced hepatic carboxyl esterase 1 (CES1) [64], which converts triglycerides into free fatty acids and thus facilitates hepatic fat mobilization and oxidation. Indeed, mice lacking CES1 developed obesity and hepatic steatosis, presumably due to defective intracellular TG mobilization [64]. Another study showed that FXR induces hepatic production of FGF21 [65], a key fasting-induced regulator of lipid oxidation and ketogenesis [66–68]. In addition to the regulation of hepatic fat content, FXR activation also induces hepatic expression of apolipoprotein CII (ApoCII) and apolipoprotein A5 (ApoA5), which are lipoprotein lipase (LPL) activators, and FXR activation represses Apolipoprotein CIII (ApoCIII), which is an LPL inhibitor [69–71]. These liver-produced apolipoproteins are carried by VLDL particles in the circulation and play critical roles in modulating LPL activity and thus VLDL-TG hydrolysis in peripheral tissues. Collectively, these studies demonstrate that FXR regulates plasma triglyceride levels via a number of mechanisms that inhibit hepatic lipogenesis and stimulate peripheral triglyceride clearance.

Oral administration of bile acids or the FXR agonist, GW4064, decrease fasting plasma glucose levels and improve insulin sensitivity in diabetic mice [58,72]. Un-repressed hepatic gluconeogenesis is a major cause of fasting hyperglycemia in type-II diabetes. Many studies have shown that FXR decreases expression of the hepatic gluconeogenic genes *phosphoenolpyruvate carboxykinase* (*PEPCK*) and *glucose 6 phosphatase* (*G6Pase*) via a SHP-dependent mechanism. Thus far, many transcriptional factors that activate PEPCK and G6Pase gene transcription, including CREB [73], FoxO1 [74], C/EBP [75], glucocorticoid receptor [76], HNF3 [77] and HNF4α [74] are inhibited by SHP via direct protein-protein interactions. In addition, a recent study showed that FGF15 can act as a postprandial hormone and regulate glucose homeostasis in the liver [78,79]. Interesting, high glucose causes FXR *O*-Glc-*N*-acylation, and this posttranslational modification potentiates the ligand-dependent trans-activating activity of FXR, therefore linking hepatic glucose influx to FXR regulation of hepatic glucose metabolism [80]. The major functions of FXR are illustrated in Figure 1.

2.1.3 FXR agonists for the treatment of cholestasis and non-alcoholic steatohepatitis (NASH)—An FXR agonist is currently being tested clinically for the treatment of two forms of liver disease: cholestasis and nonalchoholic steatohepatitis (NASH). The rationale is based on the demonstrated roles of FXR in the regulation of bile acid metabolism, lipid metabolism and inflammation in many preclinical studies.

Obeticholic acid (OCA) is a 6α-ethyl CDCA derivative and a potent FXR agonist with an EC_{50} of ~ 100 nM [81–83]. In experimentally induced cholestasis, OCA protected against cholestatic liver injury in mice [18,82]. Clinical trials also showed that OCA significantly improved liver tests in patients with primary biliary cirrhosis (PBC), indicating that OCA may be a promising therapy for PBC, especially for PBC patients that do not show an adequate response to UDCA [84,85]. Furthermore, OCA has also shown promise in treating NASH based on the outcome of several recent clinical trials [83,86]. A randomized, placebo-controlled clinical trial showed that OCA administration to patients with type-II diabetes and fatty liver disease improved insulin sensitivity and decreased liver enzymes and markers of fibrosis [87]. More recently, the FXR receptor ligand OCA in NASH treatment (the FLINT) trial, a multicenter, double-blinded, placebo-controlled clinical trial including over 200 NASH patients, reported that OCA at a daily oral dose of 25 mg for 72 weeks improved histological NASH score by at least 2 points [86]. OCA treatment was associated with the development of pruritus in some patients, and increased plasma LDL cholesterol and decreased HDL-cholesterol. Because of this, studies investigating the long-term effectiveness and safety of OCA in treating PBC and NASH are still needed. In addition, whether OCA would be effective in other cholestatic diseases, such as primary sclerosing cholangitis remains to be determined.

2.2 Pregnane X Receptor

The PXR is a nuclear receptor that functions as a xenobiotic sensor [88]. It was originally identified as a receptor that is activated by steroids, such as pregnenolone and synthetic glucocorticoids [11]. Studies over the past several decades, however, have solidified its importance as a xenobiotic sensor that promotes detoxification and excretion of potentially harmful chemicals from the body. This receptor is highly expressed in the intestine and liver [11], where it regulates expression of various cytochrome P450s (i.e., phase I detoxification pathways); phase II conjugation enzymes, such as sulfotransferases and glucuronosyltransferases; and uptake and efflux transporters (i.e., phase III metabolism) [89,90]. Coordinated regulation of these genes in cells, such as hepatocytes, promotes uptake of xenobiotics where they are detoxified by phase I and phase II metabolic pathways, and subsequently secreted into the bile via efflux transporters for elimination from the body.

As indicated above, PXR is also activated by endobiotics, such as steroids. In 2001, Staudinger and colleagues demonstrated that PXR is activated by lithocholic acid (LCA) and 3-keto-LCA. In a competitive binding assay, LCA and 3-keto-LCA bound with an IC_{50} of approximately 10 μM [9]. While this suggested that PXR may be another bile acid sensor similar to FXR, LCA concentrations in serum are less than 100 nM, and even in patients with severe cholestasis, LCA concentrations in serum remain below 100 nM [91]. At these concentrations, LCA most likely does not activate PXR. It is conceivable; however, that rupture of intrahepatic bile ducts during cholestasis could expose hepatocytes to bile, where concentrations of LCA reach as high as 10 μM [91,92]. In this case, activation of PXR could protect the liver from toxicity by increasing expression of cytochrome P450s that hydroxylate bile acids to less toxic, more hydrophilic bile acid species that are subsequently excreted into the bile. PXR also induces the bile acid conjugation enzymes SULT2A1 and UGTs that are involved in phase II bile acid metabolism and detoxification [93,94]. In

addition, studies have shown that PXR suppresses CYP7A1, which would decrease the bile acid pool potentially limiting liver injury during cholestasis [9]. Consistent with a protective role for PXR in cholestasis, mice lacking PXR were shown to be more susceptible to hepatotoxicity caused by LCA administration or BDL [9,95]. In support of a protective role for PXR in humans, treatment of patients with primary biliary cirrhosis with the PXR activator rifampicin decreased biomarkers of liver disease, indicating that activation of PXR is beneficial in conditions, such as cholestasis [96–99]. This protective effect is most likely due to detoxification of bile acids by cytochrome P4503A4 (CYP3A4)-mediated hydroxylation, as Marschall and colleagues demonstrated that rifampicin increased levels of CYP3A4 in the livers of patients with gallstone disease [100]. Interestingly, though, in this study rifampicin did not affect levels of CYP7A1 indicating that PXR may not be an important regulator of bile acid synthesis in humans [100]. Accordingly, activation of PXR by LCA during severe cholestasis may serve to limit liver injury by detoxification of bile acids.

