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Bile acids and their signaling pathways: eclectic regulators of diverse cellular functions

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Abstract. The field of bile acids has witnessed an impulse in the last two decades. This has been the result of cloning the genes encoding enzymes of bile acid synthesis and their transporters. There is no doubt that the identification of Farnesoid X Receptor (FXR, NR1H4) as the bile acid receptor has contributed substantially to attract the interest of scientists in this area. When FXR was cloned by Forman et al. [1], farnesol metabolites were initially considered the physiological ligands. After identifying FXR and other nuclear receptors as bile acid sensors [2–4], it has become clear that bile acids are involved in the regulation of lipid and glucose metabolism and that these molecules are eclectic regulators of diverse cellular functions. In this review, we will summarize the current knowledge of the functions regulated by bile acids and how their physiological receptors mediate the signaling underlying numerous cellular responses.

Keywords. Nuclear receptors, enterohepatic circulation, lipid metabolism, glucose metabolism, energy expenditure, liver regeneration.

Role of FXR and other receptors in bile acid metabolism and transport in the enterohepatic circulation

FXR (Farsenoid X Receptor) is expressed in different tissues, including the liver, intestine, kidney, adrenals, stomach, fat, and heart [5]. At least in mice four isoforms, FXRα1, FXRα2, FXRβ1, and FXRβ2, which are different transcripts from the same gene, have been identified [5]. Transfection experiments suggest that the four distinct murine FXR isoforms differentially regulate gene expression in numerous tissues.

Upon its identification as the intracellular bile acid receptor [2–4], FXR was shown to induce the transcription of the gene encoding the intestinal-bile acid binding-protein (I-BAPB) [2], an intracellular 14-kDa protein involved in the intestinal absorption of bile acids [6], via a typical FXRE constituted by an inverted repeat separated by one nucleotide (IR-1) of a canonical hormone response element (HRE) half consensus sequence. The same authors also showed that FXR plays a role in the feedback regulation of the gene encoding cholesterol 7α-hydroxylase (*CYP7A1*), the rate-limiting enzyme in the 'classical' pathway of bile acid synthesis. In fact, the overexpression of FXR in the hepatoblastoma cell line HepG2 enhances the bile acid-mediated repression of *CYP7A1* transcription [2]. However, shortly after, Chiang et al. [7] demonstrated that the function of FXR on *CYP7A1* transcription is indirect, as this receptor does not bind to this gene promoter. Notwithstanding, studies in *Fxr*$^{-/-}$ mice confirmed the relevance of this receptor in the feedback regulation of bile acid synthesis [8]. The puzzling role of FXR in the negative regulation of bile

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acid synthesis was initially disentangled when it became clear that this receptor increases the transcription of the atypical nuclear receptor Small Heterodimer Partner (SHP, NR0B2) [9, 10], which lacks a DNA-binding domain but interacts with other members of the nuclear receptor superfamily and inhibits their transcriptional activity [11]. In particular, these investigators demonstrated that liganded FXR boosts the transcription of SHP, which in turn heterodimerizes with the transcriptional activator α-Fetoprotein Transcription Factor, also known as Liver Receptor Homolog-1 or *CYP7A1* Promoter binding Factor (FTF/LRH-1/CPF, NR5A2), bound to the negative Bile Acid Responsive Element (BARE) of the *CYP7A1* promoter [9, 10]. In this context, SHP acts as a repressor of FTF, and it reduces the transcription rate of *CYP7A1*. However, subsequent experiments in *Shp*$^{-/-}$ mice revealed that the FXR-SHP axis is not the only pathway through which bile acids repress gene transcription [12, 13]. It was, in fact, shown that bile acids can repress *CYP7A1* transcription via multiple mechanisms, including the activation of SHP transcription via the c-Jun N-terminal Kinase (JNK)-dependent pathway [14], by β-Klotho, a type I membrane protein containing glycosidase-like domains [15], by the FXR-mediated increase of fibroblast growth factor-19 (FGF-19) expression in the liver [16] and of FGF-15 in the intestine [17], two secreted growth factors that signal through the FGFR4 cell-surface receptor tyrosine kinase, which strongly suppress the expression of *CYP7A1*. In particular, the discovery that bile acid-induced secretion of FGF-15 from the intestine contributes to the repression of *CYP7A1* gene transcription provides the rational for the previous observation of Pandak et al. [18] who hypothesized that a putative intestinal factor, released or absorbed in the presence of bile acids in the intestinal lumen, may play a role in the regulation of bile acid synthesis. In fact, intravenous administration of taurocholate failed to downregulate *CYP7A1*, whereas its infusion in the duodenum significantly decreased the transcription, the steady-state mRNA (messenger RNA) levels and the enzyme activity of cholesterol 7α-hydroxylase in the rat [18].

Moreover, bile acids suppress *CYP7A1* transcription via FXR/SHP-independent signaling cascades by decreasing the activity of the orphan nuclear receptor Hepatocyte Nuclear Factor-4α (HNF-4α, NR2A1), another activator that binds to the BARE of *CYP7A1* [19]. Subsequently, by using co-immunoprecipitation and chromatin immunoprecipitation (ChIP) assays the same authors demonstrated that the transcription coactivators Peroxisome Proliferator-Activated Receptor γ (PPARγ) coactivator-1α (PGC-1α) and cAMP-Response Element Binding protein (CREB)-Binding Protein (CBP) dissociate from HFN-4α and the *CYP7A1* promoter upon exposure of HepG2 cells to bile acids [20]. These effects are FXR-independent, as the FXR selective ligand GW4064 does not affect the transcription activity of HNF-4α. Interestingly, in the same study these authors demonstrated for the first time that bile acids also downregulate the expression of the key gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) at the level of gene transcription through a similar mechanism [20], highlighting an unanticipated link between bile acids and glucose metabolism.

Finally, recent studies showed that the chromatin remodeling complex containing mSin3A, Swi/Snf and Brm associated to SHP, which is also associated to the histone deacetylase (HDAC) 1, are recruited to the *CYP7A1* promoter after bile acid treatment, thus establishing a link between chromatin remodeling complexes and the regulation of cholesterol/bile acid metabolism [21, 22].

