

1 **Molecular physiology of bile acid signaling in health, disease, and aging**
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21 RUNNING HEAD: Physiology of bile acid signaling

22 **Abstract**

23

24 Over the last two decades, bile acids (BAs) have become established as important signaling
25 molecules that enable fine-tuned inter-tissue communication from the liver, their site of production,
26 over the intestine, where they are modified by the gut microbiota, to virtually any organ, where they
27 exert their pleiotropic physiological effects. The chemical variety of BAs, to a large extent
28 determined by the gut microbiome, also allows for a complex fine-tuning of adaptive responses in
29 our body. This review provides an overview of the mechanisms by which BA receptors coordinate
30 several aspects of physiology and highlights new therapeutic strategies for diseases underlying
31 pathological BA signaling.

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34 **Call out box for clinicians**

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36 Several diseases and conditions have been associated with an uncontrolled rise in BA
37 concentrations. This is often the case when the tight feedback regulation of BA synthesis is
38 compromised to the point that BAs become detrimental. BAs and their cognate receptors, FXR and
39 TGR5, however, exert many beneficial roles as they enable tissues to adapt to environmental,
40 nutritional, and physiological cues. Over the last two decades, BA mimetics targeting FXR, TGR5,
41 or both, have been proven to be efficacious in alleviating chronic metabolic and inflammatory
42 disorders, such as obesity, type 2 diabetes (T2D), atherosclerosis and non-alcoholic
43 steatohepatitis (NASH). While several aspects of BA signaling are still poorly understood, the first
44 therapeutics targeting FXR are making their way into the clinic to treat liver diseases, such as
45 primary biliary cholangitis (PBC) and NASH. Drugs targeting BA signaling may hence have a bright
46 future and the continuing efforts on studying the impact of changing BA signaling pathways in
47 humans will be beneficial to translate our emerging knowledge on BA physiology in model
48 organisms into clinical benefits.

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51 **I. Introduction**

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53 BAs are a class of structurally diverse molecules with more than 60 species currently identified in
54 mammals. This rich diversity not only suggests the existence of multiple mechanisms driving the
55 synthesis and metabolism of BAs but also indicates that each of these entities may have different
56 bioactive functions. The identification of multiple BA-responsive nuclear and membrane receptors
57 has spurred tremendous interest into the mechanisms by which BAs coordinate signal transduction
58 in various tissues and cell types. The nuclear receptor (NR) farnesoid X receptor (FXR) and the G
59 protein-coupled receptor (GPCR) Takeda G-protein receptor 5 (TGR5) are the best-studied

60 molecular mediators of BA-dependent adaptive responses and are prospective targets for multiple
61 disorders. Here, we provide an overview of the growing complexity of BA biology, their cross-talk
62 with the microbiome, as well as their role as signaling mediators of cellular and organismal function
63 in health and disease. We also cover a number of novel unanticipated functions of BAs and
64 highlight different modes of intervention in BA signaling as therapeutic options to treat chronic
65 metabolic and inflammatory disorders.

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68 **II. BAs in a nutshell**

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70 BAs are products of cholesterol catabolism and are composed of a steroid nucleus skeleton and
71 an isopentanoic acid side chain (169). They are synthesized as primary BAs in the liver through
72 well-established enzymatic pathways, which have been extensively reviewed elsewhere (363).
73 Chenodeoxycholic acid (CDCA) and cholic acid (CA) are the main hepatic BA products in humans
74 (Figure 1A-B). There are four main steps that lead to primary BA synthesis: initiation,
75 modifications of the ring structure, oxidation and shortening of the side chain, and conjugation.
76 These sequential processes are carried out in the microsomes, cytosol, mitochondria, and
77 peroxisomes, respectively. At least 7 mono-oxidases of the cytochrome P450 (CYP) family are
78 involved in the incorporation of hydroxyl groups on the ring structures of cholesterol. The bulk of
79 primary BAs is produced by the classic pathway (Figure 1A). This branch is initiated by the rate-
80 limiting enzyme, cholesterol 7 α -hydroxylase (CYP7A1). While humans synthesize CDCA, rodents
81 produce MCAs via additional C6 hydroxylation. These BAs are more hydrophilic than CDCA and
82 contribute to the species-specific differences in BA physiology (170). Sterol 12 α -hydroxylase
83 (CYP8B1) catalyzes the production of CA and its activity is a major enzymatic determinant of
84 hepatic BA composition. In contrast to the classic pathway, the alternative branch depends on the
85 chain-oxidation action of sterol 27-hydroxylase (CYP27A1), followed by 7 α -hydroxylation of its
86 product by oxysterol 7 α -hydroxylase (CYP7B1) (363) (Figure 1A). Although in physiological
87 conditions the alternative branch is only marginal, environmental factors, such as cold exposure
88 (452), high fat/high cholesterol (HF/HC) diet feeding (463), or liver disease (235), increase its
89 contribution by enhancing the expression of CYP7B1, suggesting that the pathway mediates
90 adaptive responses to various stresses. Finally, BA biosynthesis terminates with the conjugation of
91 taurine in rodents and glycine or taurine in humans. Additional forms of BA conjugation include
92 sulfation, glucuronidation, and N-acetylglicosaminidation (169).

93

94 BAs cycle between the liver and the intestine and this dynamic process guarantees the distribution
95 of adequate BA concentrations at sites of physiological actions (230). After conjugation to taurine
96 or glycine, BAs are secreted from the liver into the bile and stored in the gallbladder along with
97 other bile constituents. Food intake is the main trigger promoting bile secretion in the intestinal

98 tract. This process is mediated by the gut hormone CCK, which promotes hepatic secretion of BAs
99 and gallbladder contraction. Once released in the duodenum, the amphipathic BAs exert their
100 detergent-like activity by forming micelles with dietary lipids and fat-soluble vitamins to facilitate
101 intestinal lipid absorption. BAs return to the liver via the portal vein through active transport
102 mechanisms and undergo several enterohepatic cycles a day (173). This process, termed
103 enterohepatic circulation, is controlled by several dedicated transporters that limit fecal and urinary
104 loss (reviewed in (80, 147)) (Figure 1B). BAs in the portal circulation are taken up by hepatocytes
105 through sodium-dependent taurocholate co-transporting polypeptide (NTCP) and organic anion-
106 transporting polypeptide 1 (OATP1). Hepatic multidrug resistance protein 3 (MRP3), MRP4 and
107 organic solute transporter α/β (OST α/β) provide excretion routes for BAs into the systemic
108 circulation while bile acid export pump (BSEP) exports them across the canalicular membrane
109 (Figure 1B and reviewed in (147)). At the terminal ileum, most of the conjugated BAs are
110 reabsorbed by the enterocytes via the apical sodium-dependent BA transporter (ASBT),
111 chaperoned from the apical to the basolateral membrane by the cytosolic ileal bile acid binding
112 protein (I-BABP), and secreted into the portal circulation via basolateral BA transporters OST α/β ,
113 and MRP3. The enterohepatic circulation is efficient and recycles about 95% of the total BA pool.
114 The remaining 5% is lost in the feces but rapidly restored through *de novo* synthesis in the liver,
115 hence maintaining a constant BA pool size (363).

116
117 During their intestinal transit, BAs undergo several modifications through the action of bacteria
118 residing in the distal part of the intestine, which deconjugate BAs or produce the secondary BAs
119 deoxycholic acid (DCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA), hyocholic acid
120 (HCA), murideoxycholic acid (MDCA), ω -muricholic acid (ω MCA) and hyodeoxycholic acid (HDCA)
121 (Figure 1A-B). The details of BA biotransformation by the gut microbiota are described elsewhere
122 (430) and briefly summarized in Table 1.

123

124

125 III. BAs as signaling factors

126

127 The identification of dedicated BA receptors has triggered a remarkable rejuvenescence of the field
128 and led to the novel concept that BAs, in addition to their detergent-like properties and their use as
129 substrates for microbial metabolism (described in section IV-F), act as bona fide hormones (Figure
130 2). Below we describe in detail the main findings related to FXR and TGR5, the most extensively
131 studied BA-responsive receptors, while briefly summarizing the most pertinent studies related to
132 other, less known, BA-responsive receptors (Figure 3A).

133

134 A. FXR, a dedicated NR for BAs

135

136 FXR (also known as NR1H4) is a NR that earned its name from the identification of farnesol as an
137 activator (113). Later, BAs were demonstrated to be the natural ligands of FXR (274, 320, 434),
138 with CDCA being the most potent (Table 2). Although initially assumed to be limited to the liver,
139 intestine, kidney, and adrenal glands, subsequent studies showed that FXR is more broadly
140 expressed. Upon ligand binding, FXR heterodimerizes with the retinoic acid receptor α (RXRa;
141 NR2B1) to activate the transcription of its target genes (Figure 3B). The transcriptional activity of
142 FXR is fine-tuned by a set of coregulators, including transcriptional coactivators, such as steroid
143 receptor coactivator 1 (SRC-1) (274, 320), peroxisome-proliferator-receptor (PPAR)- γ coactivator-
144 1 α (PGC-1 α) (475), and methyltransferases represented by coactivator-associated arginine (R)
145 methyltransferase-1 (CARM-1) (13, 25) and protein arginine (R) methyltransferase-1 (PMRT-1)
146 (359). Furthermore, FXR can be post-translationally modified. Elevated concentrations of plasma
147 glucose favor FXR stabilization and function through O-Glc-N-acetylation (31), whereas acetylation,
148 methylation and SUMOylation inhibit its transcriptional activity (20, 21, 214). Moreover, AMP-
149 activated protein kinase (AMPK) phosphorylates and inactivates FXR in the context of cholestasis
150 (259).

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152 B. TGR5, a dedicated GPCR for BAs

153

154 TGR5, also known as G-protein coupled BA receptor (GPBAR1), is a member of the Rhodopsin-
155 like subfamily of GPCRs and classified as the founder BA receptor of this sub-class (411). TGR5 is
156 encoded by a single exon gene, generating a protein comprised of seven transmembrane
157 domains, three extracellular loops and three intracellular loops (279). Consistent with the signal-
158 amplifying properties of GPCRs, TGR5 is lowly to moderately expressed in almost every tissue or
159 cell type, with the exception of the gallbladder epithelium, where it is abundantly expressed (425).
160 TGR5 is activated by both conjugated and unconjugated BAs with the following order of potency
161 LCA>DCA>CDCA>CA (Table 2). The taurine-conjugated BAs are usually more potent activators
162 than the glycine-conjugated or unconjugated BAs (203). In addition to BAs, some steroid hormone
163 intermediates, such as pregnandiol and 5 α -pregnandione, also modulate TGR5 activity (210, 369).
164 Semi-synthetic agonists for TGR5 have been developed and are listed in Table 2. Upon BA
165 stimulation, TGR5 couples to G α s proteins, and activates adenylate cyclase to initiate a transient
166 cAMP rise (203), which, in turn, induces the activity of various downstream effectors, including
167 PKA (231, 337, 350), or the exchange protein directly activated by cAMP (EPAC) (231, 350).
168 TGR5 stimulation was also reported to activate MAPK signaling, mainly via ERK1/2 (191, 353,
169 427), proto-oncogene protein-tyrosine kinase (SRC) (175) and the mechanistic target of rapamycin
170 (mTOR) (333, 471) (Figure 3B). The impact of β -arrestins on TGR5 signaling has been studied by
171 several groups. Initial observations reported that TGR5 internalizes after activation (203) and that
172 induction of TGR5 anti-inflammatory signaling is dependent on β -arrestin 2 (442). However, other
173 studies demonstrated that TGR5 signaling does not require β -arrestins (191, 337). Recent

174 evidence reported that TGR5 only indirectly interacts with β-arrestin through G protein-coupled
175 receptor kinase (GRK) to activate the innate antiviral immune response (175).

176

177 C. Other receptors involved in BA signaling

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179 C.1. Nuclear receptors

180

181 Other members of the NR family, including the pregnane X receptor/steroid and xenobiotic-sensing
182 receptor (PXR/SXR; NR1I2), constitutive androstane receptor (CAR; NR1I3) and the vitamin D3
183 receptor (VDR; NR1I1) can respond to BAs (recently reviewed in (383)). Higher concentrations of
184 BAs are often required for their activation, suggesting that their functions become particularly
185 relevant during pathological conditions such as cholestasis. This is exemplified by PXR/SXR,
186 which is a xenobiotic sensor that coordinates cytochrome P450-induced detoxification and
187 inhibition of BA synthesis in conditions requiring protection from LCA overload (398, 456). PXR
188 acts in synergy with CAR to control BA clearance as well as bilirubin detoxification (142, 180, 366,
189 371, 429) but whether BAs act as ligands for CAR is still a matter of debate. On the contrary, VDR
190 binds LCA at lower concentrations than PXR and mediates the detoxification of its ligand by
191 inducing the transcription of *Cyp3a* (273). While this feature supports a protective role for VDR in
192 gut homeostasis, recent evidence suggests that the LCA-VDR axis regulates biological pathways
193 that go beyond BA detoxification, and coordinate processes as diverse as adaptive and innate
194 immunity (338, 395, 403) and gut microbiota modulation (435).

195

196 C.2. Cell surface receptors

197

198 BAs can trigger acute responses through interaction with other GPCRs including sphingosine 1-
199 phosphate receptor 2 (S1PR2), formyl-peptide receptors (FPRs) and muscarinic acetylcholine
200 receptors (mAChRs) (Figure 3A). While the main ligands for S1PR2 are sphingolipids, TCA and
201 other conjugated BAs can also induce its signaling (402). S1PR2 blockage reduces portal vein
202 pressure and liver injury, suggesting a pathological role for S1PR2 in the setting of cholestasis
203 (198, 440). FPRs are a small group of GPCRs expressed in neutrophils and monocytes (244).
204 High concentrations of CDCA (62) and DCA (61) can interfere with the binding of N-
205 formylmethionyl-leucyl-phenylalanine, an FPR agonist with potent chemoattractant properties in
206 monocytes. Although these findings suggest an anti-inflammatory effect of BAs through FPRs, it is
207 presumed that these receptors are only relevant under pathological conditions. The last group of
208 BA-responsive GPCRs comprises the muscarinic receptors, which, upon exposure to conjugated
209 secondary BAs, promote cancer cell growth in an epidermal growth factor receptor (EGFR)-
210 dependent manner (11, 63). In addition, these receptors are involved in nitric oxide-induced
211 vascular relaxation of the aorta (216), as well as in the pathology of cholestasis-induced cardiac

212 arrhythmia (181, 379). Finally, BAs can also activate membrane receptors other than GPCRs
213 (Figure 3A). TUDCA, for instance, exerts anti-apoptotic actions in hepatocytes through activation of
214 the β_1 subunit of the $\alpha_5\beta_1$ -integrin pathway (132, 392). Interestingly, TUDCA promotes also other
215 processes, such as osteoblast differentiation from mesenchymal stem cells through a similar
216 integrin-mediated pathway (57).