2.3 Vitamin D Receptor

The classic endogenous ligand of VDR is vitamin D, with vitamin D_3 as the most important form in humans. VDR is highly expressed in the osteoblasts, kidney and many types of immune cells including macrophages and T and B lymphocytes, and plays a central role in mediating the biological functions of vitamin D including the regulation of calcium homeostasis, cellular proliferation, and immunity [101–104]. In the enterohepatic system, VDR is expressed at high levels in the small and large intestines but at very low levels in the liver. In 2002, Makishima et al reported that the secondary bile acid LCA and its metabolite 3-keto-LCA acted as endogenous ligands of VDR in the intestine [10]. Activation of VDR by toxic secondary bile acids induced bile acid metabolizing cytochrome p450 CYP3A4 that detoxified bile acids in the intestine [10]. LCA and 3-keto-LCA activated human VDR with an EC_{50} of ~ 8 μM and 3 μM, respectively [10]. The LCA derivatives LCA acetate and LCA propionate were later identified as more potent VDR agonists and both activated VDR with an EC_{50} of ~0.4 μM [105,106]. In contrast, the primary bile acids CDCA, CA, the secondary bile acid DCA and the hydrophilic bile acid MCA do not activate VDR [10]. Further studies showed that activation of VDR by LCA or 1,25 VD_3 regulates genes involved in bile acid synthesis, conjugation, transport and metabolism. These findings revealed a crosstalk between vitamin D signaling and bile acid/drug metabolism.

The intestine is constantly exposed to high concentrations of bile acids. Although most conjugated primary and secondary bile acids are efficiently re-absorbed in the terminal ileum and transported back to the liver, unconjugated bile acid species enter the colon where they can be either re-absorbed via passive diffusion or be excreted into feces [107]. Particularly, highly toxic secondary bile acids DCA and LCA are thought to promote bowel inflammation and colon carcinogenesis [108]. LCA is efficiently detoxified by CYP3A enzymes in the intestine and only trace amounts of LCA reach the liver under normal conditions. Two studies first showed that treating intestine derived cells with 1, 25 VD_3 induced the expression of CYP3A4 via a promoter ER6 motif that is recognized by VDR/RXR heterodimer, suggesting vitamin D signaling regulates drug metabolism [109,110]. The identification of LCA and LCA metabolites as endogenous VDR ligands

revealed a novel role of VDR as an intestine bile acid sensor in protecting the gut from bile acid toxicity. In enterocytes, CYP3A4 catalyzes the hydroxylation of LCA, and hydroxylated LCA can further undergo sulfation mediated by SULT2A1. LCA and its metabolites can be effluxed via the bile acid and the drug transporter MRP3. Indeed, VDR activation induced both SULT2A1 [111] and MRP3 [112], suggesting that VDR activation promotes phase I, II and III bile acid detoxification in the intestine. In the small intestine, 1, 25 VD_3 activation of VDR induced *ASBT* gene transcription and promoted ileal bile acid transport, which may play a role in regulating the enterohepatic bile acid circulation under normal physiology [113]. Administration of 1, 25 VD_3 to mice fed bile acids reduced hepatic and plasma bile acid levels and increased renal bile acid excretion [114]. Intestine-specific *vdr* knockout mice were more susceptible to LCA-induced hepatotoxicity, which was attenuated by CYP3A4 over-expression in the intestine [115].

Numerous clinical studies and basic research support a role of intestine VDR signaling in the pathogenesis and treatment of inflammatory bowel diseases [116]. Vitamin D deficiency was associated with higher risk of inflammatory bowel diseases, while higher vitamin D intake lowers this risk. Inflammatory bowel disease is an idiopathic inflammatory disorder whose pathogenesis is thought to involve alterations of the mucosal barrier function and the immune responses to gut bacteria and pathogens [117,118]. Inflammatory bowel diseases are frequently associated with bile acid malabsorption and increased intestinal bile acid levels, which alter gut permeability and integrity and promote disease progression [119–121]. Bile acids in the intestine are known to act as potent anti-microbial agents and controls gut bacteria growth and gut microbiome composition. The increasing prevalence of Western diet and life style has been linked to altered bile acid metabolism and gut dysbiosis, providing a potential mechanistic explanation for higher risk of inflammatory bowel diseases in the obese and diabetic populations [122]. Studies in animal models of inflammatory bowel disease suggest that the protective effects of VDR activation against inflammatory bowel disease can be attributed to attenuated gut epithelial cell apoptosis and improved mucosal barrier function [123,124]. VDR inactivation not only diminishes the bile acid detoxification mechanisms, but also disrupts bile acid homeostasis, causing enlarged bile acid pool size and hydrophobicity [125]. These studies support a mechanistic link.

Despite low expression of VDR in the liver, treating primary human hepatocytes with 1, 25 VD_3 induced CYP3A, CYP2B, and CYP2C [126], suggesting a functional VDR signaling in the liver. During cholestasis, CYP7A1 is transcriptionally repressed to decrease bile acid synthesis. In addition to FXR and PXR, studies have suggested that VDR may also play a role in mediating bile acid inhibition of CYP7A1 in the hepatocytes [127,128]. Consistently, a recent study showed that *vdr* knockout mice had higher hepatic *cyp7a1* gene expression and enlarged bile acid pool size, while 1, 25 VD_3 treatment repressed hepatic *cyp7a1* gene expression in mice [125]. VDR activation transcriptionally induced intestine FGF15 to repress hepatic CYP7A1, and 1,25 VD_3 failed to repress CYP7A1 in *fgf15* knockout mice. In contrast, Chow et al. recently showed that injecting mice with 1, 25 VD_3 increased hepatic CYP7A1 by decreasing hepatic SHP expression and lowered cholesterol levels [129]. Such discrepancy between studies in *vdr* knockout mice and 1α, 25-dihydroxyvitamin D_3 treated mice is still not clear.