Interestingly, the plant sterol guggulsterone, an active agent present in extracts of the gum resin of the guggul tree (*Commiphora mukul*), is an FXR antagonist. It has been proposed that its cholesterol-lowering activity may be due to its FXR antagonist property [23, 24]. However, the hypocholesterolemic activity of this compound does not correlate with increased bile acid synthesis. In fact, guggulsterone has no effect on FXR-mediated repression of the *CYP7A1* gene, but strongly inhibits the human *CYP7A1* gene by activation of pregnane X receptor (PXR, NR1I2) [25]. PXR has been recognized as a receptor for lithocholic acid and bile acid precursors [26–28], and it is essential for detoxification of the liver from xenobiotics and to avoid pathologic conditions such as cholestasis and liver damage. Since guggulsterone inhibits bile acid secretion from the liver by antagonizing the effect of bile acid on FXR-mediated upregulation of bile salt export pump (BSEP), it has been proposed that the cholesterol lowering effect of guggulsterone may be secondary to the decrease of intestinal cholesterol absorption caused by inhibition of bile acid secretion [25]. The activation of PXR leads to the repression of bile acid synthesis because it physically interacts with HNF-4α and causes the dissociation of the transcriptional coactivator PGC-1α from the *CYP7A1* gene promoter [29, 30]. In analogy with *CYP7A1*, ligand-activated PXR represses the transcription of *PEPCK* [29], underscoring inhibitory cross-talk between drug metabolism and cholesterol, bile acid and glucose metabolism.

Because of their detergent properties bile acids are also potentially toxic; therefore, their intracellular concentrations must be controlled tightly to avoid

cell damage. Two bile acid-conjugating enzymes, uridine 5′-diphosphate-glucuronosyltransferase 2B4 (UGT2B4) and uridine 5′-diphosphate-glucuronosyltransferase 1A3 (UGT1A3), transform bile acids into their glucuronide derivatives in the liver [31, 32]. Thus, glucuronidation of bile acids represents a means to reduce their toxicity and to decrease their ability to activate FXR. The genes encoding these two enzymes are respectively regulated by FXR [31] and by fibrates [32], which are hypolipidemic agents binding to the nuclear receptor PPARα (NR1C1). Thus, these studies show that different nuclear receptors may contribute to decrease the biological activity of bile acids towards FXR activation and to enhance their elimination via transformation to a more soluble form, avoiding excessive accumulation and possible toxic effects of these potentially harmful molecules.

Bile acids cycle through several organs of the enterohepatic circulation, including the liver, the bile ducts, the gallbladder and the intestine, and they return to the liver via the portal vein. They play a key function in the emulsification, digestion and absorption of fats derived from the diet. Specialized transporters located in these organs allow the proper transport of bile acids, and these transporters are often regulated by bile acids and related nuclear receptors. The bile salt export pump (BSEP), also known as sister of P-glycoprotein (SPGP), is a canalicular ATP-dependent bile acid transporter belonging to the family of ATP-Binding Cassette (ABCB11) transmembrane proteins. The importance of BSEP in exporting bile acids out of the hepatocyte is proven by the fact that subjects carrying mutations in the *BSEP* gene develop progressive familial intrahepatic cholestasis (PFIC, type II), a disease that eventually leads to severe liver damage [33]. Not surprisingly, *BSEP* is regulated by bile acids through their intracellular receptor FXR, which binds as a heterodimer with RXR to an IR-1 in the *BSEP* promoter [34–36] and increases *BSEP* transcription in response to bile acids, thus generating bile acid-dependant bile secretion. It is also worth mentioning that the studies in $Fxr^{-/-}$ mice, which display decreased levels of BSEP, revealed that hepatic cells counteract the increased intracellular concentrations of bile acids by increasing the expression of other ABC transporters like the multidrug resistance proteins MRP3 (ABCC3) and MRP4 (ABCC4), which are likely regulated by other nuclear receptors such as PXR/SXR [35].

Bile acids also positively regulate transcription of the gene encoding the human multidrug resistance MDR3, a P-glycoprotein member of the ABC transporters (ABCB4), which mediates the translocation of phospholipids (phosphatidylcholine) through the canalicular membrane of hepatocytes [37]. FXR binds as RXR heterodimer to a conserved FXR response element in the distal promoter of *ABCB4* [38]. It could be inferred that the bile acid-mediated upregulation of MDR3 may help to cope with the toxicity of bile acids by favoring the formation of mixed micelles containing cholesterol, phospholipids and bile acids. In fact, MDR3 deficiency typically causes the type III progressive familial intrahepatic cholestasis (PFIC) characterized by high serum levels of γ-glutamyltransferase [39].

ABCB11 and ABCB4 are critical in maintaining the proper solubility of cholesterol in the bile. $Fxr^{-/-}$ mice show the typical phenotype of cholesterol gallstone disease, which is secondary to decreased expression of the hepatic bile acid and phospholipid transporters Abcb11 and Abcb4 [40]. In addition, when mice susceptible to gallstone disease are treated with the synthetic FXR agonist GW4064, the cholesterol saturation index improves as a consequence of the enhanced expression of Abcb11 and Abcb4, which in turn leads to higher concentrations of bile acids and phospholipids and helps to maintain the solubility of cholesterol in the bile [40].

Hepatocytes take up bile acids from the sinusoidal/basolateral membrane via several transporters. The main ion-dependent transporter is the Na^+-taurocholate cotransporting polypeptide (Ntcp, gene symbol *SLC10A1*). In the cholestatic liver the mRNA and protein levels of Ntcp are strongly reduced [41–43]. Several mechanisms of downregulation of *Ntcp* by bile acids have been proposed. These include the action of SHP, which interferes with the RAR–RXR heterodimer bound to a response element in the rat *Ntcp* promoter [44]. However, as was observed with *CYP7A1* and other genes encoding bile acid biosynthetic enzymes, in $Shp^{-/-}$ mice fed cholic acid-enriched diet, *Ntcp* gene transcription is still repressed [13], indicating that additional mechanisms may account for the negative effect of bile acids on the transcription of this gene. Later, Li et al. showed that bile acids may induce the phosphorylation of RXR and the subsequent dissociation of the RAR-RXR heterodimer from the *Ntcp* promoter [45]. However, given the differences observed in the promoter sequences of *Ntcp* in different species, it has been proposed that bile acids regulate the transcription of *Ntcp* via alternative mechanisms differentially operating in various species [46].