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218

219 **IV. BA signaling in health, disease, and aging**

220

221 A. Enterohepatic regulation of bile homeostasis

222

223 Bile is a physiological fluid composed of water and a mixture of organic and inorganic solutes of
224 diverse complexity, including BAs, cholesterol, phospholipids, and bilirubin (40). Bile is formed in
225 hepatocytes, further processed in the biliary epithelial cells, and stored in the gallbladder, until
226 released postprandially in the gut lumen where the BA fraction facilitates lipid emulsification and
227 absorption. Its main constituents are intrinsically interconnected and are subject to complex
228 regulatory mechanisms in the liver. BA biosynthesis for instance requires hepatic cholesterol as a
229 substrate, yet is tightly controlled by negative feedback regulation involving both liver and gut-
230 driven mechanisms (Figure 4). In addition to its regulatory impact on BA synthesis, BA signaling
231 coordinates the hepatic secretion of biliary cholesterol, BAs, phospholipids, and bilirubin through
232 transporter-mediated mechanisms. As a consequence, BA-responsive receptors play a pivotal role
233 in maintaining cholesterol solubility in bile and in coordinating bile formation and flow (extensively
234 reviewed in (147, 169, 265)). While FXR is considered as an essential regulator of these
235 processes, TGR5 complements these functions by coordinating various aspects of biliary
236 physiology. The emerging roles of liver TGR5 in other non-parenchymal cells is reviewed
237 elsewhere (211).

238

239 A.1. FXR as a regulator of bile and cholesterol homeostasis

240

241 **Control of BA pool size and composition:** Already in 1958, it was demonstrated that the amount
242 of bile supplied to the liver via the portal circulation influences the synthesis rate of BAs in rats
243 (29). Several laboratories confirmed the transcriptional nature of this regulation, with *Cyp7a1* being
244 the main target. Among the transcription factors that control BA synthesis (37, 361, 363), FXR is
245 now recognized as being the master regulator of the BA pool size. The first studies in *Fxr*^{-/-} mice
246 established that hepatic FXR is a cell-autonomous rheostat that regulates BA concentrations by
247 repressing their synthesis and hepatic uptake, while concomitantly stimulating their export (386). In
248 the liver, hepatic FXR contributes to the regulation of *Cyp7a1* via the induction of small
249 heterodimer partner (SHP; NR0B2) (137, 266) (Figure 4, right upper quadrant). SHP is an atypical

NR with corepressor activity that potently inhibits its dimerizing NR partners, including the liver receptor homolog-1 (LRH-1; NR5A2) (137, 266), hepatocyte nuclear factor-4 α (HNF-4 α ; NR2A1) (222) and liver X receptor alpha (LXR α ; NR1H3) (41). This molecular network of NRs contributes to the cell-autonomous regulation of *Cyp7a1*. Studies in *Shp*^{-/-} mice have corroborated the importance of SHP in this negative regulatory cascade, however, they also suggested that other mechanisms contribute to this process (215, 436). In fact, additional studies revealed that feedback regulation of hepatic BA production is also mediated by a gut-driven mechanism, involving the induction of FGF15/19 (FGF15 in mice (185); FGF19 in human (472)). This enterokine is expressed in the enterocytes of the terminal ileum, and was originally discovered as an enterohepatic signaling factor able to blunt hepatic BA synthesis (reviewed in (390)). Tissue-specific *Fxr*^{-/-} mouse models furthermore established that eliminating FXR in the intestine profoundly disrupts BA homeostasis (218). Mechanistically, FGF15/19 reaches the liver via the portal circulation and inhibits *Cyp7a1* expression through hepatic fibroblast growth factor receptor 4 (FGFR4) and ERK/MAPK signaling (172, 185, 253, 393, 467), as well as through SRC-dependent FXR activation (253) (Figure 4, right upper quadrant). FGF15/19 binds to the FGFR4- β -Klotho complex (234, 261) and activates the non-receptor Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2 (SHP2) (253). Accordingly, *Fgfr4*^{-/-}, *Klb*^{-/-} and hepatocyte-specific *Shp2*^{-/-} mice are unable to suppress BA synthesis upon FGF15/19 stimulation (188, 253, 468). Of note, intestinal BA-mediated secretion of FGF15/19 also signals, in part, through SHP by increasing its stability in the liver through ERK-dependent phosphorylation that inhibits its proteasomal degradation (291). A more recent study established that FXR signaling also controls BA synthesis independently of SHP and FGF15/19 by regulating *Cyp7a1* mRNA stability (407). Further studies will be needed to establish the relative contribution of these FXR-mediated post-transcriptional responses on BA production.

Activation of FXR signaling also significantly blunts *Cyp8b1* expression, which controls the production of CA. Studies conducted in tissue-specific *Fxr*^{-/-} mouse models showed that unlike *Cyp7a1*, which is more sensitive to inhibition via the intestinal FXR-FGF15 pathway, *Cyp8b1* repression requires FXR activation in the liver, indicating differential regulation of the enzymes controlling the synthesis of the two main BA products (218). Although the molecular basis for this tissue-specific control is still poorly understood, it likely involves complex cross-talk with metabolite- and hormone-sensing transcription factors.

Regulation of BA and bile homeostasis: Secretion of bile constituents, such as cholesterol, BAs, phospholipids, glutathione and bilirubin, is tightly controlled by FXR signaling, which coordinates the expression of hepatic transporters involved in bile formation and flow as extensively reviewed in (80, 147) (Figure 5). Moreover, FXR activation induces the expression of transporters that provide spillover routes for BA efflux to avoid toxic BA overload (reviewed in (414)). Briefly, FXR upregulates the expression of canalicular transporters, including BSEP (12, 336, 386) and MDR3

(Mdr2 in rodents) (263) to increase the biliary concentration of BAs and phospholipids and prevent cholesterol crystallization (302). FXR-dependent protection from hepatic BA overload also occurs via modulation of OST α/β which acts as an alternative export system to BSEP at the hepatic sinusoidal membrane (239, 486). In addition to the BA transporters, BAs upregulate MRP2 (200) to excrete bilirubin and glutathione conjugates, as well as ABCG5/8 (469, 479) in charge of cholesterol efflux. FXR activation by obeticholic acid (OCA) (Table 2) however is not associated with increased biliary cholesterol secretion, suggesting that the effects on hepatic ABCG5/8 induction do not necessarily result in increased transport activity (458). Of note, most of the bile constituent transporters are also upregulated in human liver slices when exposed to OCA (184), which is of relevance for cholestatic disease, as described in section IV-A.3. After participating in the digestion and absorption of dietary lipids in the gut, intestinal BAs are reabsorbed through different mechanisms (81). While only a fraction can diffuse passively in the duodenum (79), most of the BAs are taken up by the terminal ileum through active transport (Figure 5). Intestinal FXR activation downregulates the expression of ASBT (252) while it increases I-BABP and OST α/β (114, 218, 247, 486) to efficiently export BAs from the enterocytes to the portal blood.

303

Control of intestinal cholesterol homeostasis: In mice, activation of FXR signaling by obeticholic acid (OCA) (458) and PX20606 (81) (Table 2) changes the BA pool composition leading to inhibition of intestinal cholesterol absorption (458) and increase of intestinal cholesterol excretion (81). Similarly, the FXR agonist GW4064 also stimulates plasma cholesterol clearance by enhancing its fecal elimination and reducing its intestinal absorption (479). Both the hepatic and intestinal pathway of FXR signaling seem to contribute to this process. As described above, hepatic FXR controls *Abcg5/8*. However, it also represses *Cyp8b1* expression, thereby reducing CA levels (218). These changes render the BA pool more hydrophylic and less efficient in emulsifying lipids. In addition to this effect, intestinal FXR stimulates transintestinal cholesterol elimination (TICE), a transport mechanism in the intestine that controls cholesterol homeostasis by increasing its intestinal elimination (190) (Figure 6). Studies revealed that this mechanism largely involves intestinal ABCG5/8 transporter activity and that enhanced excretion rather than decreased absorption of cholesterol accounts for FXR-mediated fecal sterol loss (81, 190). The coordinated activation of FXR in the enterohepatic organs thus not only controls BA production, bile formation and flow; it also ensures the tight control of cholesterol levels in our body.

319

320 A.2. TGR5 and biliary physiology

321

322 TGR5 influences BA homeostasis in a different, but complementary, manner compared to FXR in
323 part explained by the distinct expression profile of both receptors along the enterohepatic axis
324 (Figure 6). While *Fxr* is abundant in hepatocytes and enterocytes, only marginal levels of *Tgr5*
325 mRNA are found in these cell types. In contrast, *Tgr5* is robustly expressed in cholangiocytes and

326 gallbladder epithelium where TGR5 activation promotes chloride (Cl^-) secretion through cAMP-
327 regulated induction of CFTR. The generated Cl^- gradient is subsequently used by the anion
328 exchanger 2 (AE2) to secrete bicarbonate (HCO_3^-) across the apical membrane (207). In cystic
329 fibrosis, defective CFTR is responsible for impaired biliary secretion of Cl^- and HCO_3^- promoting
330 ductal cholestasis, which can evolve into sclerosing cholangitis and cirrhosis (110). TGR5 is
331 furthermore localized on cholangiocyte cilia, where its activation modulates bile flow and
332 composition by regulating resorptive and secretory mediators (212). These findings underscore
333 TGR5 as a pivotal regulator of biliary secretion, which is in line with the reduced bile flow in *Tgr5*^{-/-}
334 mice (254) (Figure 6). *Tgr5*^{-/-} mice are furthermore susceptible to BA overload-induced liver injury
335 potentially linked to a more hydrophobic BA pool (92, 327), and a compromised biliary epithelium
336 barrier function (290). These findings underscore TGR5 not only as a regulator of biliary secretion
337 and flow, but also as a cytoprotective protein involved in preserving tight junction structure and
338 function.

339 In addition to these functions, activation of TGR5 by LCA or the semi-synthetic BA, INT-777 (329,
340 410) (Table 2), promotes gallbladder smooth muscle cell relaxation (243, 254) (Figure 6). A similar
341 phenotype is observed when BAs activate the intestinal FXR-FGF15 axis. *Fgf15*^{-/-} mice have an
342 empty gallbladder even in the fasted state when it is normally filled with bile (68). This phenotype is
343 restored after FGF15 injection, causing rapid gallbladder filling without stimulation of the bile flow.
344 Mechanistically, FGF15 induces relaxation of the gallbladder smooth muscle via cAMP-induced
345 signaling (68). Both ileal FXR and cholangiocyte TGR5 signaling thus seem to converge on the
346 same cAMP axis providing a unifying mechanism for coordinated regulation of gallbladder
347 physiology.

348

349 A.3. BAs and hepatobiliary diseases

350

351 Given the broad role of BA receptors in coordinating bile homeostasis and biliary physiology, it is
352 not surprising that impaired signaling is associated with the development of hepatobiliary diseases,
353 ranging from cholestatic liver disorders, cholesterol gallstone disease (CGD) to other gallbladder-
354 related conditions.

355

356 **Cholestatic liver disorders.** Cholestasis has diverse etiologies and can result from impaired bile
357 secretion across the canalicular membrane of the hepatocytes (intrahepatic cholestasis), or from
358 impaired bile flow secondary to bile duct pathology, as is the case for primary biliary cholangitis
359 (PBC) and primary sclerosing cholangitis (PSC) (reviewed in (343, 360, 400)). Consistent with the
360 etiology of cholangitis-related disorders, genome-wide association studies (GWAS) in PBC and
361 PSC patients have highlighted a major role for immune-related genes (164). Of interest, a gene
362 variant in TGR5 has been found in PSC patients and further research should confirm the precise
363 role of TGR5 in this disease (174). Likewise, certain FXR single nucleotide polymorphisms (SNPs)

364 can predispose to intrahepatic cholestasis of pregnancy (ICP) (422) and to progressive familial
365 intrahepatic cholestasis (PFIC) (135), reinforcing the importance of a preserved FXR signaling to
366 limit pathological BA overload. Consistent with these genetic findings, ample evidence exists for a
367 beneficial role of FXR agonism in various preclinical models of cholestasis (extensively reviewed in
368 (209, 298). Stimulation of FXR signaling restores bile flow, reduces BA synthesis and stimulates
369 phospholipid secretion, thereby decreasing the detergent capacity of BAs (109, 263, 328).
370 Furthermore, part of these effects is also mediated by selective activation of intestinal FXR-
371 FGF15/19 signaling (299), or by treatment with human FGF19 (299), or its nontumorigenic
372 analogue M70, now referred to as NGM282 (269), and protect mice from cholestatic liver damage.
373 Several of the FXR related therapeutics have been tested in PBC and PSC patients, as described
374 in section V-C.

375

376 **CGD and other gallbladder-related conditions.** Quantitative trait loci (QTL) analysis in inbred
377 mouse strains and human GWAS linked gene variants in the cholesterol transporter ABCG5/8 with
378 gallstones (46, 139, 399, 451). Low-frequency variants associated with this disease were also
379 found in genes controlling BA metabolism, including FXR, CYP7A1, ABCB11, APOB and the CCK
380 receptor CCKAR, as well as the phospholipid transporter ABCB4 (reviewed in (164, 237)).
381 Moreover, *Fxr*^{-/-} mice fed a lithogenic diet exhibit several features that contribute to the
382 development of CGD, including cholesterol supersaturation of bile, precipitation of cholesterol
383 crystals, increased BA hydrophobicity and gallbladder inflammation, whereas activation of FXR by
384 GW4064 prevents its development (302). The protective effect of FXR agonists in rodents is
385 attributed to their ability to increase the hydrophilicity of the BA pool (81, 446) and to stimulate the
386 secretion of BAs and phospholipids by inducing the expression of their transporters, BSEP and
387 Mdr2 (302). In humans, both UDCA and CDCA are effective in reversing CGD (77, 97, 116, 140,
388 278, 293). However, the mechanisms by which these BA species confer protection differ, as
389 UDCA, in contrast to CDCA, is a poor agonist for FXR. Recent reports revealed that OCA might
390 confer a higher risk for gallstone formation when administered to CGD patients (3) or to NASH
391 patients (466). Although the higher cholesterol saturation index and the elevated FGF19 levels in
392 gallbladder likely account for this effect (3), a residual activity of OCA towards TGR5 could be
393 another reason. TGR5 is highly expressed in the gallbladder epithelium where it exerts important
394 cytoprotective actions (see section IV-A.2). Potential adverse effects however could arise upon
395 chronic activation of the receptor. Gallbladder relaxation and increased size are prominent
396 phenotypes of TGR5 agonism (43, 254). In line with these findings, mice lacking TGR5 are
397 protected against gallstone formation (425). Although this represents a challenge for human
398 therapeutics, tissue-specific targeting of TGR5 may overcome this undesired effect. Future clinical
399 trials with next-generation TGR5 agonists will be needed to evaluate the exact impact of this
400 pathway on biliary (patho)physiology.

401

402 B. BAs as integrators of nutrient availability and intestinal homeostasis

403

404 Since intestinal BA levels oscillate following a rhythm that is dictated by dietary intake, these
405 molecules serve as a proxy for nutrient availability. It is thus not surprising that BA-responsive
406 receptors in enterocytes and different types of intestinal cells, including enteric neurons, smooth
407 muscle, and enteroendocrine cells, sense and relay nutrient availability to a physiological
408 response. FXR and TGR5 in particular modulate a series of events including fluid transport,
409 hormone release, expression of transport proteins, intestinal motility, and secretory responses that
410 enable the uptake and availability of nutrients, fluid, and ions along the gastrointestinal tract
411 (Figure 6).