Based on the role of VDR in the regulation of bile acid synthesis and detoxification, a number of studies have been carried out to investigate the potential effects of VDR activation or VDR deficiency on experimental cholestasis. When 1, 25 VD_3 was administered to mice undergoing bile duct ligation (BDL), major effects observed were significant reduction of hepatic inflammatory cytokine mRNA expression and reduced circulating cytokine levels [130]. Consistent with the known role of VDR in immunity [101], these results suggest that the anti-inflammatory properties of VDR may provide certain benefits during cholestasis. Administration of 1, 25 VD_3 did not significantly alter hepatic and plasma bile acid levels, but increased renal MRP2, MRP3 and MRP4 mRNA expression and increased renal bile acid secretion [114,130], suggesting VDR activation may also promote renal bile acid elimination under cholestasis conditions. VDR deficient mice were more susceptible to BDL-induced liver injury, which was accompanied by impaired adaptive induction of CYP3A, MDR2 and MRP3 [131]. Importantly, the higher susceptibility of *vdr* KO mice to bile acid-induced hepatotoxicity has also been attributed to VDR function in biliary epithelial cells to maintain bile duct integrity [131,132], similar to its role in regulating gut mucosal barrier function [123,124]. Based on current evidence, the protective role of VDR activation seemed to be independent of direct modulation of hepatic bile acid synthesis in experimental cholestasis.

GWAS studies have identified an association between *VDR* polymorphisms and the risk of obesity, insulin resistance and metabolic syndromes [133,134]. It is well known that obesity is strongly associated with vitamin D deficiency in humans [135]. For this reason, it is still largely uncertain if vitamin D deficiency actually contributes to the development of obesity and metabolic syndrome in humans [136]. So far intervention studies did not seem to suggest that vitamin D supplementation impacted body weight in humans [137]. Nevertheless, several studies in experimental animal models demonstrated that deficient VDR signaling reduced weight gain and prevented diet-induced obesity and associated metabolic disorders in mice [138–140]. The mechanisms underlying the anti-obesity phenotype of VDR deficient mice were not fully understood, but VDR deficient mice showed highly elevated *uncoupling protein-1* (*UCP-1*) gene expression in adipose tissue and increased energy expenditure. As mentioned early, *vdr* KO mice had significantly enlarged bile acid pool which was also more hydrophobic [125]. As discussed in section 3.1 of this review, bile acids are known to reduce body weight gain via activation of TGR5 signaling in adipose and muscle [141]. Studies in several animal models showed that enlarged bile acid pool size prevented diet-induced obesity in mice [141–143]. These findings indicate a possible role of bile acid signaling in linking VDR signaling and the development of diet-induced obesity in mice.

3. Activation of Signal Transduction Pathways by Bile Acids

3.1 TGR5

As discussed in sections above, bile acids produce many of their effects through modulation of gene expression by activating nuclear receptors. Early studies in the colon, however, demonstrated that bile acids stimulate a rapid increase in cAMP, suggesting activation of signal transduction pathways independent of modulation of gene expression [144,145]. This

suggested the existence of a membrane receptor for bile acids. It was not until 2002, however, that Maruyama and colleagues identified a G protein-coupled receptor activated by bile acids they named M-BAR [146]. At the same time, Kawamata and colleagues were investigating the mechanism by which high concentrations of bile acids suppress macrophage activation [147,148]. In these studies, they identified the same G protein-coupled receptor as Maruyama and colleagues, which they named TGR5 [149]. Although bile acids are most often associated with the gastrointestinal tract, TGR5 is widely distributed throughout the body and is expressed at high levels in the placenta and spleen and at lower levels in the heart, lung, liver, kidney, stomach, gallbladder, small intestine, colon, adipose tissue, and various endocrine glands [149]. In addition to these tissues, others have detected Tgr5 in the mouse spinal cord and astrocytes [150,151]. The ubiquitous nature of Tgr5 indicates that bile acid function may not be limited to digestion and the absorption of fat soluble vitamins in the gastrointestinal tract and that bile acids may have unrecognized functions throughout the body. Subsequent studies aimed at understanding the function of TGR5 have confirmed this.

In Chinese hamster ovary (CHO) cells transfected with human TGR5, the rank order of potency for activation by bile acids is LCA ≥ DCA > CDCA > CA, with taurine conjugates being more potent than glycine conjugates [149]. Bile acids stimulate production of cAMP in CHO transfected cells with EC_{50} values ranging from 0.33 uM for TLCA to 7.72 uM for CA [149]. In most cell types examined, TGR5 activates adenylate cyclase through coupling to Gs leading to the production of cAMP. In transfected CHO cells, however, activation of TGR5 not only stimulated production of cAMP, but also stimulated phosphorylation of Erk1/2 indicating that many signaling pathways may be activated by this receptor [149].

Because of the wide tissue distribution of TGR5, this receptor regulates a variety of processes in the body ranging from glucose homeostasis to immune cell regulation. As discussed above, TGR5 was identified as the receptor responsible for bile acid-mediated suppression of macrophage activation [149]. In these studies, bile acids inhibited macrophage phagocytosis; inhibited LPS-induced upregulation of tumor necrosis factor- α (TNF- α); and decreased basal mRNA levels of TNF- α, interleukin-1 α (IL-1 α), IL-1 β, IL-6, and IL-8. Subsequent studies in RAW264.7 macrophages demonstrated that these effects were mediated by Tgr5-dependent inhibition of NF-κB activation through an increase in cAMP [152]. In addition, this same group showed further that pharmacological activation of Tgr5 in bone marrow-derived macrophages, reduced LPS-induced chemokine production by a mechanism that required AKT-dependent activation of mTOR complex 1 (mTORC1), which stimulated production of the dominant-negative C/EBPβ isoform, liver inhibitory protein (LIP) [153]. They proposed that expression of LIP then prevented upregulation of chemokines by LPS. In addition to these mechanisms, Wang and colleagues demonstrated that Tgr5 activation stimulated β-arrestin2 to interact with IκBα, thereby inhibiting NF-κB activation [152]. Lastly, Yoneno and colleagues demonstrated that Tgr5 activation prevented phosphorylation of c-Fos in a cAMP-dependent manner, which they proposed contributed to inhibition of macrophage activation [154]. Collectively, these studies demonstrate that bile acid activation of Tgr5 inhibits macrophage activation by several mechanisms. Although it is unclear why this mechanism of macrophage inhibition evolved, it is possible that activation of this receptor on macrophages in the gut may limit their activation by bacterial products. In

addition, it is possible that post-prandial concentrations of bile acids, which are increased in the liver, limit Kupffer cell activation as products of digestion from the intestine enter the liver through the portal circulation. This may prevent Kupffer cells from reacting to innocuous contents in the food, which may otherwise stimulate an inflammatory response.