Bile acids also repress another bile acid transporter expressed in the basolateral/sinusoidal membrane of hepatocytes, the organic anion transporting polypeptide 1B1 (OATP1B1, gene symbol *SLCO1B1*, formerly known as OATP-C) [47], which is the major Na^+-independent bile acid uptake protein of the sinusoidal membrane. In this case, the negative effect

of bile acids is indirect, as it is secondary to the SHP-mediated reduction of the activity and to the decreased binding of the nuclear receptor HNF-4α on the promoter of the gene encoding the liver-enriched transcription factor hepatocyte nuclear factor-1α (HNF-1α), a major transcription activator of *OATP1B1* transcription [47].

In contrast to OATP1B1, the other Na^+-independent anion transporter that can also transport bile acids through the basolateral membrane, OATP1B3 (gene symbol *SLCO1B3*, formerly known as OATP8) is induced by bile acids via the FXR-RXR heterodimer binding to a canonical IR-1 element [48]. Besides bile acids, OATP1B3 transports the intestinal peptide cholecystokinin 8, the opioid peptide deltophin II, and the cardiac glycosides digoxin and ouabain, and is also expressed in extrahepatic tissues [49]. Studies with fluorescent chenodeoxycholic acid (CDCA) indicate that OATP1B3 is a high, affinity bile acid transporter (Michaelis-Menten constant for the fluorescent CDCA derivative is 0.54 μM) [49]; therefore it may contribute substantially to the uptake of certain bile acids through the sinusoidal membrane of hepatic cells. Although the opposite effect of bile acids on the expression of OATP1B1 and OATP1B3 might seem paradoxical, it has been proposed that the bile acid-mediated induction of OATP1B3 expression may help the cholestatic liver to improve the uptake of xenobiotics and therefore to diminish the potential side effects of these molecules in patients affected by cholestasis [48].

Bile acids are essential molecules in digestive processes and absorption of fats as well as lipid soluble vitamins from the diet in the intestine. The intestine extracts the majority of bile acid pool mostly via membrane transporters, whereas less than 10 % of bile acids are eliminated in the feces. The major bile acid membrane transporter is the apical sodium-dependent bile salt transport (ASBT) system in ileal enterocytes, formerly know as the ileal Na^+/bile acid cotransporter (gene symbol *SLC10A2*) [50, 51]. ASBT is a 348-amino acid membrane protein, and mutations in the human *ASBT* gene sequence are linked to an idiopathic intestinal disorder associated with congenital diarrhea, steatorrhea, interruption of the enterohepatic circulation of bile acids and reduced plasma cholesterol levels [51]. The transcription of the gene encoding ASBT is differentially regulated by bile acids in various species. The mouse and the human, but not the rat, genes are repressed by bile acids [52]. However, the mechanisms of *ASBT* gene repression are different in these two species. In the mouse bile acids repress *Asbt* gene transcription via a classical FXR-SHP-FTF regulatory axis as observed with the *Cyp7a1* gene, whereas in humans multiple mechanisms may coexist [53, 54], as bile acid-induced SHP interferes with RAR-RXR transactivation and possibly with the glucocorticoid-mediated regulation of *ASBT* gene transcription. In fact, it has been shown that SHP may interfere with the glucocorticoid receptor (GR, NR3C1) and repress the transcription of the gene encoding the main gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) by competing with the transcriptional activator PGC-1α for interaction with the GR [55]. These studies identify molecular mechanisms of regulation that may have therapeutical implications in different disorders such as cholestasis and inflammatory bowel diseases.

As already mentioned at the beginning of this section, bile acid-activated FXR positively regulates transcription of the *I-BABP* gene in the enterocyte. I-BABP serves the intracellular transport of bile acids from the apical to the basal membrane of intestinal cells [56], thus contributing to the enterohepatic circulation of bile acids. In addition, because of their detergent properties bile acids may harm the cell; therefore it has been proposed that I-BABP also protects cells by sequestering bile acids once they enter the enterocyte [57].

A recently described feature of bile acids is their ability to prevent bacterial overgrowth and to protect the intestinal mucosa in the small intestine [58]. The obstruction of bile flow causes proliferation of intestinal microflora, mucosal injury and eventually bacterial translocation across the mucosal barrier, which can lead to systemic infection [59]. Oral administration of certain bile salts, in particular sodium deoxycholate, can prevent endotoxemia and renal dysfunction in patients with obstructive jaundice [60] through the activation of genes with known antibacterial properties like Angiogenin (*Ang1*), inducible nitric oxide synthase (*iNos*) and interleukin 18 (*Il18*) [58]. These observations indicate that bile acids and synthetic FXR agonists may have therapeutic value in the prevention of intestinal epithelial damage caused by bacterial proliferation in patients with obstructed bile flow.

It should be pointed out that excessive concentrations of bile acids in the intestine might be harmful. In particular, the secondary bile acid lithocholic acid (LCA) is highly toxic and a potential carcinogen in the gastrointestinal (GI) tract [61, 62]. The vitamin D3 receptor (NR1I1) has recently been shown to be a bile acid sensor in the intestine that protects the enteric system from the potentially harmful consequences of high concentrations of LCA [63]. The binding to VDR of both LCA and vitamin D may activate a feed-forward catabolic pathway that increases *CYP3A* expression, a cytochrome P450 involved in bile acid

Table 1. A partial list of genes regulated by bile acids in the liver and in the gastrointestinal tract.

Gene name	Function	Effect of bile acids	Receptors involved
CYP7A1	bile acid synthesis	↓	FXR, SHP, HNF-4, FTF, PXR
PEPCK	gluconeogenesis	↓	HNF-4, FXR, SHP, GR
UGT2B4	bile acid conjugation	↑	FXR
ABCB11/BSEP	hepatic bile acid secretion	↑	FXR
ABCC3/MRP3	hepatic bile acid secretion	↑	PXR
ABCC4/MRP4	hepatic bile acid secretion	↑	PXR
ABCB4/MDR3	hepatic phospholipid secretion	↑	FXR
SLC10A1/NTCP	hepatic bile acid transport	↓	FXR, SHP, RAR, RXR
SLCO1B1/OATP1B1	hepatic bile acid transport	↓	FXR, SHP, HNF-4*
SLCO1B3/OATP1B3	hepatic bile acid transport	↑	FXR
I-BAPB	intracellular bile acid transport	↑	FXR
ASBT	intestinal bile acid uptake	↓	FXR, SHP, FTF, RAR, RXR, GR**

↑ = stimulation, ↓ = repression.
* Indirect effect, none of these receptors is recruited directly to this promoter.
** The mechanism varies between the human and mouse genes.

detoxification. Moreover, these observations provide a possible rationale for the protective effect of vitamin D against colon cancer under normal physiologic conditions. In fact, mice lacking VDR not only have rickets but also show signs of increased cellular proliferation in the colon [64].