412

413 B.1. Secretion of enteroendocrine hormones

414

415 BAs are essential regulators of appetite- and metabolism-modulating gut hormones. The incretin,
416 glucagon-like peptide-1 (GLP-1), has received major attention because of its therapeutic potential
417 to lower blood glucose concentrations. GLP-1 is secreted from enteroendocrine L cells following
418 food ingestion. While glucose and free fatty acids are established nutrient-derived triggers for GLP-
419 1 secretion (307), BAs have been identified as equally potent postprandial stimulators. TGR5 is
420 expressed in L cells and mediates BA-induced GLP-1 release both *in vitro* and *in vivo* through a
421 cAMP-dependent mechanism (202, 268, 410) (Figure 7). In addition, dependent on the type of
422 agonist, activation increases intracellular calcium levels (44, 319, 410). Receptor activation can
423 also promote GLP-1 production by inducing its precursor preproglucagon (155). TGR5 is
424 predominantly located on the basolateral membrane of L cells, suggesting that BAs first have to
425 cross the intestinal epithelium before stimulating GLP-1 release (44, 49, 229). A similar mechanism
426 is proposed for peptide YY (PYY) and neuropeptide Y, whose secretion is also blunted in *Tgr5*^{-/-} mice
427 (229). The discovery of TGR5 agonists as GLP-1 secretagogues is currently used as a basis to
428 identify regulatory nodes that would synergistically elevate endogenous GLP-1 levels. An
429 interesting discovery in this respect is the functional synergism between TGR5 and GPCRs
430 involved in fatty acid signaling, such as FFA1R (134, 160), which is consistent with the
431 exacerbated response of BAs during high-fat diet (HFD) feeding (155, 410). Another way to
432 enhance TGR5-mediated GLP-1 secretion is to combine TGR5 agonists with somatostatin
433 receptor 5 antagonists, which would remove the brake on GLP-1 release (42). These discoveries
434 suggest that targeting complementary signaling pathways is more effective than TGR5 activation
435 alone in modulating the GLP-1 response.

436 Contrary to TGR5, FXR is proposed to counteract GLP-1 signaling, either by blocking precursor
437 synthesis via a mechanism involving carbohydrate-responsive element-binding protein (ChREBP)
438 repression (413) or by reducing the expression and signaling of the short-chain free fatty acid
439 receptor 2 (FFAR2) (95) (Figure 7). These studies would suggest that FXR most likely functions to

440 regulate later phases of GLP-1 secretion. On the other hand, other studies showed that
441 fexaramine-mediated FXR activation (325) (Table 2) as well as concurrent activation of both FXR
442 and TGR5 pathways significantly induce GLP-1 secretion (324) by priming and enhancing TGR5
443 expression and signaling (324) (Figure 7). These unexpected observations reinforce the notion that
444 both BA sensors are functionally required in the coordinate regulation of GLP-1 signaling.

445

446 B.2. Secretion of enterokines

447

448 As already outlined in section IV.A, FGF15/19 is an established ileal FXR target that signals to the
449 liver to limit hepatic BA production (185). In addition to its regulatory role in BA homeostasis,
450 FGF15/19 regulates several aspects of the hepatic postprandial response, including inhibition of
451 gluconeogenesis (341) and increase in glycogen and protein synthesis (221). FGF15 furthermore
452 coordinates a physiological feedback loop promoting gallbladder refilling after CCK-induced
453 gallbladder emptying (68). FGF15/19 can also reach the brain where it exerts central metabolic
454 actions including reduction of food consumption and the regulation of glucose homeostasis (238,
455 277, 300, 364). Pharmacological administration of this hormone promotes other beneficial actions
456 including the increase in energy expenditure and fat mass loss, improvement of insulin sensitivity
457 and decrease in blood triglycerides and cholesterol levels (120). However, abrogation of FGF15/19
458 signaling confers protection against diet-induced obesity (DIO) in *Klb*^{-/-} mice due to changes in the
459 BA composition (389). More details on these dedicated effects are described in the sections below.

460

461 B.3. Intestinal electrolyte and fluid balance

462

463 BAs are established regulators of colonic fluid balance and can both stimulate or inhibit electrolyte
464 and fluid secretion, depending on the type of BA species and its abundance (reviewed in (161)).
465 Chronic exposure to physiological concentrations of BAs inhibits the actions of Ca²⁺ and cAMP-
466 dependent secretagogues, a process that likely involves BA receptors (204). FXR activation with
467 GW4064 inhibits the Ca²⁺ and cAMP-dependent secretory responses (304) restoring the osmotic
468 driving force for colonic fluid absorption. In addition, FXR stimulation attenuates diarrhea in a
469 mouse model of ovalbumin-induced diarrhea and cholera toxin (CTX)-induced intestinal fluid
470 accumulation (304). Since food is often absorbed together with water, this effect of BAs might
471 represent a physiological role whereby food-triggered colonic delivery of BAs simultaneously
472 stimulate water absorption. On the other hand, studies using colonic epithelial cell lines and
473 primary isolated colonic crypts showed that supraphysiological concentrations of BAs increase
474 intracellular Ca²⁺ levels, which in turn promote epithelial Cl⁻ secretion to drive intestinal fluid
475 secretion (89, 90), causing a water secretory diarrhea. Three forms of BA diarrhea (BAD) exist,
476 resulting from compromised ileal BA absorption associated with underlying bowel-related
477 pathologies (type I or secondary BAD) (286), from BA overproduction due to decreased FGF15/19

478 levels (type II or primary, idiopathic BAD) or following cholecystectomy or other gastroenterological
479 conditions (type III, miscellaneous) (206, 432). A prospective clinical study showed that FXR
480 activation with OCA improves the consistency of the stool and diarrhea symptoms both in primary
481 and in secondary BAD patients with short ileal resection (431). These data suggest that, in addition
482 to the well-established BA sequestrants, FXR could be a promising target for the development of
483 novel antidiarrheal therapeutics (reviewed in (206)).

484 Although acute exposure of natural and synthetic TGR5 agonists has been reported to reduce Cl⁻
485 secretion in rat colon (444), the role of TGR5 in coordinating intestinal fluid balance remains poorly
486 defined. Intriguingly, in the gallbladder, TGR5 rather stimulates Cl⁻ and bicarbonate excretion
487 through activation of CFTR (207). CFTR is mutated in cystic fibrosis, a disease characterized by
488 the production of abnormally viscous mucus in multiple organs, including the intestinal tract (144).
489 Further studies are warranted to decipher the regulatory role of TGR5 in intestinal mucus
490 formation.

491

492 B.4. Gut motility

493

494 BAs are well-established regulators of intestinal motility (112, 330, 388) and trigger differential
495 responses according to the region in the gastrointestinal tract. BAs typically inhibit gastric
496 emptying, slow down small intestinal transit to allow nutrient absorption by a process known as
497 'ileal brake', and finally stimulate colonic peristalsis and transit (17, 381). Consistent with these
498 findings, jejunal BA infusion in healthy subjects delays small intestinal transit (330). Although some
499 of these effects could be indirect by stimulating the release of regulatory peptides such as PYY or
500 GLP-1 from L cells (17, 419) (see section IV-B.1), emerging evidence indicates that BAs can
501 directly affect some of these processes through TGR5 activation (7, 205, 339). TGR5 is expressed
502 in gastric smooth muscle, and its activation by the natural TGR5 agonist, oleanolic acid (Table 2),
503 is proposed to cause gastric muscle relaxation via RhoA inhibition (350). In the colon, secondary
504 BAs trigger the release of 5-HT and CGRP from enterochromaffin cells and intrinsic primary
505 afferent neurons, respectively, thereby stimulating peristalsis (7). Consistently, *Tgr5*^{-/-} mice suffer
506 from a constipated phenotype and a reduction in the frequency of defecation (7). Physiologically,
507 these mechanisms fit with the notion that BAs act as a proxy of nutrient availability. While being
508 released during food intake, they act as signaling molecules to prime the different regions of the
509 intestinal tract for optimal digestion and excretion. Following food consumption, BAs favor nutrient
510 absorption by slowing down the small intestinal transit. Once accomplished, BAs in the distal part
511 will stimulate peristalsis to promote defecation. Consistently, pathological alterations in BA
512 metabolism are involved in the pathophysiology of constipation and diarrhea (reviewed in (19)).

513

514 C. BAs in metabolism and energy homeostasis

515

516 C.1. FXR as a regulator of lipid and nutrient metabolism

517

518 FXR plays a pivotal role in the regulation of intermediary metabolism by influencing the expression
519 of numerous genes involved in hepatic glucose, lipid, and amino acid metabolism (Figure 4). The
520 manifold studies summarized below underscore the importance of FXR as a molecular integrator
521 of the nutritional state, thereby coordinating the fate of many nutrients. However, they also unveil
522 the complexity of this regulatory framework as evidenced by the sometimes divergent results
523 obtained from different *Fxr*^{-/-} mouse models studied under specific metabolic conditions.

524

525 **Lipid homeostasis.** It has been known for a long time that treating gallstone patients with CDCA
526 decreases hepatic VLDL production and serum TGs (374), while treating hypercholesterolemic
527 patients with BA sequestrants increases circulating TGs (14). In mouse models of
528 hypertriglyceridemia, BAs reduce VLDL secretion, serum TGs and counteract hepatic steatosis
529 (448). These effects have been confirmed by subsequent studies where FXR agonists reduced
530 circulating TGs (81, 324, 478) and steatosis (324). This beneficial remodeling of lipid metabolism is
531 orchestrated by the FXR-SHP axis, which represses sterol regulatory binding protein-1c
532 (SREBP1c), a master regulator of hepatic *de novo* lipogenesis (448) and by FXR-dependent
533 interference of ChREBP binding to the liver pyruvate kinase (LPK) promoter (55) (Figure 4, left
534 upper quadrant). In the liver, induction of the FXR-SHP axis also blunts hepatocyte nuclear factor 4
535 alpha (HNF4 α), a master regulator of microsomal triglyceride transfer protein (MTP) and
536 apolipoprotein B (ApoB) expression, two proteins important for VLDL secretion (163). Of note, FXR
537 regulates several apolipoproteins known to impact lipoprotein lipase activity (72, 201) and reverse
538 cholesterol transport (73, 127, 479), further contributing to the beneficial remodeling of lipid
539 metabolism (extensively reviewed in (59)). As expected, whole-body *Fxr*^{-/-} mice display an increase
540 in circulating TGs (98, 142, 225, 236, 386) and cholesterol (98, 142, 225, 236, 251, 386) levels,
541 together with an accumulation of hepatic lipid deposits (98, 271, 295, 386), and enhanced levels of
542 lipogenic genes in the liver (98, 225, 271, 295, 373).

543 Despite the striking steatotic phenotype in whole-body *Fxr*^{-/-} mice (386), it is still not fully
544 established how FXR signaling keeps hepatic fat deposits in check. While a comparative study in
545 liver- and intestine-specific *Fxr*^{-/-} mice demonstrate that the liver is the principal site of BA-mediated
546 protection against lipid accumulation (373), others show that FGF15/19 is sufficient to blunt
547 SREBP-1c and hepatic lipogenesis (33, 295). Another report shows that intestinal FXR activation,
548 in contrast, promotes SREBP-1c levels and lipid accumulation in the liver through ceramide-
549 dependent mechanisms (193). Future studies will have to instruct which tissues play a
550 predominating role in controlling hepatic fat accumulation, with potential contributions from immune
551 cells deserving attention.

552

553 **Glucose homeostasis.** BAs are postprandial mediators of glucose homeostasis. Hepatic FXR
554 activation reinforces the actions of insulin by inducing SHP which results in the inhibition of the
555 gluconeogenic enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose 6-
556 phosphatase (G6Pase), in part through the repression of the nuclear receptors FOXO1 and HNF4α
557 (54, 271, 459, 477) (Figure 4, left lower quadrant). Similar effects are observed when diabetic mice
558 are subject to short-term treatment with the FXR agonist GW4064 (54). The intestinal FXR-
559 FGF15/19-FGFR4 pathway also largely contributes to the abrogation of hepatic glucose production
560 through an inter-organ signaling cascade that counteracts cAMP Response Element-Binding
561 protein (CREB), a critical regulator of gluconeogenesis (341). The same intestinal axis inhibits
562 GSK3 in the liver to sustain hepatic glycogen synthesis after the decline of insulin signaling (221).
563 In a cell-autonomous fashion, hepatic FXR activation decreases the transcription of LPK resulting
564 in a shunt of glucose metabolites from glycolysis towards glycogen synthesis underscoring, once
565 again, the complementary actions of hepatic and intestinal FXR activation (98). In line with these
566 discoveries, the majority of studies reported that lean *Fxr*^{-/-} mice suffer from reduced hepatic
567 glycogen storage and reduced insulin sensitivity (53, 98). FXR also modulates glucose
568 homeostasis directly in the pancreas where its activation induces glucose-stimulated insulin
569 secretion in isolated pancreatic β-cells, an effect that is lost in islets from *Fxr*^{-/-} mice (96, 340, 378).
570 Contrary to physiological BA signaling, chronic pharmacological activation of FXR with OCA
571 enhances glucocorticoid-induced gluconeogenesis during fasting (356).

572

573 **Amino acid homeostasis.** Sustained activation of FXR by OCA (Table 2) triggers the expression
574 of amino acid catabolism and ammonium detoxification genes (281, 355). Conversely, the
575 expression of the urea cycle rate-limiting enzyme carbamoyl phosphate synthetase I (CPS1) and
576 other amino acid catabolizing enzymes is reduced in *Fxr*^{-/-} mice (281, 355) (Figure 4, right lower
577 quadrant). In addition, FXR activation in the intestine promotes *de novo* protein synthesis in the
578 liver (221). Similar to its effect on glycogen synthesis, this process is mediated by the gut-liver
579 FXR-FGF19-FGFR4 axis that triggers activation of the hepatic RAS/ERK signaling cascade and
580 phosphorylation of the eukaryotic translation initiation factor 4B and 4E (eIF4B and eIF4E) (221).
581 These proteins are components of the eIF4F complex whose phosphorylation promotes the
582 initiation of translation (131). Binding of FGF19 to FGFR4 also promotes phosphorylation of
583 ribosomal protein S6 (rpS6) which improves the efficiency of global protein synthesis by inducing
584 cap-dependent translation (221).

585

586 C.2. BAs and the metabolic syndrome

587

588 Obesity is tightly associated with the development of insulin resistance and non-alcoholic liver
589 disease (NAFLD). BAs and their receptors play a central role in the etiology of these obesity-

related conditions. Despite the existence of discrepancies among studies, the use of diverse modulators of FXR and TGR5 signaling has significantly increased our knowledge of how BA signaling intersects with multiple pathways known to promote metabolic disease. As a result, novel promising therapies are emerging that target FXR or TGR5 signaling. Especially in the context of non-alcoholic steatohepatitis (NASH), an advanced form of NAFLD, significant progress is made (described in detail in section V-C). We provide here below an overview of the most significant pre-clinical studies in various mouse models of metabolic diseases. The link between BA signaling and cardiovascular disease, another condition of the metabolic syndrome, is described in section IV.D.