In addition to macrophages, TGR5 has many functions in the gastrointestinal system. As discussed above, TGR5 is present in the stomach, liver, gallbladder, small intestine and colon [149]. In the mouse liver, Tgr5 is expressed by several cell types, including Kupffer cells, sinusoidal endothelial cells, and cholangiocytes, and in the gallbladder it is expressed in epithelial cells and smooth muscle cells [155–158]. In biliary epithelial cells, activation of Tgr5 leads to an increase in cAMP, which stimulates chloride secretion through cystic fibrosis transmembrane conductance regulator (CFTR) [155]. In addition, elevated concentrations of cAMP stimulate insertion of ABST into the apical membrane leading to bile acid uptake which stimulates mucin and fluid secretion [155]. In addition to biliary epithelial cells, Tgr5 is expressed in the smooth muscle cells of the gallbladder [159]. In these cells, activation of Tgr5 leads to opening of an ATP-dependent potassium channel, which leads to smooth muscle relaxation and gallbladder filling. In cholangiocytes it was recently shown that activation of Tgr5 stimulates cholangiocyte proliferation through a mechanism that depends upon src-dependent activation of the epidermal growth factor receptor (EGFR). In addition, it was shown that activation of Tgr5 prevents death receptor-mediated apoptosis. These same studies demonstrated that Tgr5 was overexpressed in human cholangiocarcinoma cells, indicating a potential role for this receptor in the development of this cancer [160]. Lastly, in the gut, Tgr5 is expressed in the enteric nervous system, where its activation stimulates the release of 5-hydroxytryptamine and calcitonin gene-related peptide (CGRP) which stimulate colonic motility [161,162].

In addition to the enteric nervous system, Tgr5 has been detected in the dorsal root ganglia and spinal cord of mice [150]. In particular Tgr5 is expressed in peptidergic neurons within these regions [150]. Activation of Tgr5 on these neurons stimulates release of gastrin-releasing peptide, which is responsible for mediating itch in the dorsal spinal cord. It has been suggested that pruritus, which occurs in patients with cholestasis, where bile acid concentrations are greatly increased, may result from activation of this pathway [150]. In addition to this study, it was recently shown that Tgr5 activates transient receptor potential cation channel, member A1 (TRPA1) in cutaneous afferent neurons, which may also mediate itch during cholestasis [163]. Interestingly, activation of TRPA1 by Tgr5 required $G\beta\gamma$, protein kinase C, and calcium.

One of the more surprising functions of Tgr5 was the discovery of its role in increasing energy expenditure and decreasing insulin resistance. Watanabe and colleagues demonstrated that bile acids increased levels of the thyroid hormone activating enzyme type 2 iodothyronine deiodinase (D2) in a cAMP-dependent manner through activation of Tgr5 in skeletal muscle and brown adipose tissue [141]. This led to an increase in the active form of thyroid hormone (T3) which increased energy expenditure in brown adipose tissue. In addition, they showed that feeding mice a high fat diet containing cholic acid prevented weight gain compared to mice fed a high fat diet alone [141]. This effect was associated with a decrease in adiposity in these mice. More recently, Broeders and colleagues demonstrated

that oral supplementation with CDCA increased activity in brown adipose tissue in humans [164]. In addition they showed that bile acids produced mitochondrial uncoupling in primary human brown adipocytes but not white adipocytes [164]. Lastly, consistent with studies in rodents, bile acids increased D2 mRNA levels in human brown adipose tissue. Collectively, these studies indicate an important role for Tgr5 and bile acids in regulation of energy expenditure, an effect that is currently being explored as a possible target of therapy in obesity.

In addition to energy expenditure, Thomas and colleagues showed that Tgr5 regulates plasma glucose levels. In this study, they demonstrated that activation of Tgr5 stimulates glucagon-like peptide-1 (GLP-1) release from intestinal enteroendocrine L cells in a calcium-dependent manner [165]. GLP-1 would decrease glucagon and increase insulin secretion in a glucose-dependent manner resulting in reduced plasma glucose levels. In addition to this mechanism, studies have shown that activation of Tgr5 on pancreatic beta cells stimulates insulin release through a cAMP- and calcium-dependent mechanism [166]. All of these actions of Tgr5, including the effects on energy expenditure, are of importance to pharmacology since Tgr5 agonists could decrease obesity and increase glucose tolerance, both effects that would greatly benefit individuals with metabolic syndrome. The pleiotropic actions of Tgr5 activation, however, could lead to several side-effects from agonist drugs targeting Tgr5, including pruritus and inappropriate gallbladder filling, which was shown recently [167] [150]. Furthermore, the ability of Tgr5 activation to stimulate cholangiocyte proliferation and enhance survival of cholangiocytes could increase the risk for the development of cholangiocarcinoma [160]. The major functions of TGR5 are illustrated in Figure 2.

3.2 α5β1 integrin

UDCA is the only FDA approved treatment for cholestatic liver disease. UDCA lessens disease severity in some patients by stimulating bile flow from the liver through increased insertion of transporters in the canalicular membrane of hepatocytes [168]. The mechanism by which UDCA produces this effect, however, was not known until recently. In humans, UDCA is rapidly conjugated to taurine [169]. Accordingly, in 1997, the laboratory of Dieter Haussinger began investigating the mechanism by which TUDCA stimulates choleresis by identifying signaling pathways that are activated in hepatocytes by TUDCA. In these studies, they demonstrated that TUDCA activated Erk1/2 in primary rat hepatocytes [170]. Activation of Erk1/2 by TUCDA occurred independently of the G proteins, Gi and Gs, and independently of PKC. Activation of Erk1/2, however, was inhibited by PKA activation. They showed further that Erk1/2 activation required Ras, which was activated in a PI3-kinase-dependent manner [170]. In a subsequent series of studies, they showed that TUDCA rapidly activated focal adhesion kinase (FAK), src, and p38 [171]. Inhibition of src prevented activation of p38, but did not affect activation of FAK or activation of Erk1/2 [171]. Because FAK is a down-stream target of integrins, they next determined the effect of integrin inhibition on activation of these pathways. Interestingly, inhibition of integrins with a broad-spectrum integrin antagonist prevented activation of FAK, src, Erk1/2, and p38 [171]. Most recently, this group demonstrated that TUDCA activated α5 β1 integrin in hepatocytes by a mechanism that required NTCP, which transports TUDCA into the cell

[172]. This suggested that TUDCA may activate α5 β1 by interacting with an intracellular domain of this integrin [172]. In support of this, they provided computational modeling suggesting that TUDCA may directly bind to this integrin causing changes in its structure that triggers integrin-dependent signaling [172]. Interestingly, this effect of TUDCA was selective as other conjugated bile acids did not activate α5 β1 integrin in hepatocytes. From these results, they proposed the pathway illustrated in Figure 3.