Bile acids regulate lipid metabolism

The ability of bile acids to affect lipid metabolism has been known for more than twenty years, although the mechanisms underlying their action were largely elusive. In fact, in dyslipidemic patients, bile acid-binding resins induce the hepatic production of VLDL triglycerides (TGs) [65–67]. Furthermore, treatment with CDCA, which has been used in the past in patients with cholesterol gallstones, has been shown to reduce plasma TG levels [65, 68, 69]. The relationship between bile-acid signaling and TG homeostasis has been further highlighted by the observation that *Fxr*$^{-/-}$ mice have increased hepatic and serum triglyceride levels [8]. More recently it has been shown that bile acids can influence both processes determining circulating TG at the level of their production, occurring mainly in the liver, and of their clearance.

Hepatic TG levels are determined by the fatty acid synthesis rate via SREBP-1c [70] and by fatty acid β-oxidation, which is controlled to a large extent at the level of transcription by PPARα (NR1C1) [71]. In both *KK-A*^{y} and *ob/ob* mice, FXR activation by natural (bile acids) or synthetic (GW4064) FXR agonists has been shown to reduce SREBP-1c expression, and consequently the expression of some of its target genes, such as the malic enzyme (ME) and fatty acid synthase (FAS) [72]. The molecular mechanism underlying this repression is not completely understood, but probably it is mediated by SHP, since in *Shp*$^{-/-}$ mice TG levels are not lowered in response to FXR agonists [72]. Actually, as described for mouse *Cyp7a1* repression, SHP could interfere with LXR activation, which is crucial for the expression of SREBP-1c and its downstream target genes [73, 74]. However, a more recent study in mice overexpressing SHP in the liver shows that bile acids are depleted and consequently triglycerides accumulate in the liver [75]. Apparently in contrast with previous reports, a recent study has described that FXR can also directly upregulate FAS transcription through binding to an IR-1 site in the FAS promoter [76]. The existence of this regulatory pathway could explain why FAS expression returns to control levels after chronic treatment with bile acids (7 days) despite continued SHP elevation [72]. Furthermore, the direct mechanism for bile acid activation of FAS could be a system through which FAS may bypass SHP inhibition, thus maintaining an adequate fatty acid pool for cholesterol esterification in particular situations, for example when cholesterol and bile acid levels are chronically elevated [76].

Besides affecting SREBP-1c expression, bile acids could also influence TG homeostasis through other mechanisms. In cultured human hepatocytes bile acids have been shown to induce the expression of PPARα and its target genes involved in fatty acid oxidation, such as carnitine palmitoyltransferase 1 (CPT-1) [77, 78]. However it is noteworthy that this regulation does not take place in every species, since in both C57BL/6J

and *KK-A*^{y} mice, the expression of β-oxidation genes is not increased, and in wild-type mice it is even repressed, after CA feeding [72]. Furthermore FXR activation suppresses glycolysis and enhances the utilization of fat as source of energy via the increased expression of pyruvate dehydrogenase kinase (PDK4), which in turn inactivates the pyruvate dehydrogenase complex (PDC) [79]. Moreover, bile acids reduce the secretion of VLDL by repressing the expression of microsomal triglyceride transfer protein (MTP). This protein is expressed specifically in the liver and in the small intestine, and it plays a critical role in the assembly and secretion of very low density lipoproteins (VLDLs) and chylomicrons. This down-regulation of MTP transcription is due to the increased expression of SHP, which impairs the transactivation potential of HNF-4α on MTP promoter [80].

In recent years, a link between PGC-1α, FXR and effects on triglyceride metabolism in the liver has also been demonstrated [81–83]. In fact, PGC-1α, whose levels are induced after a prolonged fast, coactivates PPARγ and/or HNF4α bound to the FXR promoter, thus promoting transcription of the FXR gene [83]. In addition PGC-1α can act as coactivator of all FXR isoforms, thus increasing the expression of FXR target genes [83]. The final effect of this activation is the decrease of plasma triglyceride levels and of hepatic TG production and secretion, which could be the consequence of increased fatty acid β-oxidation to generate more energy under fasting conditions. The central role of FXR in mediating the effect of PGC-1α on TG metabolism is highlighted by the observation that in *Fxr*$^{-/-}$ mice neither plasma TG levels nor hepatic TG secretion decline after a fasting period.

Taken together, these studies provide clear evidence of the ability of bile acids, and in particular of FXR, to affect hepatic triglyceride production and secretion. However, the physiological role for FXR in the regulation of genes involved in TG clearance has also been reported. In fact, the hypolipidemic effect of FXR results also from regulation of the expression of apolipoprotein E (apoE), induced in liver cells by natural (CDCA) and synthetic (GW4064) FXR ligands. ApoE plays a key role in the metabolism of chylomicrons and VLDL remnants by functioning as a ligand for receptor-mediated uptake of these lipoproteins by the liver [84]. In addition, FXR induces the expression of VLDL receptor (VLDL-r), a protein that binds apoE-rich VLDL and lipoprotein lipase (LPL), leading to triglyceride hydrolysis [85–87].

Consistent with the role of this nuclear receptor in regulating lipoprotein metabolism, in human hepatic cells FXR regulates the expression of syndecan-1 (SDC1), a transmembrane heparan sulfate proteoglycan that participates in the binding and internalization of extracellular ligands. The induction of SDC1 enhances hepatic clearance of lipoprotein remnants [88]. Therefore, FXR may play a role in increasing high-density lipoprotein (HDL) levels via multiple mechanisms: induction of the human and murine phospholipid transfer protein (PLTP) gene, essential in the transfer of phospholipids from VLDL to HDL [89], and repression of human hepatic lipase (HL) expression, an enzyme involved in the conversion of HDL into smaller particles, which are more rapidly cleared in the kidney [90]. However, other researchers demonstrated that bile acids act as negative regulators of human apoA-I expression via FXR. *In vivo* and *in vitro* experiments showed that FXR strongly decreases serum concentrations and liver mRNA levels of apoA-I, with subsequent reduction of serum HDL levels. ApoA-I promoter analysis revealed that FXR binds to this site as a monomer, and thus it represses transcription in a manner independent of retinoid X receptor [91, 92]. Altogether, these results suggest an unclear role of FXR in the metabolism of HDL: on the one hand, FXR seems to increase plasma HDL level, but on the other hand, it is implicated in down-regulation of apoA-I expression, the major lipoprotein of HDL. Clearly, further studies are needed to precisely elucidate the role of FXR in the regulation of HDL metabolism.