598

599 **FXR in obesity and insulin resistance.** While there is a fairly general consensus on the
600 phenotype of chow-fed lean *Fxr^{-/-}* animals, diverging findings are reported on the role of FXR
601 during obesity. As an example, several groups reported that FXR disruption in obese mice
602 attenuates body weight gain (345, 365, 476) and improves insulin sensitivity (345, 372, 476),
603 however, the same disruption in lean mice worsens glucose tolerance (54, 271, 477). Gut-
604 restricted inhibition of FXR activity with synthetic Gly-MCA (194), or natural tauro- β MCA (T β MCA)
605 (250, 455) (Table 2), or alternatively by genetic disruption of intestinal FXR (193), protects from
606 obesity and diet-induced glucose intolerance (194, 250, 455). Mechanistically, the beneficial
607 effects of intestinal FXR antagonism were attributed to reduced ileal ceramide production that
608 attenuates hepatic gluconeogenesis (455). Recent studies concluded that disruption of the
609 FXR/SHP signaling axis in the liver also improves glucose and fatty acid metabolism when fed a
610 HFD (2, 220). The exacerbation of obesity and insulin resistance in the setting of HFD feeding is
611 consistent with FXR's role as a postprandial anabolic regulator of nutrient metabolism.

612 The effects of FXR activation by various synthetic agonists (Table 2) also led to discordant results
613 in the setting of obesity. Long-term oral supplementation of GW4064 to obese and insulin-resistant
614 mice exacerbated weight gain, dyslipidemia, and glucose intolerance (446), effects that can be
615 attributed to the lower BA pool size following FXR activation. Conversely, FXR activation with the
616 FXR/TGR5 dual agonist INT-767 induces a TGR5-dependent increase in GLP-1 secretion, leading
617 to improved glucose and lipid homeostasis in diet-induced obese (DIO) mice (324). Of interest, a
618 deuterated analog the intestine-specific agonist fexaramine (93), FexD, attenuated DIO and insulin
619 resistance by increasing the thermogenic response in brown (BAT) and white (WAT) adipose fat
620 and blunting gluconeogenesis (104). The same agonist also improved alcoholic liver disease
621 through stimulation of the FXR/FGF15 axis (159), although others showed the existence of a
622 cross-talk with TGR5 as a consequence of enhanced production of TLCA (325). Of interest,
623 systemic administration of FGF19 to obese and diabetic mice induced an anti-diabetic effect (120).
624 This could be in part coordinated by the CNS since activation of central FGF19 signaling reduces
625 food intake (277, 364), body weight (238, 277, 364), and improves glucose homeostasis (238, 277,
626 300, 364) in rodent models of obesity. Consistent with these findings, a human clinical trial (Table

627 3) demonstrated that treatment with OCA (25 and 50 mg/day) increased insulin sensitivity by
628 almost 25% in a cohort of patients with NAFLD and type 2 diabetes (T2D) (305).

629

630 **TGR5 in obesity and insulin resistance.** The role of TGR5 in enhancing lipid catabolism has
631 been extensively studied in the setting of DIO. The first indication for such a role came from the
632 observation that chronic supplementation of CA protects mice against DIO and insulin resistance
633 by enhancing local thyroid signaling and mitochondrial activation in BAT and muscle (447) (Figure
634 8). This was further corroborated by the finding that dietary supplementation of HFD with INT-777
635 improves glycemic control, reduces liver steatosis, protects against weight gain (410) and induces
636 beiging of the subcutaneous WAT (427). The beiging phenotype was associated with enhanced
637 mitochondrial biogenesis and function, along with marked lipolysis and fatty acid oxidation in
638 response to environmental cues such as cold exposure or high caloric intake (427) (Figure 8).
639 Similarly, TGR5 activation with the specific agonist BAR501 (Table 2) prevented DIO and
640 increased the expression of thermogenic genes in BAT and WAT (51). In humans, CDCA oral
641 supplementation increased energy expenditure and BAT activity (45). *In vitro* assays showed that
642 CDCA induces mitochondrial uncoupling through TGR5 in brown adipocytes isolated from healthy
643 women (45), confirming the results obtained in mice. However, genetics plays an important role in
644 regulating the BA-dependent thermogenic effect, as demonstrated by the resistance of
645 129S6/SvEvTac mice to the beneficial effects of CA on body weight loss (117).

646 In addition to stimulating energy expenditure, which indirectly restores insulin resistance, TGR5
647 also directly regulates glucose homeostasis through its impact on enteroendocrine and immune
648 cells of the myeloid lineage (described in sections IV-B.1 and IV-D.2, respectively). Administration
649 of TGR5 agonists (410) or intestine-selective activators (108, 242) increases circulating GLP-1
650 levels and improves glucose tolerance in obese and insulin-resistant mice. Conversely, nutrient-
651 dependent GLP-1 secretion and glucose homeostasis are impaired in whole-body *Tgr5*^{-/-} mice
652 (410). BA sequestrants furthermore improve glucose homeostasis through TGR5-dependent GLP-
653 1 release (155, 342). Treatment with the BA sequestrant, colestipimide, reduces body weight gain
654 and increases insulin sensitivity in DIO mice, possibly via TGR5 (449). More recently, it was
655 demonstrated that TGR5 contributes to exercise-induced improvement of muscle function (367)
656 and ameliorates glucose homeostasis by increasing insulin responsiveness in skeletal muscle
657 (178).

658

659 **FXR and TGR5 in NAFLD.** NAFLD is a common disease affecting more than 70% of the obese
660 and diabetic population worldwide. It includes a spectrum of liver conditions ranging from simple
661 steatosis to more advanced NASH, which in the later stages can culminate into endstage liver
662 fibrosis and cancer. Although its etiology is complex and not fully elucidated, accumulating
663 evidence indicates that BA levels and signaling are profoundly disrupted in NAFLD (15, 65, 195,
664 347). FXR is a master regulator of hepatic lipid homeostasis (section IV-C.1) and disruption of

whole-body FXR signaling is associated with enhanced NAFLD susceptibility. Consistent with these findings, hepatic lipid accumulation is inversely correlated with FXR expression in NAFLD mouse models or patients (267, 461) and *Fxr*^{-/-} mice show marked steatosis (386), hepatic inflammation and spontaneous progression to NASH and hepatocellular carcinoma (HCC) (84, 460). Conversely, FXR activation by CA (448), OCA (71), GW4064 (477)), WAY-362450 (262, 474) or the intestine-restricted FXR agonist fexaramine (104) (Table 2), significantly dampens fat accumulation in the liver and protects against the development of NAFLD, and other hepatobiliary diseases as described in section V-C. Of note, blockage of FXR signaling by genetic disruption of the receptor in the intestine (193), or by administration of the FXR antagonist Gly-MCA (194), also protects against steatosis. These paradoxical results may be explained by the fact that some FXR agonists, such as fexaramine, also impact on TGR5 signaling outside of the enterohepatic axis (104). Indeed some of the effects of fexaramine, especially those related to browning, were blunted in *Tgr5*^{-/-} mice suggesting an indirect, yet secondary BA-dependent, activation of this receptor by fexaramine (104, 325). These results would be in line with the known role of TGR5 activation in browning (427). Alternatively, the inhibition of intestinal FXR by Gly-MCA could also impact on the gut microbiome composition and thereof on global metabolic health. Indeed, FXR antagonism in the intestine results in a stimulation of BA synthesis that protects against obesity and insulin resistance (321). This would be in line with the established association between gut dysbiosis and NAFLD (38, 136).

Similar to FXR, TGR5 activation by INT-777 or BAR501 blunts hepatic lipid accumulation in mouse models of obesity (52, 83, 410). As expected, combined pharmacological activation of TGR5 and FXR with the dual agonist INT-767 reverses the progression of several hallmarks of NAFLD and NASH (74, 176, 189, 285, 324). Of interest, TGR5/FXR dual agonism shows increased efficacy than OCA in reducing hepatic steatosis and liver damage in mouse NASH models (362).

689

690 D. BAs in immune homeostasis

691

Based on their detergent properties and capacity to disrupt cellular membranes, BAs were initially categorized as pro-inflammatory agents. This was furthermore supported by the knowledge that BA accumulation caused by bile duct obstruction or liver disease leads to hepatic inflammation (270, 412) and that systemic accumulation of BAs can damage extrahepatic tissues, particularly the kidney (107). Conversely, BAs can also elicit potent anti-inflammatory responses, as first demonstrated in patients with jaundice and elevated levels of circulating BAs, who experienced significant alleviation of rheumatic symptoms (162). Furthermore, recent evidence suggests that activation of BA receptors exerts anti-inflammatory effects in multiple inflammatory diseases, including experimental autoimmune encephalomyelitis (167, 249), atherosclerosis (143, 152, 158, 296, 297, 337, 478) and hepatic inflammation (105, 217, 285, 441, 442, 462, 474).

702

703 D.1. Immuno-regulatory properties of FXR
704
705 Compared to its abundant expression in enterocytes and hepatocytes, FXR is only discretely
706 expressed in immune cells (375). Nonetheless, anti-inflammatory responses have been reported in
707 peripheral blood mononuclear cells (PBMCs), in mouse and human myeloid cells, in dendritic cells
708 (DCs), and in hepatic natural killer T cells after exposure to FXR agonists (50, 288, 426, 462).
709 Based on these findings, several studies have been conducted to elucidate its role in modulating
710 diseases that are triggered by a disturbed immune balance. Despite these efforts, it is not yet
711 established whether the anti-inflammatory actions of FXR arise from its cell-autonomous actions
712 on immune cell modulation or rather indirectly from its potent BA and lipid lowering effect, the latter
713 being essential in protecting the tissues from lipid-induced toxicity.
714
715 **Liver disease and NASH.** The first tangible indications of an anti-inflammatory role of FXR and its
716 signaling in the liver were derived from *in vivo* studies. *Fxr*^{-/-} mice exhibit a higher incidence of
717 hepatic carcinogenesis (219, 460), and suffer from exacerbated hepatic inflammation and necrosis
718 in a model of autoimmune hepatitis (289), or after LPS-induced inflammation (441, 462). To what
719 extent these phenotypes result from an excessive accumulation of BAs or hepatic lipid deposits is
720 not fully established. Mechanistic studies proposed that the hepatic inflammatory phenotype is
721 triggered by a de-repression of NF-κB, a master transcriptional regulator of pro-inflammatory
722 cytokines (441). FXR is also tightly connected with inflammation and cholestasis. Activation by
723 GW4064 ameliorates cholestatic liver damage in rats (263), and ischemia/reperfusion-induced
724 hepatic damage by upregulating SHP in Kupffer cells (196). BAs and FXR furthermore modulate
725 sepsis via control of the NLRP3 inflammasome, which could be relevant for cholestasis-associated
726 sepsis. Cholestasis is a common complication in patients with sepsis and significantly increases
727 mortality rate (401). In this pathological context, BAs have been proposed to act as a new class of
728 danger-associated molecular pathways (DAMPs), triggering a hyperinflammatory response via
729 activation of both signal-1 and -2 of the NLRP inflammasome (153). Remarkably, FXR would act
730 as a negative regulator of the NLRP3 inflammasome via direct physical interaction with NLRP3
731 and caspase 1, hence preventing its assembly in the mitochondria of activated macrophages
732 (153). Additionally, FXR could also inhibit the inflammasome indirectly by reducing endoplasmic
733 reticulum (ER) stress in hepatocytes (150). Of note, engineered FGF19 analog treatment also
734 blunts hepatic inflammation, along with a significant amelioration of cholangiopathies and NASH in
735 mouse models (481, 482). The protective role of FXR/FGF19 signaling in different immune-related
736 liver diseases, including NASH, PBC and PSC, has been confirmed in patients, as described in
737 section V-C.
738
739 **Intestinal inflammation.** Several mouse models of colitis, including dextran sulfate sodium (DSS)-
740 and 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis demonstrated that functional

disruption of FXR increases, whereas small molecule FXR agonist treatment suppresses, mucosal inflammation (124, 280). Similar phenotypes were found in two independent models of intestinal hyperpermeability and inflammation, i.e. cholestatic liver injury (428), and ischemia-reperfusion injury (56). Mechanistically, colons from mice with DSS-induced colitis treated with OCA displayed reduced pro-inflammatory cytokine (mainly IL-1 β , IL-6) and chemokine (CCL2) expression (124). OCA also repressed TLR4-induced pro-inflammatory gene expression in intestinal epithelial cells (IECs) (426) and attenuated inflammatory cytokine and chemokine expression in cultured human CD14+ monocytes and DCs (124). Thus, FXR appears to limit mucosal inflammatory responses by acting on both IECs and innate immune cells. Of note, intestinal FXR expression was decreased in patients with colitis and its activation reduced disease severity (308, 313, 426). More recently, the bacteria-derived secondary BA, 3 β -hydroxydeoxycholic acid (isoDCA), was shown to further refine the immunological balance of the colon by limiting FXR activity in DCs to allow the differentiation of pTreg cells (50). This highlights the complex interplay between BAs, the gut microbiome, and FXR, a topic discussed in detail in section IV-F.3.

755

Cardiovascular disease. The role of FXR in atherosclerosis is still under debate. An increase in the atherosclerotic lesion area and an altered plasma lipid profile was observed in a *Fxr*^{-/-} *ApoE*^{-/-} double knockout (DKO) mouse model fed a HF/HC diet (152). Conversely, two other studies showed reduced atherogenic lesion size after FXR disruption in mice on a *Ldlr*^{-/-} or *ApoE*^{-/-} background, together with unexplained differences in plasma lipids (143, 478). Studies using FXR agonists, however, observe protection against lesion formation in *ApoE*^{-/-} or *Ldlr*^{-/-} atherosclerosis prone mice (158, 288). FXR signaling is also functional in vascular smooth muscle cells (VSMCs) (35) and its stimulation blunts the inflammatory response and reduces cell migration. Mechanistically, FXR induces SHP and inhibits the expression of both cyclooxygenase-2 and inducible nitric oxide synthase (256).

766

767 D.2. Immuno-regulatory properties of TGR5

768

TGR5 is highly expressed in cells of the myeloid lineage (203), and is considered a negative modulator of inflammation (reviewed in (334) and Figure 8). In addition to its cross-talk with master regulators of inflammation, such as NF- κ B and C/EBP β (discussed below), indications exist that the BA-TGR5 axis shift macrophages towards a more regulatory and anti-inflammatory phenotype (34, 171, 285, 333, 433). The anti-inflammatory role of TGR5 signaling in monocytes and macrophages profoundly modulates the physiology of metabolic tissues, such as liver, adipose tissue, and vasculature, and consequently influences the development of NASH, T2D and atherosclerosis.

777

778 **Liver disease and NASH.** Stimulation of TGR5 in myeloid cells exerts potent immunosuppressive
779 actions and dampens NF- κ B-mediated cytokine expression in mouse models of LPS-induced
780 hepatic inflammation (442). Furthermore, dual activation of FXR and TGR5 by INT-767 improved
781 NAFLD and increased the number of intrahepatic anti-inflammatory monocytes, suggesting that
782 both receptors act hand in hand to reduce liver inflammation (285). More recently, it was
783 demonstrated that TGR5 agonism by itself can rescue the hepatic and vascular damage caused by
784 exposure to a high fat-high fructose diet (52). TGR5-dependent suppression of cytokine production
785 in Kupffer cells is furthermore potentiated following bile duct ligation in rats, indicating a protective
786 role of TGR5 in cholestasis-induced liver injury (208).