3.3 Sphingosine-1-phosphate Receptor 2

Similar studies by the laboratory of Dr. Phillip Hylemon and other investigators have investigated the mechanism by which bile acids activate various signal transduction pathways in hepatocytes. These studies showed that the MAP kinase, Jnk1/2, was activated by DCA, TCA, TDCA, and TCDCA, but not by TUDCA in hepatocytes [173]. Interestingly, activation of Jnk1/2 by DCA required ligand-independent activation of the FAS receptor [174]. Activation of the FAS receptor required sphingomyelinase and the generation of ceramide [174]. This pathway appears to be important for the regulation of bile acid synthesis, as activation of Jnk1/2 by bile acids led to upregulation of SHP which suppresses *CYP7A1* gene transcription [173]. While these studies demonstrated an important role for the FAS receptor and ceramide in DCA-mediated activation of Jnk1/2, whether conjugated bile acids activate Jnk1/2 through this pathway remains to be determined.

Studies showed further that DCA and other bile acids activated the epidermal growth factor receptor (EGFR) and the insulin receptor (IR) in primary rat hepatocytes in a ligand-independent manner[175,176]. Activation of Erk1/2 by DCA was prevented by inhibition of either EGFR or IR and by inhibition of Ras, MEK, and PI3-kinase [176]. In addition to DCA and TUDCA, Raf-1 and Erk1/2 were activated by GUDCA, TCA, GCA, TDCA, GDCA, TCDCA, UDCA, and GCDCA, but interestingly not by the primary bile acid CA, indicating that conjugation of CA was necessary for activation of this pathway [177]. Furthermore, activation of Erk1/2 by bile acids was not the result of the detergent properties of these chemicals, as the detergent CHAPS did not affect Erk1/2 activation. In addition to Erk1/2 and Jnk1/2, DCA also activated p38 independent of Erk1/2 activation. Further studies by this group demonstrated that activation of MAP kinases by DCA occurred through a mechanism distinct from that of conjugated bile acids. These studies showed that DCA stimulated production of reactive oxygen species by mitochondria, which inactivated phosphatases in hepatocytes [178]. This allowed for a shift towards a phosphorylated, activated form of EGFR, which then activated MAPKs. Interestingly, activation of EGFR by conjugated bile acids, but not DCA, was prevented by pretreatment with pertussis toxin, indicating that conjugated bile acids signal through a G protein-coupled receptor coupled to Gi [179]. Further examination indicated that conjugated bile acids activated sphingosine 1 phosphate receptor-2, which presumably transactivates the EGFR and the IR leading to activation of PI3-kinase and MAP kinases [180]. They propose that this pathway may be important for regulation of glucose metabolism, through activation of the IR, and bile acid metabolism, through upregulation of SHP, in hepatocytes [181,182]. Although studies in mice indicate that this might be important for glucose and bile acid homeostasis, it remains to be determined whether this pathway is important in humans. In cultured hepatocytes, activation of this signaling pathway began at 5 μM TCA [180]. In humans, concentrations of total

conjugated bile acids in blood are typically below 1 μM in fasted individuals with postprandial bile acid concentrations reaching as high as 5 μM [183]. Accordingly, in healthy individuals it is possible that this pathway is important for regulating glucose and bile acid metabolism in particular after a meal. Certainly in patients with obstructive cholestasis, where serum concentrations of conjugated bile acids reach as high as 156 μM, S1PR2 could be activated by bile acids leading to activation of Jnk1/2, upregulation of SHP, and suppression of CYP7A1 [91]. The contribution of this pathway relative to the FXR-FGF-15/19 (FGF15/19) pathway, however, remains to be determined. It is possible that these pathways may act in synergy resulting in tight regulation of bile acid synthesis. Interestingly, similar to FXR, activation of S1PR2 by bile acids increases glycogen synthesis, again adding another layer of complexity and redundancy in the regulation of glucose metabolism by bile acids [180,184].

In addition to regulation of bile acid synthesis, activation of this pathway may be important for producing hepatic inflammation during cholestasis. Our studies have shown that hepatocytes exposed to pathological concentrations of conjugated bile acids produce proinflammatory cytokines in an Erk1/2-, Jnk1/2-, and PI3-kinase-dependent manner [185–188]. We have shown further that this pathway is critical for hepatic inflammation during cholestasis and is dependent upon upregulation of the transcription factor early growth response factor-1 (Egr-1) [186,188]. In contrast to the concentrations of conjugated bile acids needed to decrease bile acid synthesis and stimulate glycogen synthesis through activation of S1PR2, however, upregulation of inflammatory cytokines in hepatocytes requires 40-fold higher concentrations of bile acids [188]. One possible explanation for the difference in bile acid concentrations needed for these different effects is that studies have shown that SHP, which is upregulated at low bile acid concentrations, suppresses Egr-1 [189]. This mechanism may limit Egr-1 upregulation at physiological concentrations of bile acids. At higher concentrations of bile acids, however, this inhibitory mechanism may be overcome resulting in Egr-1 transcription and upregulation of inflammatory cytokines. Accordingly, physiological concentrations of bile acids would be anti-inflammatory through this mechanism, whereas pathological concentrations of bile acids, which occur during cholestasis, would elicit an “emergency” signal resulting in the release of pro-inflammatory cytokines by hepatocytes. If this mechanism depends upon S1PR2 then inhibition of S1PR2 might be a novel therapy for the treatment of cholestatic liver disease. An alternative explanation, however, may be that, in addition to S1PR2, pathological concentrations of bile acids may activate an additional receptor that remains to be identified, which would stimulate production of pro-inflammatory cytokines by hepatocytes. This remains to be determined, however. The major proposed roles of S1PR2 after activation by bile acids hepatocytes are illustrated in Figure 4.

4. Conclusions

Research over the last several decades has identified several previously unrecognized functions of bile acids which are mediated by activation of a group of bile acid receptors. Many of the pathways regulated by these receptors, including regulation of bile acid synthesis, regulation of glucose homeostasis, regulation of lipid homeostasis, pruritus, and regulation of energy expenditure and body weight may be exploited therapeutically for the

treatment of several diseases, including cholestatic liver disease, metabolic syndrome, and NASH. As discussed in section 2.1.3, drugs that activate FXR are in clinical trials and already show promise for the treatment of some forms of cholestatic liver disease. Further research in this field should continue to move bile acids beyond “simple detergents” and towards complex regulatory molecules that regulate clinically relevant physiological process that may be targeted by bile acid receptor agonists or antagonists.