In both human cells and in mice, FXR activation also induces the expression of apoC-II, an important activator of lipoprotein lipase (LPL) activity responsible for the hydrolysis of TGs in chylomicrons. This regulation is mediated by the binding of the FXR-RXR heterodimer to the FXREs present in the hepatic control regions HCR.1 and HCR.2 located on the apoC-II promoter [93]. Furthermore, promoter transfection experiments and chromatin immunoprecipitation assays revealed that in mice and human hepatocytes FXR suppresses the expression of apoC-III, an inhibitor of LPL activity [94].

Recent studies showed that activation of FXR plays a key role in adipocyte differentiation and function. FXR has been suggested to increase the expression of complement component C3, known to influence lipid metabolism. In fact in adipose tissue, C3 is converted to C3a by the action of factors B and D (adipsin) and subsequently to acylation-stimulating protein (ASP). ASP increases free fatty acid uptake and triglyceride synthesis, leading to a decrease in plasma triglyceride levels [95, 96]. Interestingly, it has been demonstrated that the synthetic FXR ligand, INT-747, promotes adipocyte differentiation, adipogenesis and lipid storage *in vivo* and *in vitro*. In addition, the activation of FXR enhances the expression of C/EBPα, PPARα, FABP and SREBP-1c, while it inhibits the expression

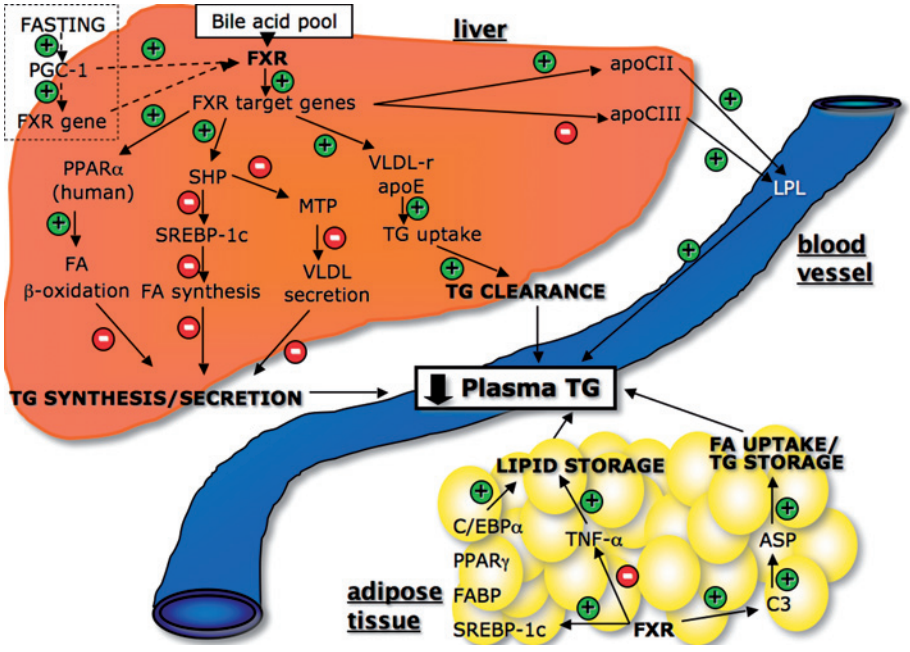

Figure 1. Schematic summary of the roles of bile acids and FXR in the regulation of triglyceride metabolism.

of TNF (tumor necrosis factor)-α, a mediator of lipolysis [97]. Consistent with this finding, some researchers showed that murine embryonic fibroblasts isolated from *Fxr*$^{-/-}$ mice were unable to correctly accumulate triglycerides during the course of adipocyte differentiation. In fact, *Fxr*$^{-/-}$ mice exhibit decreased fat mass and reduced adipocyte size. Surprisingly, these mice exhibit increased expression of genes involved in fatty acid transport (fatty acid transport protein-1 and lipoprotein lipase) even when the lipid storage process is impaired. Probably in *Fxr*$^{-/-}$ mice the unidentified defect in triglyceride metabolism acts at a step distal from fatty acid uptake in adipose tissue [98].

All these results demonstrate that FXR activation decreases triglyceride levels 1) by reducing the synthesis of fatty acids in the liver; 2) by increasing TG clearance by modulating LPL activity; 3) by inducing PPARα in humans; and 4) by increasing lipid storage in the adipose tissue (Fig. 1).

Regulation of glucose metabolism: role of FXR and bile acids

The expression of FXR in rodent liver is reduced in different models of diabetes and is affected by the nutritional state [99, 100]. Moreover, glucose increases FXR mRNA and protein levels via the pentose phosphate pathway, whereas insulin counteracts this effect [100]. These observations focused the attention on the involvement of FXR in carbohydrate metabolism, but at present, some results seem to be contradictory. For example, it has been shown that bile acids regulate the expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase (PEPCK) through the activation of FXR. However, different studies reported a positive [101] or negative [20, 102] effect of bile acids or GW4064 on *PEPCK* gene expression.

Comparison between glucose metabolism in *Fxr*$^{-/-}$ mice and in wild-type mice demonstrated the role of FXR in glucose homeostasis, since its disruption leads to hyperglycemia (Fig. 2). This is consistent with peripheral insulin resistance in the fed state, when insulin-dependent glucose uptake is the major determinant of glucose clearance. In particular, *Fxr*$^{-/-}$ mice showed reduced inhibition of glucose production in the liver after insulin stimulation and altered glucose disposal in peripheral tissues [103]. These could reflect blunted insulin signaling in both hepatic and extrahepatic tissues, probably associated with lipid accumulation. In fact, *Fxr*$^{-/-}$ mice are characterized by fatty liver and high triglyceride and free fatty acid (FFA) levels in skeletal muscle [103].