787

788 **Intestinal inflammation.** TGR5 activation by natural BAs or INT-777 suppresses LPS-induced
789 inflammatory cytokine expression, whereas these responses are elevated and unresponsive to
790 BAs in macrophages lacking TGR5 (70, 464). In mouse models of TNBS- or DSS-induced colitis,
791 TGR5 activation attenuates the symptoms of inflammatory bowel disease (IBD), whereas
792 functional disruption of TGR5 impairs intestinal barrier and exacerbates the inflammatory response
793 (70, 126). In addition, activation of TGR5 by BAR501 was shown to switch mucosa-associated
794 macrophage phenotypes from M1 (pro-inflammatory) to M2 (tissue-protective) during chemically
795 induced colitis (34). In this setting, TGR5 activation reduced the
796 expression of proinflammatory cytokines (TNF α , IL-1 β , IL-6, and IFN- γ) and increased the
797 expression of anti-inflammatory cytokines (TGF- β and IL-10) (34). Induction of IL-10 in
798 macrophages allowed the recruitment of Treg cells to inflamed colonic tissue (34). These TGR5-
799 mediated anti-inflammatory pathways not only acutely suppress innate immune responses, but
800 also guide the downstream priming of inflammatory T cell responses. In particular, activation of
801 TGR5 by BAs directs the differentiation of monocytes toward tolerogenic DCs that secrete low
802 levels of TNF α and IL-12, cytokines required for the priming of pro-inflammatory Th1 responses
803 (182). In addition, *ex vivo* treatment of mucosa-associated macrophages isolated from Crohn's
804 disease patient biopsies reduced inflammatory cytokine expression, including TNF α (464),
805 suggesting that disturbed BA circulation and/or metabolism during chronic intestinal inflammation
806 may limit endogenous TGR5 activation.

807

808 **Cardiovascular and metabolic disease.** The role of TGR5 as an anti-inflammatory mediator has
809 also been studied in the context of atherosclerosis. *In vivo* experiments showed that INT-777
810 supplementation blunts the development of atherosclerosis in *Ldlr* $^{-/-}$ mice fed a HC diet. This anti-
811 atherogenic effect is driven by cAMP induction, followed by repression of NF- κ B-activation and
812 cytokine production in macrophage resident plaques (337). Similar results were observed in *ApoE* $^{-/-}$
813 and *Ldlr* $^{-/-}$ treated with the dual FXR/TGR5 agonist INT-767 (297), an effect that was lost in the
814 triple *Ldlr* $^{-/-}$, *Fxr* $^{-/-}$ and *Tgr5* $^{-/-}$ mice (296). In other metabolic tissues, additional mechanisms
815 contribute to the TGR5-mediated anti-inflammatory effects. For instance, insulin resistance is

816 exacerbated by increased inflammation, especially in white fat depots. TGR5 activation of adipose
817 tissue macrophages reduces LPS-induced chemokine expression and protects DIO animals from
818 adipose tissue-associated insulin resistance (333) (Figure 8). Specifically, INT-777 treatment of
819 macrophages activates mTOR complex 1 (mTORC1) which induces the differential translation of
820 the liver-enriched inhibitory protein (LIP) to reduce cytokine transcription and macrophage
821 migration (333). In line with these observations, a recent study demonstrated that activation of the
822 TGR5-cAMP-PKA pathway in innate macrophages induces phosphorylation and degradation of the
823 NLRP3 inflammasome, resulting in an improvement of insulin sensitivity and glucose tolerance
824 (141).

825

826 **Antiviral response and senescence.** In addition to its role in macrophages, TGR5 has been
827 suggested to control antiviral innate immunity through the activation of an AKT/IRF3 (457) and the
828 β-arrestin-SRC signaling axis (175). Furthermore, TGR5 modulates cytokine levels in the context
829 of cell proliferation and senescence, as INT-777 prevents IL-1 β induction of cell senescence in
830 human chondrocytes (177), indicating that the anti-inflammatory effect of TGR5 signaling is wide-
831 spread.

832

833 E. BAs in tissue plasticity and remodeling

834

835 Tissue plasticity and regeneration are dynamic processes that involve multiple signaling pathways.
836 Several lines of evidence suggest that BAs are implicated in liver regeneration through modulation
837 of FXR and TGR5 signaling. In addition, BA signaling contributes to cellular reprogramming, a
838 process with great potential for the treatment of hematopoietic, immune and metabolic diseases.

839

840 E.1. BAs in liver regeneration

841

842 The liver is one of the few organs that can robustly regenerate itself in response to partial ablation
843 or injury. BAs, together with cytokines and growth factors, activate specific signaling pathways and
844 gene expression programs essential for hepatic regeneration. Several studies demonstrated an
845 inhibition of liver regeneration following interruption of the normal enterohepatic biliary circulation
846 (314, 418). BAs were also found to directly stimulate hepatocyte proliferation (24) and a study
847 based on a 70% partial hepatectomy (PHx) mouse model demonstrated that low doses of BAs
848 promote liver regeneration (179) (Figure 9). Conversely, reduction of total BA levels with BA
849 sequestrants delayed liver regeneration (179). FXR and TGR5 display distinct roles in this complex
850 adaptive process.

851

852 **Hepatocyte FXR and liver regeneration.** FXR was initially described as the master regulator of
853 BA-mediated homeotropic liver growth during hepatic regeneration (179). Enhanced activity of

both intestinal and hepatic FXR contributes to this process (Figure 9). The first physiological change during PHx is the redistribution of portal and arterial blood supply to the remnant liver in place of the entire organ. As a result, hepatocytes become exposed to a ~3-fold greater amount of regenerative factors, including BAs that are mainly supplied by the portal vein (292). This leads to a robust activation of hepatic FXR that induces the expression of the forkhead box M1b (FOXM1B), a key transcription factor controlling hepatocyte DNA replication during liver regeneration (60, 179). FXR post-translational modifications can also impact on hepatocyte regeneration as illustrated by SIRT1-mediated deacetylation of FXR that inhibits its activity and impairs hepatocyte proliferation after PHx (125). In addition to directly stimulating hepatocyte proliferation, FXR activation promotes the active efflux of BA from hepatocytes through the transcriptional upregulation of dedicated transporters (described in section IV-A.1) (12). BA efflux from the remnant liver is further reinforced by coordinated activation of TGR5 in cholangiocytes (327) (see section below). This harmonized mechanism helps to protect the remnant liver from apoptosis triggered by the cytotoxic effects of BA overload (327, 443) and leads to an acute, but temporary, increase in BA levels in the intestine and systemic circulation (310). In turn, BAs activate intestinal FXR that stimulates FGF15 secretion whose signaling is also implicated in liver regeneration. Mechanistically, the FGF15/FGFR4 axis reinforces the effects of hepatic FXR activation by upregulating FOXM1B and its downstream mitogenic target genes (*Cdc25b*, *Ccnd1*, and *Pcna*) (420). In addition, FGF15 helps to protect hepatocytes against apoptosis triggered by high levels of BAs by suppressing *Cyp7a1* transcription and thus, *de novo* BA synthesis (473). Consequently, *Fgf15^{-/-}* mice were found to suffer from severe liver injury and exacerbated mortality after PHx. This effect is attenuated upon treatment with the BA sequestrant, cholestyramine, or after adenoviral delivery of FGF15 (420). Kong et al. (224) observed similar effects in *Fgf15^{-/-}* mice and identified additional mitogenic pathways controlled by this growth factor. *Fgf15^{-/-}* mice exhibited reduced activation of the JNK and p38 pathways confirming earlier reports on FGF15-induced MAPK signaling (226). The mutant mice also suffered from reduced activation of the JAK/STAT pathway (226), a pathway known to be activated during liver regeneration (76, 255). Mechanistically, the mitogenic effects of STAT3 appear to be mediated by FOXM1B (287, 317) suggesting that both cell-autonomous (FXR-mediated) and non-cell autonomous (FGF15-mediated) effects of BAs on proliferation converge on this transcription factor. Interestingly, selective activation of intestinal FXR or treatment with FGF19 also reduces inflammation and liver necrosis after obstructive cholestasis induced by bile duct ligation (299). In addition to their role in pathological settings, BAs have been reported to mediate FXR-dependent hepatocyte proliferation under physiological conditions. For instance, during pregnancy, FXR is important for fetal liver growth and its loss of function reduces fetal liver enlargement (294).

Cholangiocyte TGR5 and liver regeneration. While the role of FXR in liver regeneration has been extensively studied, less is known about TGR5 in this process. Nonetheless, TGR5 is an

important player involved in cholangiocyte proliferation while simultaneously protecting the liver against BA overload. A study demonstrated that PHx was followed by cholestasis and hepatocyte necrosis and markedly delayed liver regeneration in *Tgr5*^{-/-} mice (327). At the molecular level, the mechanisms through which TGR5 protects the remnant liver from BA cytotoxicity are different and complementary from those of FXR. The origin of this difference lays in the divergent patterns of expression of these two receptors with FXR being highly expressed in hepatocytes, while TGR5 is especially enriched in the gallbladder and biliary tract (207) where it contributes to adapt bile composition in ions after PHx. Indeed, in cholangiocytes TGR5 controls CFTR-dependent Cl⁻ secretion (207) and the observed TGR5-dependent increase in biliary HCO₃⁻ and Cl⁻ output after PHx likely constitutes an adaptive mechanism to enhance bile secretion, fluidity, and consequently protect the overloaded remnant liver from BA toxicity (327) (also discussed in III-A.2). In line with the idea that TGR5 contributes to increase bile turnover during liver regeneration is the observation that TGR5 facilitates BA elimination in the urine, protecting the entire organism from BA overload (327). Another mechanism through which TGR5 protects the liver from BA toxicity during regeneration is through its control of BA hydrophobicity. Several studies demonstrated that *Tgr5*^{-/-} mice exhibit a more hydrophobic BA composition (92, 254, 327), which exacerbate hepatocyte injury immediately after PHx. Accordingly, liver injury in *Tgr5*^{-/-} hepatectomized mice can be rescued by BA resins (327). Consistently, an enlargement of a hydrophobic BA pool was also associated with an inhibition of liver regeneration in a model of PHx (125).

BA feeding is also known to induce cholangiocyte proliferation (8), an effect later on attributed to their potential to activate TGR5 (353) (Figure 9). Mechanistically, conjugated LCA and TGR5-selective agonists were shown to induce cholangiocyte proliferation through elevation of reactive oxygen species (ROS) and SRC-mediated EGFR transactivation. Subsequent MAPK phosphorylation induced proliferation in *Tgr5*^{+/+}, but not *Tgr5*^{-/-} derived cells (353). Similar interactions between BA signaling and transactivation of the EGFR have been reported to control the proliferation of other cell types (258, 309, 391, 450) suggesting that it may represent a universal and novel mitogenic branch of BA signaling.

919

920 E.2. BAs in differentiation and cellular reprogramming

921

922 **FXR in stromal cell differentiation.** Mesenchymal stromal cells give rise to osteoblasts and adipocytes. FXR activation regulates this process by promoting both osteoblast (67, 183) and adipocyte differentiation (1). The pro-adipogenic phenotype was attributed to a synergism with the master regulator of adipogenesis PPAR γ and to the suppression of the Wnt/ β -catenin signaling pathway (1). Surprisingly, the FXR antagonist, guggulsterone (421), impairs osteoblast differentiation but induces the expression of adipogenic markers, suggesting a role for FXR in the regulation of the osteoblast/adipocyte balance (183). Altogether these studies show that FXR disruption significantly impacts diverse aspects of bone homeostasis and adipogenesis. A recent

930 study demonstrates that overexpression of FXR in WAT alters its architecture underscoring the
931 need for a tight regulation of FXR expression/activity in white fat (423).

932

933 **TGR5 in adipocyte reprogramming.** The white-to-brown conversion of adipose tissue, a
934 phenomenon referred to as beiging, is a dynamic process involving the genetic rewiring towards a
935 mitochondrial phenotype. Beiging is triggered by chronic cold exposure and β -adrenergic
936 stimulation, and multiple cell types, including adipocyte precursors, immune cells and mature
937 adipocytes, participate in this process (69). TGR5 is required for the emergence of beige
938 adipocytes within WAT upon cold exposure (427) (Figure 8). Pharmacological stimulation of TGR5
939 induced beige remodeling during HFD feeding (51, 427), independently of adrenergic stimulation
940 (427). Mechanistically, TGR5 activation leads to lipolysis, mitochondrial fission and mitochondrial
941 biogenesis over time (427). These results highlight a critical role of the TGR5 signaling axis in
942 mitochondria dynamics that could underlie a general feature linked to cell differentiation and/or
943 reprogramming.

944

945 E.3. BAs as components of the intestinal stem cell niche

946

947 Epithelial cells of the intestine undergo rapid renewal to counteract intestinal damage and
948 disruption of the barrier function (128). Renewal and patterning of the intestinal epithelium are
949 carried by intestinal stem cells (ISCs) that reside at the bottom of intestinal crypts (128). These
950 crypts define an ISC niche that regulates the balance between self-renewal and cell fate
951 specification (128). Recent studies demonstrated that BAs constitute an intrinsic regulatory
952 component of the ISC niche capable of regulating both the renewal and the specification of ISCs
953 (268, 396). In particular, BAs were shown to foster epithelial regeneration under both physiological
954 and colitis-induced conditions by activating TGR5 in the ISC compartment through a mechanism
955 involving yes-associated protein 1 (YAP) and its upstream regulator SRC. Importantly,
956 endogenous BA release in the intestinal lumen was found to be sufficient to coordinate ICS
957 renewal and proliferation (396). These findings suggest that the physiological cycles of food intake
958 followed by discharge of BAs in the intestinal lumen represent an intrinsic stimulus that dictates
959 ISC proliferation rhythms to sustain daily regeneration (396). BAs also seem to play a role in the
960 patterning of the intestinal epithelium as another study reported that the BAs/TGR5 axis regulates
961 L-cell differentiation and abundance in the intestinal epithelium (268). *In vivo*, TGR5 activation
962 elevated GLP-1 secretory capacity and improved glucose tolerance (268). While BAs appear to be
963 an integral component of the ISC niche, their levels and chemical structure must be kept in check
964 as both quantitative and qualitative changes in the BA pool can initiate and drive the proliferation of
965 cancer ISCs (121). Indeed, BA species known to antagonize FXR (mainly T β MCA and DCA) were
966 shown to induce proliferation and DNA damage in *Lgr5*⁺ cancer stem cells (121). Therapeutically,
967 FexD, a gut-biased FXR agonist, delayed tumor progression and profoundly increased survival in

968 APC^{min/+} mouse models of adenoma and adenocarcinoma (121), suggesting that restoring a
969 healthy BA balance might represent a therapeutic approach to treat colorectal cancer.

970

971 F. BAs, gut microbiota, and host metabolism

972

973 The gut is home to one of the most complex eco-systems known, the gut microbiome, which
974 impacts on nearly every aspect of physiology (reviewed in (376)). How the host and the
975 microbiome communicate with one another is an intense area of research. Because the BA pool is
976 generated by the host and actively modulated by intestinal bacteria, these molecules are key in
977 mediating this symbiotic communication (Figure 6). Furthermore, BAs actively shape the
978 microbiome at the highest taxonomic levels. This interlinked dependence turns the BA-microbiome
979 axis into a chief determinant of health and disease.