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Abbreviations

ABCB	ATP-binding cassette sub-family B
Apo	apolipoprotein
ASBT	apical sodium dependent bile acid transporter
BDL	bile duct ligation
BSEP	bile salt export pump
CA	cholic acid
CDCA	chenodeoxycholic acid
C/EBP	CCAAT-enhancer-binding protein
CES-1	carboxyl esterase-1
CFTR	cystic fibrosis transmembrane conductance regulator
CGRP	calcitonin gene-related peptide
CHO	Chinese hamster ovary
ChREBP	carbohydrate response element binding protein
CREB	cAMP response element-binding protein
CYP	cytochrome P450
D2	deiodinase
DCA	deoxycholic acid
EGFR	epidermal growth factor receptor
Egr-1	early growth response factor-1
ER6	everted repeat separated by 6 nt
FAK	focal adhesion kinase

FAS	TNF superfamily receptor 6
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FXR	farnesoid X receptor
FSR-2	fosmidomycin resistance protein
FOX01	forkhead box 01 gene
G6Pase	glucose 6 phosphatase
GCA	glycocholic acid
GCDCA	glycochenodeoxycholic acid
GDCA	glycodeoxycholic acid
GLP-1	glucagon-like peptide-1
GUDCA	glycoursodeoxycholic acid
GWAS	genome-wide association study
HDCA	hyodeoxycholic acid
HDL	high-density lipoprotein
HNF	hepatocyte nuclear factor
I-BABP	intestine bile acid binding protein
IκBα	interleukin kappa beta alpha
IL	interleukin
IR	insulin receptor
Jnk	jun N-terminal kinase
LBD	ligand-binding protein
LCA	lithocholic acid
LDL	low-density lipoprotein
LIP	liver inhibitory protein
L-PK	liver pyruvate kinase
LPL	lipoprotein lipase
LPS	lipopolysaccharide
LRH-1	liver receptor homologue-1

LXXLL	leucine-X-X-leucine-leucine
MAFG	v-maf musculoaponeurotic fibrosarcoma oncogene homolog G
MAPK	mitogen-activated protein kinase
M-BAR	membrane bile acid receptor
MCA	muricholic acid
MRP	multidrug resistance protein
mTORC1	mammalian target of rapamycin complex-1
NASH	non-alcoholic steatohepatitis
NR	nuclear receptor
NTCP	sodium-taurocholate co-transporting polypeptide
OATP	organic anion-transporting polypeptide
OCA	obeticholic acid
OST	organic solute transporter
PBC	primary biliary cirrhosis
PEPCK	phospheonol pyruvate carboxykinase
PI3-kinase	phosphatidylinositide 3-kinase
PXR	pregnane X receptor
RXR	retinoid X receptor
SHP	small heterodimer partner
S1PR2	sphingosine-1-phosphate receptor 2
SREBP-1c	sterol regulatory element binding protein-1c
SULT2A1	sulfotransferase family, cytosolic, 2A, dehydroepiandrosterone (DHEA)-preferring member 1
UCP-1	uncoupling protein-1
UDCA	ursodeoxycholic acid
UGTs	UDP glucuronosyltransferases
T3	triiodothyronine
TCA	taurocholic acid
TCDCA	taurochenodeoxycholic acid

TDCA	taurodeoxycholic acid
TGR5	G protein-coupled bile acid receptor 1 (also known as GPBAR1)
TLCA	taurolithocholic acid
TNF	tumor necrosis factor
TRPA1	transient receptor potential cation member 1
TUDCA	tauroursodeoxycholic acid
VDR	vitamin D receptor
VLDL	very low-density lipoprotein

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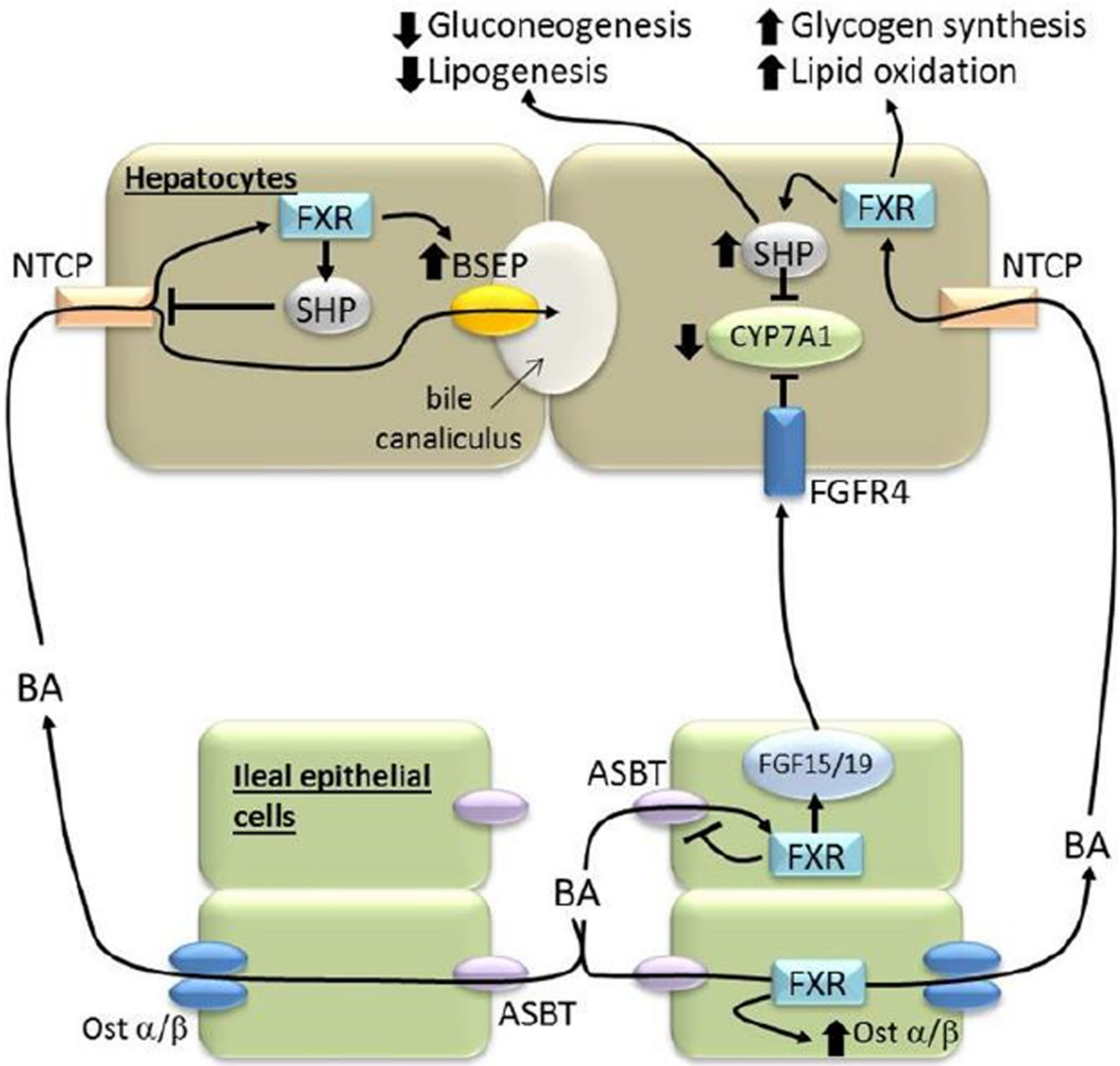

Figure 1.