In another recent study, Cariou et al. [98] revealed a strong dissociation between hepatic and peripheral insulin sensitivity in *Fxr*$^{-/-}$ mice in the basal state, without insulin stimulation. After short-term fasting, blood glucose and insulin levels are significantly lower in *Fxr*$^{-/-}$ mice as compared to wild type [98], suggesting a defect in hepatic glucose production (Fig. 2). Thus, in this situation, the metabolic phenotype of these mice mainly reflects the loss of hepatic FXR. On the other hand, during the glucose tolerance test, which mimics a postprandial state, glucose levels in *Fxr*$^{-/-}$ mice were

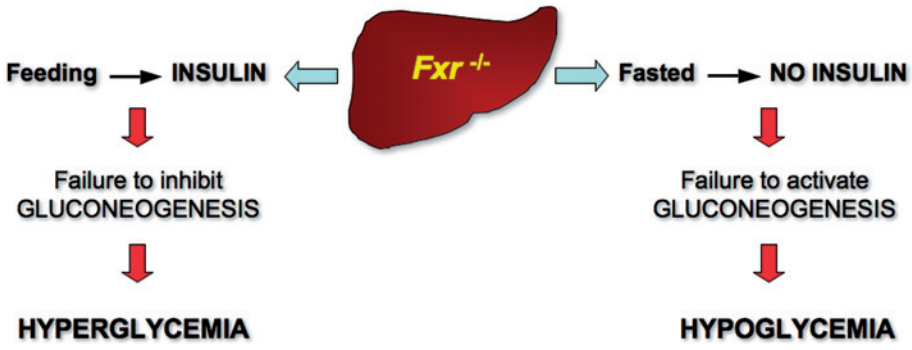

Figure 2. Effect of FXR ablation on glucose homeostasis. In *Fxr*$^{-/-}$ mice insulin fails to suppress gluconeogenesis leading to hyperglycemia, whereas fasted *Fxr*$^{-/-}$ mice are hypoglycemic because of the defective induction of gluconeogenesis.

higher than in wild-type mice, and insulin tolerance tests demonstrated that the decreased clearance of plasma glucose was due to altered insulin sensitivity in peripheral tissues [98]. Peripheral insulin resistance observed in *Fxr*$^{-/-}$ mice could not be explained by alteration in circulating adiponectin, which was not altered in *Fxr*$^{-/-}$ mice, but both mRNA and plasma levels of leptin were strongly reduced in *Fxr*$^{-/-}$ mice, probably reflecting the reduced adiposity. Since FXR is not expressed in skeletal muscle, its deficiency could act on this tissue in an indirect way. As discussed above (see bile acids and lipid metabolism), *Fxr*$^{-/-}$ mice show high levels of circulating FFA, which may contribute to peripheral insulin resistance. Moreover, these authors proposed that the reduced fat mass or the impaired ability of adipose tissue to accumulate fats causes a redirection of the FFA flux from adipocytes to skeletal muscle. Another possible explanation for peripheral insulin resistance in *Fxr*$^{-/-}$ mice may be the activation of PPARα in the muscle. A recent study suggested that activation of muscle PPARα is linked to the development of insulin resistance in diabetic mice without altering the phosphorylation of insulin-signaling molecules [104]. Therefore, the absence of FXR leads to insulin resistance. But does its activation promote insulin sensitivity? The treatment of a mouse model of insulin resistance with a synthetic agonist of FXR, GW4064, improved insulin sensitivity [98], repressed hepatic gluconeogenic genes and increased hepatic glycogen synthesis [105]. Moreover, adenovirus-mediated overexpression of constitutively active FXR in the liver significantly lowered blood glucose levels in both diabetic and wild-type mice [105]. It is important to notice that GW4064 and dietary cholic acid reduced the expression of different genes involved in gluconeogenesis and lowered plasma glucose levels in wild-type, but not in *Fxr*$^{-/-}$ mice [103, 105].

Intriguingly, *Fxr*$^{-/-}$ mice subjected to an overnight fasting followed by refeeding with a high carbohydrate diet showed faster and more pronounced induction of genes involved in both glycolytic and lipogenic pathways in comparison to wild-type mice. These changes in gene expression correlate with increased hepatic *de novo* triglyceride synthesis [99]. In fact, upon refeeding the induction of hepatic expression of liver pyruvate kinase (*Lpk*), fatty acid synthase (*Fas*) and acetyl CoA (coenzyme A) carboxylase-1 (*Acc-1*) was more rapid in *Fxr*$^{-/-}$ than in wild-type mice. Since insulin and glucose regulate the glycolytic and lipogenic pathways [106], the impaired response of *Fxr*$^{-/-}$ mice to high carbohydrate refeeding may reflect enhanced hepatic insulin sensitivity and/or potentiation of carbohydrate-induced signaling. Although a recent study reported that bile acids could interfere with insulin signaling in hepatocytes [107], Duran-Sandoval et al. were unable to detect any modification of hepatic insulin sensitivity in *Fxr*$^{-/-}$ mice [99].

Therefore, FXR seems to be involved in the regulation of the shift from hepatic glucose production to hepatic glucose utilization during the transition from fasting to refeeding. The enhanced expression of *CYP7A1*, a negatively regulated FXR target gene [9, 10, 108], during fasting [20], would increase the bile acid pool for digestion after a subsequent meal. After refeeding, bile acids return to the liver through the portal vein, where they activate FXR as well as other signaling pathways. This activation leads to inhibition of *de novo* lipogenesis acting on *Fas* and *Acc-1* and inhibition of glycolysis, via inhibition of *Lpk* expression, to promote glycogen storage. Then, the rise of plasma insulin levels upon refeeding reduces FXR expression, inducing a switch of the glucose flux toward glycolysis in the inter-prandial state [99]. Taken together, these data provide new evidence of the important role of FXR in the maintenance of normal glucose homeostasis and insulin sensitivity, and highlight a link between glucose and lipid metabolism mediated by FXR.