980

981 F.1. The gut microbiome shapes the BA pool

982

983 Microbial conversion of primary into secondary BAs increases BA diversity and promotes
984 hydrophobicity of the BA pool (430). Several studies using germ-free (GF) or antibiotic-treated
985 rodents revealed both a quantitative and a qualitative modification of the BA pool, characterized by
986 an overall enlargement of the BA pool size and an increased ratio of primary conjugated to
987 secondary BAs (213, 370, 377, 406). In the host, TGR5 signaling is particularly affected by the
988 microbiome as the secondary BAs, LCA and DCA, and their conjugated forms are potent TGR5
989 activators. In fact, microbial transformation of primary to secondary BAs represents the most direct
990 link between BA 7 α -dehydroxylating gut bacteria and host health. This is exemplified in humans,
991 who unlike rodents, cannot reconvert secondary BAs into primary ones by hepatic 7 α -
992 hydroxylation (357). Therefore, dietary or pharmacological interventions (e.g. antibiotics) that
993 modulate the proportion of intestinal bacteria with 7 α -dehydroxylation activity alter the availability
994 of endogenous TGR5 ligands (123). In fact, dietary modification including changes in protein (445)
995 or fat (88, 197) source, can modulate the gut microbiota composition and consequently the
996 intestinal BA pool. In turn, major changes in the BA pool, such as those triggered by antibiotics,
997 can influence whole-body energy and glucose homeostasis (Figure 6) (470). Other environmental
998 cues, including cold exposure (64, 452, 485) induce similar phenotypes (Figure 6). In line with
999 these findings, a recent study demonstrated that broad-spectrum antibiotics given to healthy adults
1000 prior and subsequent to seasonal influenza vaccination significantly impaired H1N1-specific
1001 neutralization (146). This was accompanied by a 1,000-fold reduction in serum secondary BAs,
1002 which was highly correlated with AP-1/NR4A signaling and inflammasome activation suggesting an
1003 involvement of TGR5 signaling in systemic immune homeostasis as described in section IV-D.2
1004 (146).

1005 The microbiome also directly affects quantitative aspects of the BA pool size which is nearly
1006 doubled in GF mice (370). The mechanisms explaining this effect are only starting to be
1007 understood and involve the gut microbiome-mediated shift of BA composition from FXR
1008 antagonists to agonists. For instance, the absence of microbiota resulted in the accumulation of
1009 BAs with FXR antagonizing properties, such as T β MCA, which were identified as the main
1010 endogenous FXR antagonists that could not be metabolized in the absence of intestinal bacteria
1011 (370). Consistent with the obesogenic phenotype of mice after long-term FXR agonist treatment
1012 (446), accumulation of T β MCA enhanced BA synthesis and recycling (370), which in turn
1013 contributed to the resistance against DIO observed in GF *Fxr*^{-/-} mice (321). Similarly, administration
1014 of glycine- β -MCA (Gly-MCA), a β -MCA analog resistant to bacterial deconjugation, improves
1015 metabolic homeostasis by inhibiting FXR specifically in the intestine (194). Of note, novel gut
1016 microbiome-produced secondary BAs have recently been discovered that would act as FXR
1017 agonists (348). In addition to the well-studied BA deconjugating activity, gut bacteria of the
1018 *Clostridium* species were shown to conjugate cholate with phenylalanine, tyrosine and leucine
1019 through a yet unknown enzymatic reaction (348). These novel BA conjugates are absent upon
1020 antibiotic treatment and seem to be increased in HFD-fed mice and IBD patients (348), indicating a
1021 potential role of these metabolites in metabolic and inflammatory disorders.

1022 Antioxidants and drugs can similarly impact on the BA pool because of their effects on BA
1023 metabolizing members of the microbiome. For instance, remodeling of the gut microbiota with the
1024 antioxidant tempol increases T β MCA levels, resulting in an inhibition of intestinal FXR signaling
1025 and a decrease in obesity (250). Probiotic supplementation can also positively or negatively
1026 modulate BA synthesis in the liver. Treating mice with the VSL#3 probiotic formulation increased
1027 BA deconjugation and fecal excretion along with an induction of hepatic BA synthesis (85).
1028 Conversely, *Lactobacillus rhamnosus* GG supplementation reduced hepatic BA levels by
1029 promoting the synthesis of FXR antagonists which prevented excessive BA-induced liver injury and
1030 fibrosis in mice (264). Finally, it should be noted that the glucose-lowering effects of metformin are,
1031 in part, mediated by the intestinal reduction of *Bacteroides fragilis* leading to an increase in the
1032 production of the intestinal FXR antagonist glycoursoxycholic acid (GUDCA) (404). Conversely,
1033 certain pathological conditions can lead to a microbiota-host cross-talk in which the modified BA
1034 profile will propel the disease. For instance, progressive hypercholanemia during pregnancy was
1035 recently reported to originate from an altered microbiome associated with a lowering of ileal FXR
1036 activity, and subsequent enhancement of hepatic BA synthesis leading to an elevation of
1037 circulating BAs (316). UDCA can treat this condition but only in women with a microbiome
1038 characterized by a high ratio of *Bacteroidetes* to *Firmicutes* (316). In these women, it is suggested
1039 that UDCA could be converted to CDCA leading to an activation of ileal FXR and to an increase of
1040 the FGF19-mediated enterohepatic feedback on BA production (315). On the other hand, UDCA
1041 has also been described as an FXR antagonist able to increase BA synthesis and reduce FGF19
1042 levels in obese patients (306). Similarly, a *Clostridia*-rich microbiota and their BA metabolites,

1043 including UDCA, were shown to suppress intestinal FGF19 expression contributing to excessive
1044 BA excretion in patients with diarrhea-predominant irritable bowel syndrome (480). Remodeling of
1045 the gut microbiota and alteration of the BA profile also takes place after chronic alcohol
1046 consumption (159). In turn, this altered BA pool was shown to promote alcoholic liver disease that
1047 could be ameliorated by treating alcoholic mice with the intestine-restricted FXR agonist
1048 fexaramine or by overexpression of a non-tumorigenic FGF19 variant (159). Finally, the metabolic
1049 benefits of surgical interventions also seem to depend on changes in the gut microbial
1050 communities and affect FXR-dependent processes (365). This topic is further developed in section
1051 V-B.

1052

1053 F.2. The BA pool shapes the gut microbiome.

1054

1055 The effects of the microbiome on the BA pool are bidirectional since BAs also modulate the gut
1056 microbiota composition. Similar to HFD feeding which stimulates bile secretion (352), BAs reshape
1057 the microbial landscape and shift the ratio of bacterial phyla (187) through both direct antimicrobial
1058 effects (27), and indirect effects mediated by FXR-induced antimicrobial program (186). The
1059 antimicrobial properties of BAs are a function of their hydrophobicity. DCA, for instance, is a more
1060 potent antimicrobial agent than CA, owing to its high hydrophobicity and detergent properties on
1061 bacterial membranes (405). DCA promotes the survival of microbe populations that resist BA-
1062 induced membrane damage (233). Complex and significant changes in the gut microbiome are
1063 observed when rats are fed BAs. A high-CA (5 mmol/kg) diet profoundly alters the gut microbiome
1064 both at the taxon- and phylum-level (187), with significant inhibition of the *Bacteroidetes* and
1065 *Actinobacteria*, two of the three major phyla reported in human microbiomes (187). Consequently,
1066 expansion of the *Firmicutes*, in particular *Clostridium cluster XVa*, increased the number of DCA-
1067 producing bacteria highlighting the bi-directionality of the BA-microbiome axis (187). While the
1068 potential contribution of BA-responsive receptors to this phenotype was not investigated in this
1069 study, it is now recognized that the effects of BAs on the microbial landscape can also be mediated
1070 through these receptors. It was recently demonstrated that FXR activation by OCA reduces
1071 endogenous BA levels and increases the proportion of Gram⁺ bacteria (115), demonstrating that
1072 the human microbiome can dynamically respond to BA modulation. Modulating the BA pool can
1073 also be a therapeutic strategy in the fight against intestinal infections, in particular nosocomial
1074 infections caused by *Clostridium difficile* (CDI). This infection often arises following the depletion of
1075 intestinal bacterial species after antibiotic treatment (409). In this context, *Clostridium scindens*, a
1076 species able to 7 α -dehydroxylate BAs, was identified to confer protection by generating secondary
1077 BAs that block the germination of *Clostridium difficile* spores (47). Similarly, LCA was recently
1078 demonstrated to lock Vancomycin-resistant Enterococcus bacteria in diplococcal mode, impairing
1079 their biofilm formation, and increasing their susceptibility to the antibiotic daptomycin
1080 demonstrating that BAs not only select bacteria but also actively shape their morphotype (284).

1081 Thus, BA pool size and composition appear to be some of the most important host factors in
1082 regulating gut microbial density, community, and structure in humans.

1083

1084 F.3. The BA-microbiome axis modulates intestinal immunity along the gastrointestinal tract.

1085

1086 Immune cells at the mucosal surface of the gut are challenged with the rapid detection and
1087 elimination of pathogenic microorganisms, while also maintaining tolerance toward commensal
1088 bacteria (28). Genetic or environmental insults can disrupt this balance and precipitate chronic
1089 intestinal inflammation characteristic of IBD (276). The BA-microbiome axis finely shapes intestinal
1090 inflammation along the gastrointestinal tract by defining a series of unique immunoregulatory
1091 microenvironments. In the ileum, high (millimolar) concentrations of conjugated primary BAs
1092 prevent bacterial overgrowth through both direct antimicrobial effects (reviewed in (27)), and
1093 indirect, FXR-mediated, induction of an antimicrobial program (186). In the colon, the
1094 immunological balance requires further adjustments during microbial colonization when immune
1095 cells need to develop tolerance toward commensal bacteria (28). The BA-microbiome axis plays a
1096 key role in this process as the bacteria-derived secondary BA 3 β -hydroxydeoxycholic acid
1097 (isoDCA) limits FXR activity in DCs to diminish their immunostimulatory properties (50). The anti-
1098 inflammatory phenotype acquired by DCs, in turn, allows the differentiation of pTreg cells that help
1099 dampen immune responses during bacterial colonization (50). In the colon, microbiome-derived
1100 secondary BAs can also maintain a healthy pool of FOXP3 $^{+}$ ROR γ^{+} Treg cells by selectively
1101 activating VDR signaling (395). Colonic, microbiome-derived BAs further modulate TGR5 activity in
1102 DCs to instruct tolerance toward commensal microbes. Specifically, BA-dependent activation of
1103 TGR5 by secondary BAs channels the differentiation of human monocytes into tolerogenic DCs
1104 that secrete low levels of TNF α and IL-12 cytokines (182). Similarly, two BA microbial metabolites
1105 were recently shown to fine-tune intestinal immunity (151). 3-oxo-LCA blocked TH17 differentiation
1106 via retinoid-related orphan receptor- γ t (ROR γ t) while isoaloo-LCA increased Treg differentiation
1107 through a mitochondrial ROS-FOXP3-dependent signaling (151), possibly by activating TGR5
1108 (Figure 8). These data suggest that the host-BA-microbiome axis defines a BA-mediated, pan-
1109 genomic network of communication. Immunological tolerance towards commensal bacteria is
1110 instructed by the microbiome itself through complex modifications of the host's BA profile.
1111 Disturbance of this BA-based communication network can propel the development of inflammatory
1112 diseases. Indeed, reduced microbial metabolism of primary BA precursors into secondary BA
1113 products during states of dysbiosis negatively impacts on TGR5 signaling during intestinal
1114 inflammation, as observed in IBD (78, 387). Therapeutically, restoration of secondary BA levels
1115 directly through rectal administration (387) or indirectly through administration of a hydrolyzed
1116 protein diet (437) can help in the management of these diseases.

1117

1118 G. BAs and aging

1119
1120 Aging is defined as the progressive decline of cellular and ultimately organismal function. Although
1121 BAs are known to be beneficial in the treatment of chronic metabolic and inflammatory disorders,
1122 their effect on lifespan remains elusive in mammals. There are, nonetheless, indications that
1123 steroid acids with BA-like features or bona fide BAs can regulate longevity in *C. elegans* (129, 272,
1124 303, 380). The first tangible evidence for a role of BAs in lifespan regulation stems from high-
1125 throughput screens in yeast in which the secondary BA LCA was identified to extend the
1126 chronological lifespan in a calorie restriction-independent fashion (133). Another report proposed
1127 that intracellular LCA modifies the inner mitochondrial membrane lipidome to enlarge mitochondria
1128 and increase the number of disconnected cristae (26). This remodeling would enhance respiration,
1129 ATP synthesis and production of ROS, resulting in a global increase of mitochondrial long-term
1130 stress resistance (26, 48).

1131 In mammals, age-related changes in the BA composition of bile (246), liver and serum (122) have
1132 been reported. Although the nature of these modifications differs according to various factors,
1133 including gender, aging is mainly associated with a decline in BA levels (118). In further support of
1134 this notion, long-lived dwarf mice (*Ghrhr*^{lit/lit}), characterized by a defect in growth hormone/IGF-1
1135 signaling, exhibit an enlarged BA pool size (9). Of interest, xenobiotic detoxification is enhanced in
1136 these mice, most likely through a BA-mediated mechanism (9). Moreover, CA administration in
1137 wild-type mice mimics the changes in drug-metabolizing enzymes observed in *Ghrhr*^{lit/lit} mice,
1138 suggesting that the xenobiotic stress response induced by BAs could contribute to extending
1139 lifespan (10). Remarkably, methionine restriction was found to extend healthspan and lifespan of
1140 progeroid mice by normalizing a dysfunctional BA pool (22). The same phenotype could be
1141 recapitulated by dietary intervention with CA (22). Premature aging was also delayed in progeroid
1142 mice by fecal microbiota transplantation of healthy wild-type mice (23), and the reconstitution of the
1143 secondary BA pool size was identified as a mechanism that accounts for the prolonged lifespan.
1144 Although these observations point to a role for TGR5 in this process, its exact role remains to be
1145 identified. It is however noteworthy that the expression of FXR and TGR5 declines with age and
1146 that dual agonists for TGR5 and FXR delay age-related kidney deterioration (439), as well as
1147 osteoporosis, another age-related disease (257). The intricate relationship between BA signaling,
1148 healthspan and longevity thus seems to represent an interesting area of future investigations that
1149 will undoubtedly shed light on how BAs modulate lifespan.

1150
1151
1152 **V. Strategies to modulate BA signaling**
1153
1154 A. Physiological and environmental cues
1155

1156 Food ingestion and circadian rhythmicity are well-established physiological cues that coordinate
1157 BA homeostasis. Recent evidence, however, indicates that multiple environmental factors
1158 dramatically alter this tightly regulated process (Figure 6). Often, these effects imposed by the
1159 environment go along with changes in the gut microbiota. In the last decade, the role of HFD
1160 feeding on microbiota-host interactions has been the focus of intense research. In addition to its
1161 marked impact on the gut microbial community (18), HFD significantly influences the BA pool size
1162 and composition (121). The consumption of HFD increases the synthesis of CA and DCA and
1163 decreases the levels of CDCA in healthy subjects (36). In rodents, secondary BAs are significantly
1164 higher in HFD compared to CD fed controls (102, 121). Cold exposure also dramatically alters the
1165 microbiome and counteracts metabolic disease. This was first illustrated by the observation that
1166 bacteria transplanted from cold-exposed mice improve the metabolic outcome of recipient mice
1167 (64) and that BAs could play a role in this process (452, 485). Cold exposure increased the ratio of
1168 conjugated BAs (452, 485), and enlarged the BA pool through selective induction of the alternative
1169 BA synthesis pathway (452). In support of the latter finding, *Cyp7b1^{-/-}* mice were unable to adjust
1170 their BA pool and displayed lower body temperature after cold challenge. A similar phenotype on
1171 body temperature was observed in adipose-specific *Tgr5^{-/-}* mice, suggesting that an adequate
1172 thermogenic response requires TGR5 in adipocytes (427). Furthermore, one of the main BA
1173 species to be increased in response to cold is the FXR antagonist, T β MCA (485). Altogether, these
1174 results suggest that cold, as an environmental cue, impacts the gut microbiota in such a way that it
1175 induces TGR5 signaling while concomitantly attenuating FXR activation. Another environmental
1176 factor that enhances energy expenditure is exercise. Morville et al., observed that several BAs are
1177 significantly altered following endurance and resistance exercise. Amongst those, the TGR5
1178 endogenous agonists LCA and DCA were consistently induced (301). The hallmarks of exercise-
1179 induced phenotypes, such as increased energy expenditure and improved glucose tolerance, may
1180 hence be coordinated, at least in part, by an activated TGR5 signaling pathway.