Summary of the physiological functions of FXR. In the intestine, bile acids (BAs) are transported into ileal epithelial cells by ASBT. Activation of FXR in ileal epithelial cells suppresses ASBT, upregulates FGF15/19, and upregulates Ost α/β. BAs are transported into hepatocytes by NTCP. Activation of FXR in hepatocytes upregulates SHP which suppresses CYP7A1, NTCP, gluconeogenesis, and lipogenesis. FXR upregulates BSEP which transports BAs into the bile canaliculus. FXR also increases glycogen synthesis and increases lipid oxidation. FGF15/19 activates FGFR4 on hepatocytes which suppresses CYP7A1.

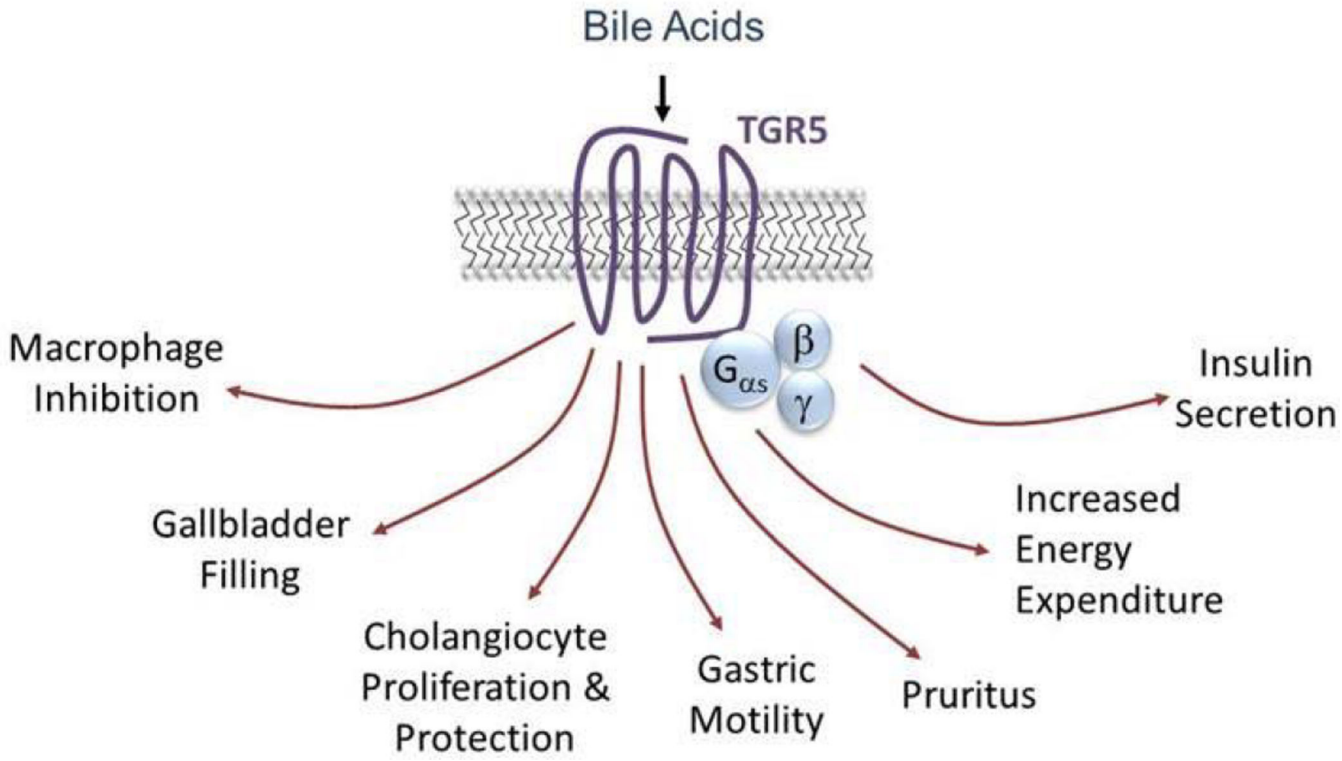

Figure 2.
Summary of the physiological functions of TGR5. See text for complete details.