Regulation of energy expenditure: role of the membrane bile acid receptor Gpbar1/Tgr5

Recently, two groups independently discovered a novel G-protein-coupled receptor (GPCR), Gpbar1/Tgr5 (also known as BG37), which responds to bile acids [109, 110]. Bile acids induce receptor internalization, activation of extracellular signal-regulated kinase, and intracellular cAMP production in Gpbar1/Tgr5-expressing HEK293, CHO cells or human enteroendocrine NCI-H716 cells in a dose-dependent manner [109, 110]. Furthermore, these authors showed that this response does not involve nuclear bile acid receptors. Maruyama et al. also identified the mouse and the rat TGR5 sequences, which share 82–91% amino acid identity with the human sequence [110]. Northern blot analysis indicates that Gpbar1/Tgr5 is almost ubiquitously expressed in human tissues, including heart, skeletal muscle, spleen, kidney, liver, small intestine, placenta and leukocytes, but not in brain, colon (without mucosa), thymus or lung. The role of this membrane bile acid receptor is not fully understood, but it seems to be implicated in diverse processes such as the suppression of macrophage functions [109] and the secretion of glucagon-like peptide-1 (GLP-1) in murine enteroendocrine STC-1 cells [111]. Recently, Watanabe et al. demonstrated the determinant role of Gpbar1/Tgr5 in energy metabolism [112] (Fig. 3). They showed that the administration of bile acids to mice increases energy expenditure in brown adipose tissue, preventing obesity and insulin resistance. This novel metabolic effect of bile acids is critically dependent on the induction of the cAMP-dependent thyroid hormone activating enzyme, type 2 iodothyronine deiodinase (D2), as shown by the loss of this effect in $D2^{-/-}$ mice. Treatment of brown adipocytes and human skeletal myocytes with bile acids increases D2 activity and oxygen consumption. These effects are FXR-independent and instead are mediated by increased cAMP production that stems from the binding of bile acids with the G-protein-coupled receptor Gpbar1/Tgr5. In both rodents and humans, the most thermogenically important tissues are specifically targeted by this mechanism since they coexpress D2 and TGR5. These authors concluded that the bile acid-Gpbar1/Tgr5-cAMP-D2 signaling pathway is therefore a crucial mechanism for fine-tuning energy homeostasis that can be targeted to improve metabolic control. Maruyama et al. [113] also observed that *Gpbar1/Tgr5*-null mice fed a high-fat diet have significant fat accumulation and increased body weight as compared to wild-type mice, thus confirming that this membrane bile acid receptor plays an important role in energy expenditure and lipid homeostasis.

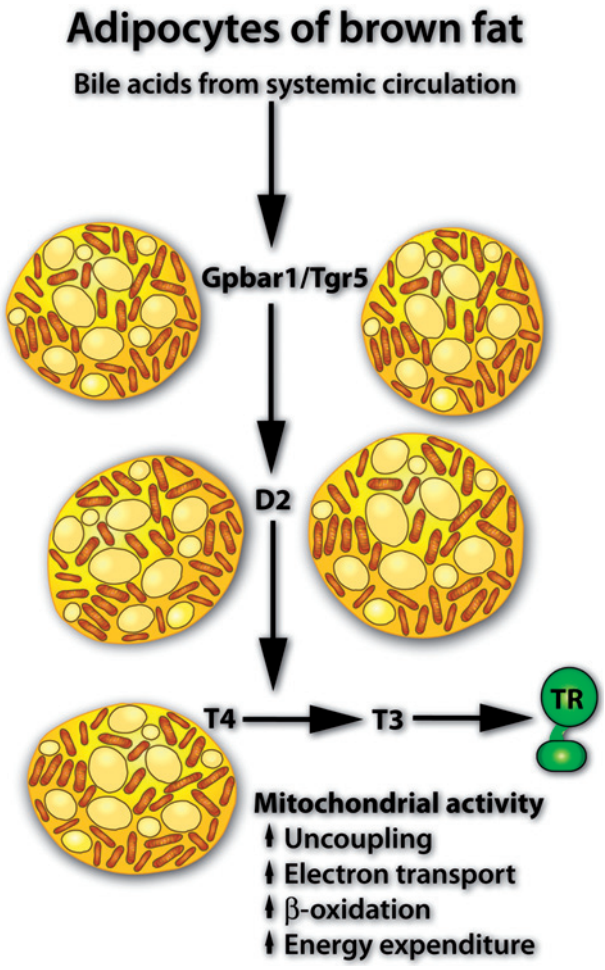

Figure 3. The role of the membrane bile acid receptor in energy expenditure in brown fat. Activation of the bile acid membrane receptor Gpbar/Tgr5 in brown adipocytes stimulates the activity of type 2 iodothyronine deiodinase (D2), which converts T4 to T3. The activation of the thyroid hormone receptor by T3 leads to increased expression of uncoupling protein 1, electron transport, fatty acid β-oxidation and energy expenditure.

Bile acid signaling in liver regeneration, cell proliferation and survival

In recent investigations, bile acids have been shown to affect processes related to tissue regeneration, cell proliferation and survival. Huang et al. [114] recently identified bile acids as stimulatory factors in liver regeneration. They demonstrated that increased bile acid levels stimulate liver regeneration, whereas decreased levels inhibit liver regrowth in mice after partial hepatectomy (Fig. 4). The effect seems to be FXR-dependent since in $Fxr^{-/-}$ mice liver regeneration is inhibited. Their data suggest a homeostatic mechanism for determination of liver size. Decreased liver function leads to accumulation of bile acids, which activate FXR. Apart from inducing negative feedback pathways that protect hepatocytes from bile acid

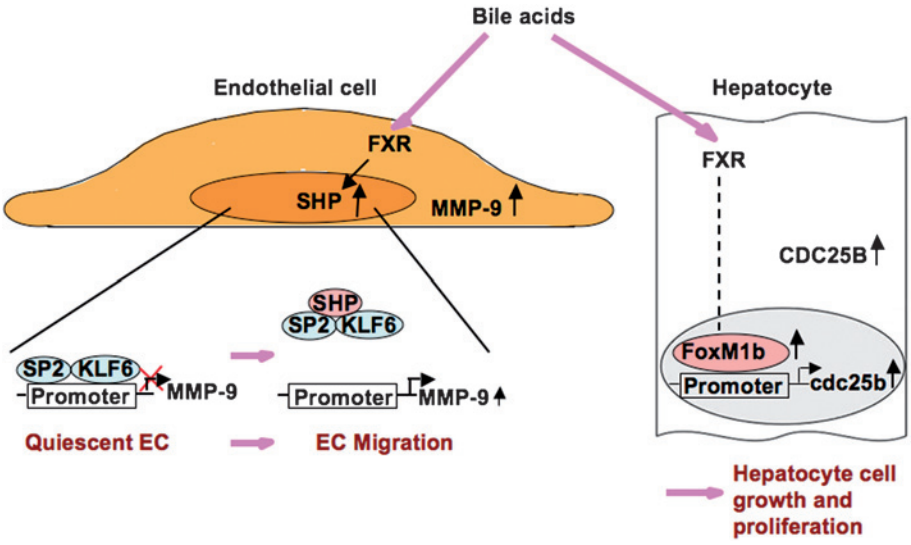

Figure 4. FXR affects liver regeneration and endothelial cell migration. Bile acids increase the expression of the transcription factor FoxM1b in hepatocytes through an FXR-dependent mechanism. This leads to increased expression of a known target of FoxM1b, Cdc25b phosphatase, known to be essential for progression into mitosis. In endothelial cells, bile acids induce EC migration through an FXR/SHP-dependent mechanism that disrupts the repression complex SP2/KLF6.