1181

1182 B. Surgical interventions

1183

1184 Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG) and bile diversion to the
1185 ileum (GB-IL) are surgical procedures that promote weight loss and induce a rapid remission of
1186 T2D in patients. Although the mechanistic basis for this phenomenon is not fully established,
1187 elevated concentrations of circulating incretin hormones is a hallmark that may contribute to these
1188 metabolic improvements (reviewed in (138)). In 2009, Patti et al., demonstrated for the first time
1189 that serum BAs are also significantly elevated in patients following RYGB and proposed TGR5 as
1190 a putative mechanism by which improvements in glucose and body fat management can be
1191 achieved (326), later confirmed by other studies (5, 385). A subsequent study confirmed that DCA,
1192 a very strong TGR5 agonist, is increased in patients 24-months after RYGB, while UDCA and its
1193 conjugated forms are the most changed BAs one month after surgery (5). While some studies

1194 reported TGR5 as a mediator of the RYGB-mediated metabolic improvements, including GLP-1
1195 secretion (471), others failed to confirm these findings (154). Furthermore, although there is
1196 agreement that activation of TGR5 improves glucose response and attenuates fatty liver disease
1197 (91, 283), controversy exists relative to its role in energy expenditure in the context of VSG. A
1198 study using a DKO model of TGR5 and glucagon receptor suggested that TGR5 is not critical for
1199 the secretion of proglucagon-derived peptides (322). While sustained elevation in circulating BAs is
1200 a phenotypic consequence of all bariatric procedures, they are also typified by a relocation of BA
1201 delivery to more distal segments of the small intestine and an induction of the ileal signaling factor
1202 and FXR target, FGF19 (344). Two independent studies demonstrated that DIO germline or
1203 intestine-specific *Fxr*^{-/-} mice can no longer recapitulate the metabolic improvements observed after
1204 VSG (365) or GB-IL (4). Further studies are required to identify the missing link between gastric
1205 bypass surgeries, FXR, and weight loss, but dynamic alterations of the BA pool and the gut
1206 microbiome seem to play a key role in this process (199) (Figure 6). Consistently, fecal microbiota
1207 transplantation from postbariatric donors improved metabolic parameters in patients with metabolic
1208 syndrome (82).

1209

1210 C. Pharmacological interventions

1211

1212 In addition to surgery, a series of FDA-approved chemicals exists that modulate BA signaling
1213 thereby improving metabolic disorders. The oldest group of BA-modifying drugs are the BA
1214 sequestrants, initially designed to interrupt the enterohepatic circulation. BA sequestrants are
1215 effective in lowering LDL cholesterol and inducing GLP-1 release, by promoting the hepatic
1216 conversion of elevated cholesterol levels into BAs and by coordinately modulating intestinal FXR
1217 and TGR5 activities. IBAT/ASBT inhibitors have a similar mechanism of action preventing BA re-
1218 uptake across the intestinal epithelium (extensively reviewed in (230, 397, 414)). Only recently,
1219 antibiotics have regained new interest, not so much because of their impact on the size, but rather
1220 on the composition of the BA pool (Figure 6). The decrease in secondary BAs after short-term use
1221 of antibiotics was recently shown to reduce serum glucose and triglyceride levels (232). However,
1222 caution should be taken when developing therapeutic strategies as the same antibiotic-driven
1223 reduction in secondary BAs was linked to the development of cholestasis in pediatric patients
1224 (454), and to *Clostridium difficile* outgrowth in the large intestine (408).

1225 Therapies using natural BAs, such as UDCA, have proven to be successful in a subset of patients
1226 with cholestatic disorders (32). UDCA is the first-line therapy for PBC, and is effective in
1227 approximatively 60% of patients (318). While its efficacy is still debated for PSC (241) and
1228 NAFLD/NASH (16), the UDCA-homologue 24-norursodeoxycholic acid (*nor*UDCA) seems to be
1229 effective for PSC (106). Finally, promising therapeutic opportunities with selective FXR and/or
1230 TGR5 modulators have made their appearance. Several selective and dual agonists, but also
1231 antagonists, have been developed (Table 2) and tested in human subjects for their ability to

1232 prevent or delay cholestatic liver disorders, obesity, T2D, NASH, atherosclerosis, and IBD, as
1233 described above. While to date only one TGR5 agonist has been studied in T2D patients with
1234 unexpected outcomes on glucose management (168), numerous FXR agonists have been tested
1235 in clinical trials (Table 3). Of these, the most advanced is the CDCA semi-synthetic derivative,
1236 OCA (328), which has been FDA-approved as second-line therapy for UDCA-unresponsive or -
1237 intolerant PBC patients (416). OCA treatment blunts cholestasis and inflammation in PBC patients
1238 (166, 227, 312, 416), and stabilizes or even improves hepatic damage and fibrosis (39). While the
1239 most common adverse effect of OCA is pruritus, severe non-hepatic ascites and varices can occur
1240 in a minority of patients, and worsening of liver disease in cirrhotic patients has been reported (99).
1241 In non-cirrhotic NASH patients, however, OCA treatment is beneficial and diminishes liver
1242 steatosis, inflammation and fibrosis, while enhancing insulin sensitivity (305, 311, 466). FXR
1243 activation, however, also increased total and LDL cholesterol and decreased HDL cholesterol
1244 levels in NASH patients (311) and healthy volunteers (331), warranting long term studies to further
1245 assess the clinical relevance of this dyslipidemia. Phase III clinical trials (REGENERATE AND
1246 REVERSE) are currently ongoing to assess clinical outcomes and long-term safety, as well as
1247 OCA efficacy in cirrhotic NASH patients (REVERSE trial). Interestingly, similar improvements on
1248 fibrosis were reported in patients after a 3-year follow-up, suggesting long-term clinical benefits
1249 (351, 466).

1250 In addition to the steroid OCA compound, which is the most advanced in the clinic, several non-
1251 steroid FXR agonists, including Tropifexor (417), Nidufexor (66), EDP305 and Cilofexor (Table
1252 2), have reached the phase II clinical test stage and have the potential to become novel
1253 therapeutic agents for NASH (323), PSC (415) and PBC (417). Likewise, the FGF19 analog,
1254 NGM282, has also been evaluated in clinical trials and has proven efficacy in PSC (165), PBC
1255 (282) and NASH (86, 156, 157).

1256

1257

1258 VI. Undesired side effects of BA signaling

1259

1260 **BAs and cancer.** Exposure to elevated BA levels has been linked with higher cancer incidence in
1261 several digestive organs. Already in 1940, BAs were demonstrated to be inducers of cancer in
1262 rodents that were subcutaneously injected with DCA (75). The consensus hence was that BAs,
1263 especially hydrophobic species, were tumor-promoting molecules. Subsequently, several
1264 pathways linking BAs to cancer were identified, including oxidative stress with DNA damage and
1265 genomic instability, apoptosis, and interactions with gut microbiota (reviewed in (192)). These
1266 mechanisms can also be secondary to environmental stimuli (diet, lifestyle, exposure to
1267 environmental toxins) and affect predominantly the hepato-gastrointestinal tract (reviewed in
1268 (192)), especially the liver (465), biliary tract (223), and colon (121). The main mechanisms
1269 involved are the increased intracellular production of reactive oxygen and nitrogen species (30)

1270 and the altered expression of tumor suppressor/promoting genes (438). In this process, the degree
1271 of hydrophobicity dictates the oncogenic potential of BAs as illustrated by the fact that in the liver,
1272 feeding various concentrations of BAs produced the following hepatotoxicity:
1273 UDCA<CA<CDCA<DCA<LCA (394). Consistently, *Fxr^{-/-}* mice develop spontaneous liver cancer
1274 because of increased levels of BAs (460) and lowering their BA pool with cholestyramine
1275 significantly inhibits tumor lesions (460). While intestine-restricted FXR agonists are usually seen
1276 as having positive therapeutic impacts, it should be noted that chronically elevated levels of
1277 circulating FGF19 are linked with liver cancer (482). The pro-tumorigenic effects of FGF19 are due
1278 to a non-cell autonomous activation of IL-6/STAT3 signaling (484). Interestingly, an FGF19
1279 engineered analog NGM282, which differs from wild-type FGF19 in the amino terminus, retains the
1280 ability to repress *Cyp7a1* expression without triggering the activation of STAT3, eliminating FGF19-
1281 associated tumorigenicity (157, 481, 483). Recently, a direct link between BAs and cancer
1282 progression was described. T β MCA was shown to not only initiate colorectal cancer through DNA
1283 damage but also to actively promote cancer stem cell proliferation via inhibition of FXR activity in
1284 *Lgr5⁺* intestinal stem cells (121). Therapeutically, restoring FXR activation with FexD, a gut-biased
1285 FXR agonist, delayed tumor progression and profoundly increased survival of APC^{min/+} mouse
1286 models of adenoma and adenocarcinoma (121). Similarly, the growth of lymph node-metastatic
1287 melanoma was shown to depend on BA-mediated activation of YAP (245). Unexpectedly, this
1288 study suggests that lymph node-metastatic tumors themselves can upregulate *Cyp7a1* and
1289 produce BAs in an autocrine manner to further stimulate their own growth (245). Importantly,
1290 evidence also exists in support of an oncoprotective role for BAs. While some studies involve direct
1291 effects of BAs on cancerous cells (248, 332, 335), a new report demonstrated that the gut
1292 microbiome can use BAs to shape immunity against liver cancer (270). In this study, the authors
1293 demonstrated that microbiome-mediated primary-to-secondary BA conversion triggers CXCL16
1294 expression in liver sinusoidal endothelial cells enabling the recruitment of natural killer T cells to
1295 mediate liver-selective tumor inhibition (270).

1296

1297 **BAs and adverse cardiovascular outcomes.** Despite the established benefits of BA signaling in
1298 cardiometabolic homeostasis (see section IV-D), elevated BAs can be cardiotoxic and lead to
1299 progressive cardiomyopathy (reviewed in (424)). Conjugated BAs, in particular TCA, furthermore
1300 induce arrhythmic contractions in human atria (349), underscoring once more the potential
1301 detrimental action of BAs in disease. While BA responsive receptors are expressed in the heart,
1302 their contribution to human cardiac disease is not completely understood. FXR activation triggers
1303 apoptosis in cardiomyocytes while conversely, inhibition of FXR is protective against ischemia-
1304 induced cardiac insults (346). In addition, long-term FXR activation by OCA in humans can
1305 elevate LDL cholesterol levels (311). This unfavorable and atherogenic serum lipid profile may
1306 originate from the ability of FXR to blunt BA synthesis and LDL clearance via repression of *Cyp7a1*
1307 (59) and hepatic pro-protein convertase subtilisin/kexin type 9 (*Pcsk9*) expression (130, 240),

1308 respectively. However, HDL-cholesterol is also decreased (311). The FXR-dependent repression
1309 of apolipoprotein A-1 (ApoA-I) (73) and paraoxonase 1, involved in the inactivation of pro-
1310 atherogenic lipids (145, 382), may contribute to this effect and ultimately lead to long-term adverse
1311 clinical outcomes. Further studies will be needed to fully understand the underlying mechanisms.

1312 Although less studied, cardiovascular concerns have been raised for TGR5 as well. TGR5 has
1313 been proposed to mediate cardiac hypertrophy in a mouse model of liver injury by triggering AKT
1314 signaling (87), and reflex tachycardia (as a result of reduced vascular tone and blood pressure)
1315 has been observed in dogs treated with a synthetic TGR5 agonist (119). Other studies, however,
1316 attribute a cardioprotective role to TGR5 by improving the myocardial response to cardiac stress
1317 (100), as well as by reducing atherosclerosis (337). In line with this, LCA negatively correlates with
1318 atheroma presence in patients and its levels can predict the disease (94). Dedicated studies and
1319 clinical trials will be required to identify the exact impact of TGR5, as well as the other non-
1320 canonical BA receptors, such as the muscarinic receptors, on cardiovascular risk.

1321

1322 **BAs and pruritus.** Although itching can be seen as a protective reflex to remove pathogens and
1323 skin irritants, chronic pruritus is associated with pathological states and significantly impacts the
1324 quality of life. TGR5 is expressed in peripheral neurons of the dorsal root ganglia where its
1325 activation stimulates the release of neuropeptide transmitters of itch. The TGR5-dependence of
1326 this effect was proven *in vivo* where DCA treatment induced spontaneous scratching in *Tgr5^{+/+}* but
1327 not in *Tgr5^{-/-}* mice (6). Later, it was reported that the neuronal hyperexcitability followed by TGR5
1328 stimulation is mediated through activation of the transient receptor potential ankyrin 1 (TRPA1)
1329 channel, required for the acute pruritogenic response (260). However, it should be mentioned that
1330 TGR5 activation in the dorsal root innervation can also attenuate pain through an opioid-dependent
1331 mechanism (6) thus blunting the perception of what was initially considered as an unfortunate side
1332 effect. Of note, BA derivatives predominantly targeting FXR, such as OCA, can also trigger itching
1333 (311). Furthermore, no adverse effects of itching were observed in humans with the selective
1334 TGR5 agonist, SB-756050 (168). The mechanism underlying pruritus may, therefore, be more
1335 complex than originally proposed.

1336

1337

1338 **VI. Final remarks and future perspectives**

1339 BA signaling has many beneficial roles as it enables tissues to adapt to environmental, nutritional,
1340 and physiological cues. However, this signaling can also become maladaptive, especially when the
1341 tight feedback regulation of BA synthesis is compromised to the point that BAs become cytotoxic.
1342 Several diseases and conditions, as diverse as cholestasis, fibrosis, cardiomyopathy, gallbladder
1343 stones, cancer, and pruritus, have been associated with an uncontrolled rise in BA concentrations
1344 or observed after BA treatment. Whether these correlate with human pathologies are the focus of
1345 intense research aimed at better understanding the molecular basis of BA-induced disease

1346 progression. However, the field should remain cautious about the contrasting features of BAs,
1347 swiftly fluctuating between good and bad.

1348
1349 The prime effectors of BA signaling are the receptors, FXR and TGR5, that evolved often
1350 complementary functions. Their balanced contributions translate the signals conveyed by the many
1351 different BAs to shape not only cellular responses but also tissues and even entire systems to the
1352 quality and quantity of BAs. There are still many challenges ahead to grasp the full complexity of
1353 BA signaling and their role in many contexts are only starting to be elucidated. For instance, we
1354 are only on the verge of understanding how the gut microbiome affects BA composition and levels,
1355 which constitutes a prime way for the microbiome to synchronize a wide range of physiological
1356 processes. There is still controversy about the metabolic benefits of intestinal FXR agonists versus
1357 antagonists, and a more in-depth analysis of its impact on the microbiota will be needed to fully
1358 elucidate the intricate interplay of microbial and host factors. Likewise, we know very little about
1359 the signaling roles of BAs in the brain, although bile has been postulated to affect our mood since
1360 ancient times. Furthermore, we are only starting to understand how convergent signaling by two
1361 BA receptors controls cellular processes as fundamental as cell proliferation, differentiation, and
1362 death. In this respect, the discovery that BAs influence stem cell homeostasis opens a new field
1363 that may fuel novel opportunities in regenerative medicine. Finally, from an evolutionary point of
1364 view, we still need to understand the impressive species-specific differences in BA production and
1365 signaling pathways.