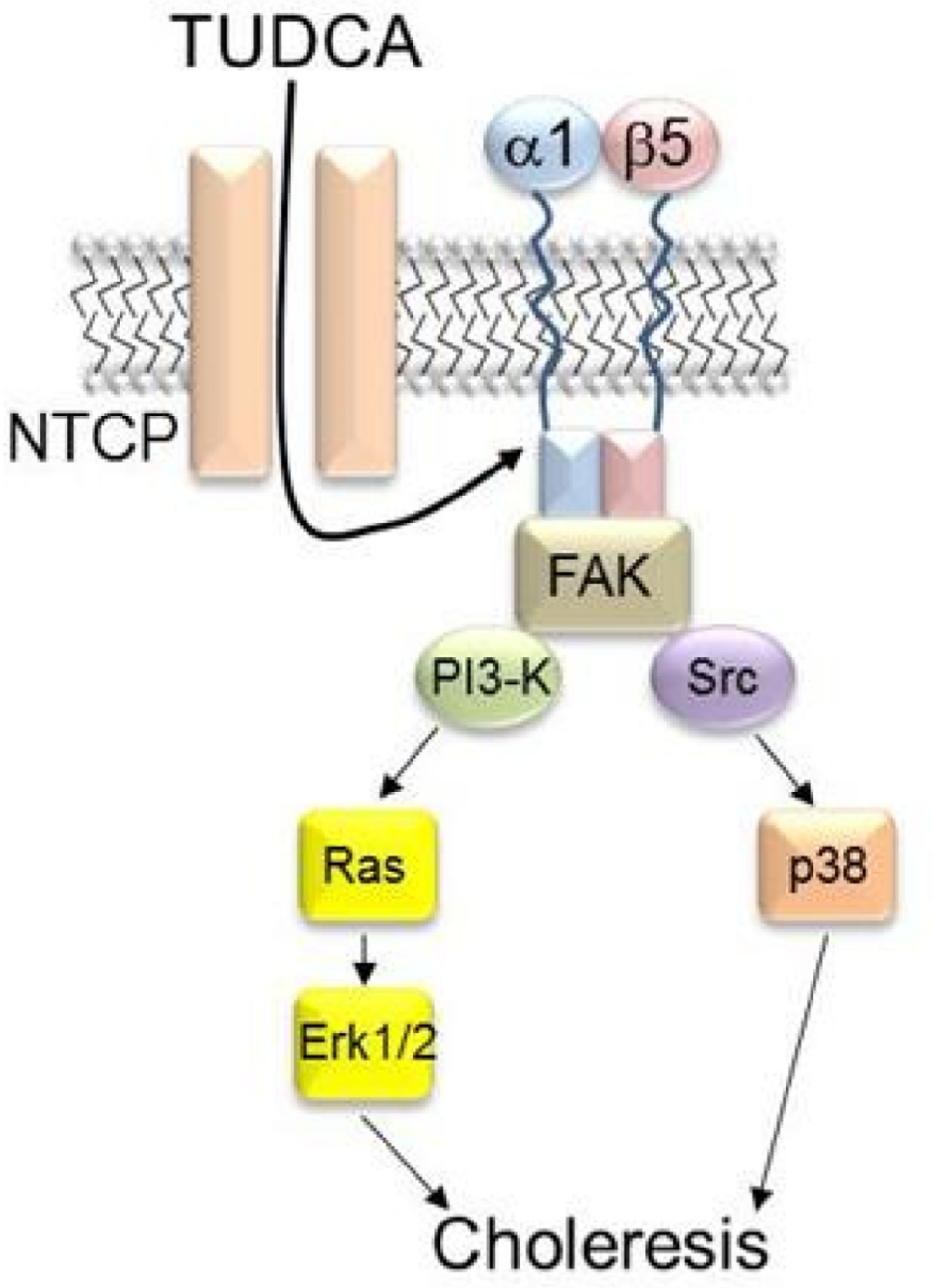

Figure 3.
Mechanism by which TUDCA stimulates choleresis. See text for details

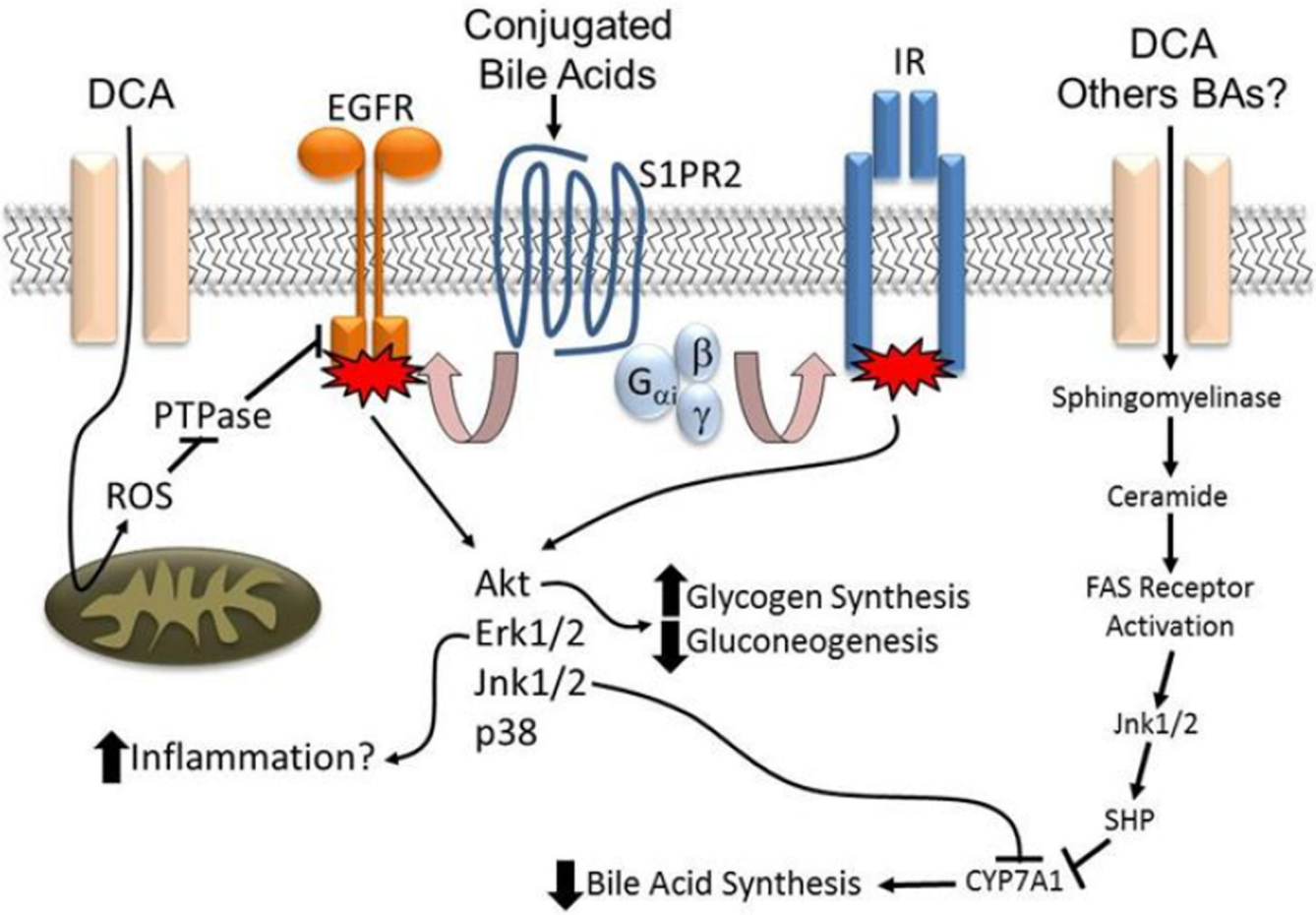

Figure 4.

Summary of the effects of S1PR2 activation in hepatocytes by bile acids. Conjugated bile acids activate sphingosine-1-phosphate receptor 2 (S1PR2), which transactivates the epidermal growth factor receptor (EGFR) and the insulin receptor (IR). EGFR and/or IR activate Akt, which increases glycogen synthesis and decreases gluconeogenesis; activate Erk1/2, which increases expression of proinflammatory genes; and activates Jnk1/2, which suppresses CYP7A1. DCA stimulates mitochondrial production of ROS (reactive oxygen species) which inhibit phosphatases (PTPase) leading to the activation of EGFR. DCA also activates sphingomyelinase which generates ceramide. This activates FAS receptors, which activates JNK1/2 leading to upregulation of SHP and suppression of CYP7A1.