toxicity, activated FXR induces pathways that promote liver growth. As liver size increases, liver function returns to normal as well as bile acid levels, which leads to loss of the proliferative stimulus. Moreover, these investigators found that bile acid signaling is necessary for the induction of FoxM1b after partial hepatectomy and for the increased expression of the direct FoxM1b target *cdc25b* [115] (Fig. 4). The transcription factor FoxM1b regulates the expression of cell cycle genes required for hepatocyte proliferation during liver regeneration [115] and thus may account for the observed effects of bile acids on liver regeneration.

Bile acids may also contribute to liver regeneration by affecting vascular remodeling. In a number of *in vitro* assays Das et al. [116] demonstrated the importance of FXR for endothelial cell (EC) motility. Through an SHP-dependent mechanism FXR induces dissociation of SP2/KLF6 repressor complex from the Sp1 motif of the matrix metalloproteinase-9 (MMP-9) gene promoter (Fig. 4). Accordingly, the consequent increase in MMP-9 expression leads to enhanced cell motility. These results raise the possibility that bile acids might contribute to the liver regeneration process additionally by providing the signals for vascular remodeling [116]. However, it could also be hypothesized that by affecting EC motility, bile acids may stimulate the development of blood vessels in tumors and consequently cancer progression and metastasis.

Another possible mechanism by which bile acids may affect process of metastasis has been demonstrated for breast cancer. The bile salt sodium deoxycholate (DCA), contained in bone tissue, promotes survival and induces migration of metastatic human breast cancer MDA-MB-231 cells [117]. This finding could explain why bone is the most common site to which breast cancer cells metastasize. On the contrary, higher concentrations of DCA caused apoptosis in the metastatic human breast cancer cell line MDA-MB-231 [117]. Other reports also demonstrate that activation of FXR induces apoptosis in vascular smooth muscle cells [118] and breast cancer cells [119]. Indeed, synthetic FXR agonists are currently being developed as possible antineoplastic drugs [120].

The effect on cell survival has similarly been demonstrated in Barrett's esophagus-derived cell line, in which the FXR antagonist guggulsterone induces apoptosis, suggesting that FXR activation promotes survival in these cells [121].

All these contradictory observations suggest that activation of FXR may lead to opposite effects in terms of cell proliferation in different cells and tissues; therefore it will be important to define the mechanisms underlying the differential effects linked to the FXR activation in various cell types to explore the possibility of using selective FXR activators in certain types of tumors.

Other tissues

FXR is also expressed in nonclassical bile acid target tissues. By using human cardiovascular tissue arrays, Bishop-Bailey et al. [118] found that FXR is expressed at high levels in a variety of normal and pathological human tissues, such as the vasculature and in a number of different metastatic cancers. Interestingly, when vascular smooth muscle cells are challenged with FXR ligands, they undergo apoptosis and increase the expression of phospholipid transfer protein and SHP,

two classical FXR targets. The authors propose that FXR is a functional protein in the vasculature that may provide a direct target for the treatment of cardiovascular and dyslipidaemic diseases.

FXR also plays a role in endothelial homeostasis. It has been reported that pulmonary artery endothelial cells also express FXR [122]. Here, activated FXR downregulates endothelin-1 gene expression via SHP-mediated repression of the transcription factor AP-1, a major activator of endothelin-1 (ET-1) gene transcription. ET-1 is the most potent vasoconstrictive substance known [123] and may play an important role in the development of both primary and secondary pulmonary hypertension [124]. These results indicate that FXR ligands control ET-1 expression in vascular endothelial cells and may be useful to pharmacologically manipulate endothelial functions.

Conclusions

The view that bile acids serve mainly as detergents that assist the digestion and absorption of fats and lipid-soluble components of the diet is nowadays too narrow in light of the vast body of evidence accumulated in less than a decade which show that these molecules regulate a wide range of cellular functions by acting through different signaling cascades. More surprisingly, the numerous reports thus far published reveal that bile acids interfere with many processes beyond bile acid metabolism and transport. By acting through a number of receptors and signaling pathways, bile acids not only modulate metabolic pathways but also other functions critical for cellular homeostasis. It has been shown, in fact, that bile acids have a wide range of effects: they may be used to dissolve cholesterol gallstones and for the management of cerebrotendinous xanthomatosis, hypertriglyceridemia, congenital liver diseases, rheumatoid arthritis and constipation. The finding that one of the bile acid receptors, FXR, is also expressed in nonclassical bile acid target tissues suggests that potentially it has a far greater number of roles throughout the body than originally assumed. The realization of these concepts opens new perspectives for the potential use of bile acid derivatives and of synthetic molecules acting upon their receptors in therapy, but at the same time it poses new questions. For example, what is the biological significance of the effects of bile acids in tissues that are not the canonical site of actions of these molecules? Bile acids typically affect gene expression in cells of the GI tract; however, one of their receptors, FXR, is also expressed in the vasculature. As bile acids activate FXR at concentrations that are not likely reached outside the GI tract, it is tempting to hypothesize that bile acids are not the only natural ligands for FXR, and perhaps in cells of the vascular wall other endogenous molecules may affect receptor activity. Finally, given the pleiotropic actions of bile acids on multiple cell types and the expression of FXR as well as Gpbar1/Tgr5 in different tissues, it will be important to assess the multiple effects of receptor activation when new synthetic molecules affecting either FXR, or other nuclear receptors or Gpbar1/Tgr5, are tested for future therapeutic interventions. The design of selective modulators of FXR, as well as of other receptors for bile acids, will be a fundamental strategy to obtain molecules with a therapeutic value and with limited undesirable effects.

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