1366
1367 While many aspects of BA signaling still need to be deciphered, the first therapeutics targeting
1368 FXR are making their way into the clinic. Likewise, it is expected that TGR5-based therapies for
1369 targeted diseases will soon arise, although a creative approach will be needed to generate
1370 compounds with a more restricted bioavailability and/or activity. Similarly, OCA, the current FDA-
1371 approved FXR agonist for the treatment of PBC is safe and effective, but the existence of
1372 undesired side-effects urges the development of next-generation drugs with fewer side effects.
1373 Overall, given the wide distribution and numerous actions of FXR and TGR5, the future of these
1374 molecules will lie in the development of selective FXR and TGR5 modulators, whose activities
1375 should be tailored to target only a set of functions that are relevant to the type of disease. In sum,
1376 drugs targeting BA signaling have a bright future and the continuing efforts on studying the impact
1377 of changing BA signaling pathways in humans will be extremely useful to translate our emerging
1378 knowledge on BA physiology in model organisms into clinical benefits.

1379 **VII. References**

1380

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- 2825 **VIII. Figure legends**
- 2826
- 2827 **Figure 1. BA synthesis and transport. A:** Scheme depicting the main biochemical
2828 transformations during BA synthesis in liver. Primary BAs (white rectangles with dashed lines) are
2829 produced from cholesterol by the classic or alternative pathway. BA 7 α -hydroxylation is catalyzed
2830 by CYP7A1 (classic pathway) or CYP7B1 (alternative pathway). Sterol ring modification is mainly
2831 catalyzed by HSD3B7 and CYP8B1, while side-chain oxidation and shortening requires CYP27A1.
2832 BAs are then conjugated (grey rectangles) in the liver, released in the gut where they are modified
2833 by the gut microbiome into secondary BAs (white rectangles) and recycled back to the liver where
2834 they are re-conjugated. **B:** Summary of sites of hydroxylation on steroid nucleus of BA species

2835 indicated in panel A. **C:** Schematic representation of the main BA transporters in the enterohepatic
2836 system.
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BAs, bile acids; CYP7A1, cholesterol 7 α -hydroxylase; CYP27A1, sterol 27-hydroxylase; HSD3B7, hydroxy-delta-5-steroid dehydrogenase; CYP7B1, oxysterol 7 α -hydroxylase; CYP8B1, sterol 12 α -hydroxylase; CA, cholic acid; CDCA, chenodeoxycholic acid; α MCA, alpha-muricholic acid; β MCA, beta-muricholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; T α MCA, tauroalpha-muricholic acid; T β MCA, taurobeta-muricholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; UDCA, ursodeoxycholic acid, HCA, hyocholic acid; MDCA, murideoxycholic acid; ω MCA, omega-muricholic acid; HDCA, hyodeoxycholic acid; C6, carbon 6; C7, carbon 7; C12, carbon 12; H, hydrogen; α -OH, alpha hydroxyl group; β -OH, beta hydroxyl group; OST α , organic solute transporter α ; OST β , organic solute transporter β ; MRP3, multidrug resistance protein 3; MRP4, multidrug resistance protein 4; MRP2, multidrug resistance protein 2; ASBT, apical sodium-dependent BA transporter; BSEP, bile acid export pump; I-BABP, ileal bile acid binding protein; NTCP, sodium-dependent taurocholate co-transporting polypeptide; OATP1, organic anion-transporting polypeptide 1.

Figure 2. Triple action of BAs. The chemical structure of BAs highlights the presence of a hydrophobic and a hydrophilic side (left panel) that allow BAs to act as detergents that facilitate intestinal lipid absorption. BAs also act as substrates for the gut microbiome (middle panel) and control multiple cellular processes through the activation of dedicated nuclear and membrane receptors, such as FXR and TGR5, respectively (right panel).

TGR5, Takeda G-protein receptor 5; FXR, farnesoid X receptor.

Figure 3. BA receptors and signaling. **A:** Table depicting the BA-responsive nuclear and membrane receptors. **B:** Molecular mechanisms and signaling cascades by which TGR5 and FXR relay BA signals into adaptive cellular responses.

FXR, farnesoid X receptor; VDR, vitamin D3 receptor; PXR/SXR, pregnane X receptor/steroid and xenobiotic-sensing receptor; CAR, constitutive androstane receptor; TGR5, Takeda G-protein receptor 5; S1PR2, sphingosine 1-phosphate receptor 2; FPR, formyl-peptide receptor; mAChR, muscarinic acetylcholine receptor; SRC-1, steroid receptor coactivator 1; PGC-1 α , peroxisome-proliferator-receptor (PPAR)- γ coactivator-1 α ; CARM-1, coactivator-associated arginine (R) methyltransferase-1; PMRT-1, protein arginine (R) methyltransferase-1; EPAC, exchange protein directly activated by cAMP; PKA, protein kinase A; mTOR, mechanistic target of rapamycin; ERK1/2, extracellular signal-related kinase 1/2; RXR α , retinoic acid receptor α ; PTM, post-translational modification.

Figure 4. FXR-mediated BA signaling in hepatocytes. Molecular mechanisms by which FXR controls multiple metabolic processes in hepatocytes. Hepatic FXR and intestinal FXR (through

2873 FGF15/19 release and activation of the FGFR4- β -KLOTHO signaling) synergize in the control of
2874 lipid, glucose and amino acid homeostasis, as well as in the feedback regulation of BA synthesis.
2875 FXR target genes are highlighted in blue.

2876 FXR, farnesoid X receptor; FGF15/19, fibroblast growth factor 15/19; FGFR4, fibroblast growth
2877 factor receptor 4; FAS, fatty acid synthase; ACC, acetyl-CoA carboxylase; SCD1, stearoyl-CoA
2878 desaturase-1; SREBP1c, sterol regulatory binding protein 1c; LPK, liver pyruvate kinase; ChREBP,
2879 carbohydrate-responsive element-binding protein; SHP, small heterodimer partner; VLDL, very low
2880 density lipoprotein; MPT, microsomal triglyceride transfer protein; ApoB, apolipoprotein B; HNF4 α ,
2881 hepatocyte nuclear factor 4 alpha; SHP2, Src homology region 2 (SH2)-containing protein tyrosine
2882 phosphatase 2; ERK, extracellular signal-regulated kinase; CYP7A1, cholesterol 7 α -hydroxylase;
2883 PEPCK, phosphoenolpyruvate carboxykinase; G6Pase, glucose 6-phosphatase; CREB, cAMP-
2884 response element binding protein; GSK3, glycogen synthase kinase 3; eIF4B, eukaryotic
2885 translation initiation factor 4B; eIF4E, eukaryotic translation initiation factor 4E; rpS6, ribosomal
2886 protein S6.

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2888 **Figure 5. Transport of bile components in the enterohepatic organs.** Schematic of the main
2889 bile component transporters in the enterohepatic system. FXR target genes are highlighted in blue.
2890 BA, bile acid; NTCP, sodium-dependent taurocholate co-transporting polypeptide; OATP1, organic
2891 anion-transporting polypeptide 1; OST α , organic solute transporter α ; OST β , organic solute
2892 transporter β ; MRP3, multidrug resistance protein 3; MRP4, multidrug resistance protein 4; BSEP,
2893 bile acid export pump; MRP2, multidrug resistance protein 2; ABCG5, ATP-binding cassette sub-
2894 family G member 5; ABCG8, ATP-binding cassette sub-family G member 8; MDR2/3, multidrug-
2895 resistant protein 2/3; ASBT, apical sodium-dependent BA transporter; MDR1, multidrug-resistant
2896 protein 1; I-BABP, ileal bile acid binding protein.

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2898 **Figure 6. TGR5- and FXR-mediated BA signaling in the enterohepatic organs.** Physiological
2899 and environmental cues, as well as disease or disease intervention (grey rectangles on top),
2900 modulate gut microbiome and BA pool size/composition to control TGR5 and FXR signaling in the
2901 various cell types of the enterohepatic system. These receptors act in a synergistic (one arrow) or
2902 complementary manner (two arrows) to regulate the physiological processes indicated in the green
2903 rectangles. Green arrows indicate an increase while red arrows indicate a reduction.

2904 TGR5, Takeda G-protein receptor 5; EEC, enteroendocrine L cell; GLP-1, glucagon-like peptide-1;
2905 CGRP, calcitonin gene-related peptide; FXR, farnesoid X receptor; BA, bile acid; TG, triglyceride;
2906 VLDL, very low density lipoprotein; FGF15/19, fibroblast growth factor 15/19; H₂O, water; TICE,
2907 transintestinal cholesterol excretion.

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2909 **Figure 7. TGR5- and FXR-mediated BA signaling in the enteroendocrine L cell.** Molecular
2910 mechanisms and signaling cascades by which FXR and TGR5 control preproglucagon (*Gcg*) gene
2911 transcription and GLP-1 secretion in intestinal enteroendocrine (EEC) L cells.
2912 EEC, enteroendocrine L cell; SGLT1, sodium-glucose cotransporter 1; FXR, farnesoid X receptor;
2913 *Gcg*, glucagon; ChREBP, carbohydrate-responsive element-binding protein; Ffar2, free fatty acid
2914 receptor 2; Gbpar1, G protein-coupled bile acid receptor 1; PC1/3, prohormone convertase 1/3;
2915 FFAR1/2, free fatty acid receptor 1/2; Ca²⁺, calcium; TGR5, Takeda G-protein receptor 5; ATP,
2916 adenosine triphosphate; cAMP, cyclic adenosine monophosphate; AC, adenylyl cyclase; PKA,
2917 protein kinase A; GLP-1, glucagon-like peptide-1.

2918
2919 **Figure 8. BA-TGR5 signaling in adipose tissue and immune cells.** Physiological and
2920 environmental cues (grey rectangles on top) modulate gut microbiome and BA pool
2921 size/composition to control TGR5 signaling in the depicted cell types and regulate the physiological
2922 processes indicated in the green rectangles. Green arrows indicate an increase while red ones
2923 indicate a reduction.

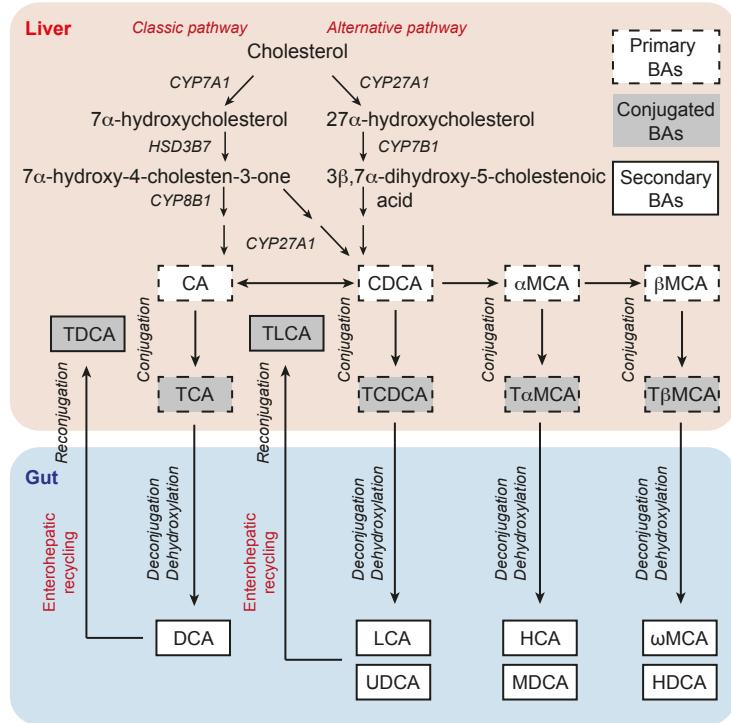
2924 TGR5, Takeda G-protein receptor 5; T_{reg}, Regulatory T cell; T_H17, T helper 17 cell.

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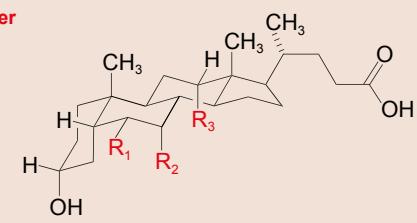
2926 **Figure 9. BA signaling in liver regeneration.** Molecular mechanisms by which sudden rise in BA
2927 concentration following partial hepatectomy coordinate liver regeneration. FXR and TGR5 play
2928 complementary roles in stimulating proliferation in hepatocytes and cholangiocytes, respectively.
2929 FXR, farnesoid X receptor; FOXM1B, forkhead box M1b; JAK/STAT, janus kinase/signal
2930 transducer and activator of transcription; MAPK, mitogen-activated protein kinase; FGF15/19,
2931 fibroblast growth factor 15/19; FGFR4, fibroblast growth factor receptor 4; ROS, reactive oxygen
2932 species; SRC, steroid receptor coactivator; EGF, epidermal growth factor; EGFR, epidermal
2933 growth factor receptor; TGR5, Takeda G-protein receptor 5.

Figure 1

A



B



R₁(C6) R₂(C7) R₃(C12)

CA	H	α-OH	α-OH
CDCA	H	α-OH	H
α-MCA	β-OH	α-OH	H
β-MCA	β-OH	β-OH	H

Gut

R₁(C6) R₂(C7) R₃(C12)

DCA	H	H	α-OH
LCA	H	H	H
UDCA	H	β-OH	H
HCA	α-OH	α-OH	H
MDCA	β-OH	H	H
ω-MCA	α-OH	β-OH	H
HDCA	α-OH	H	H

C

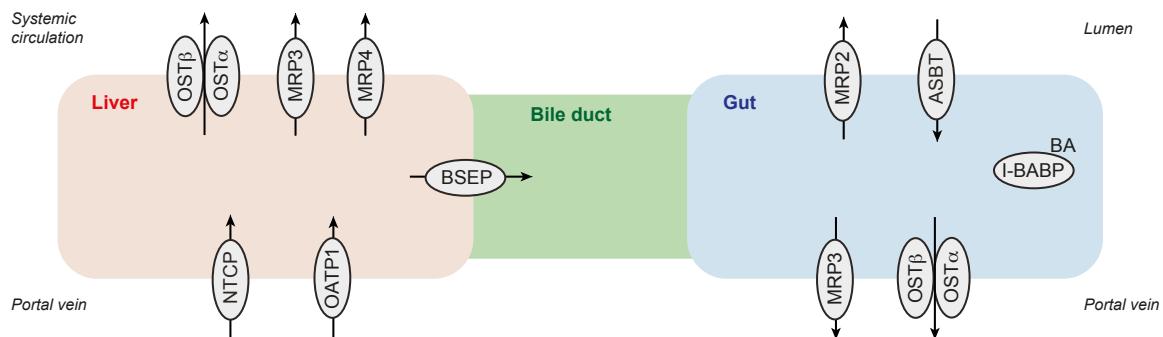
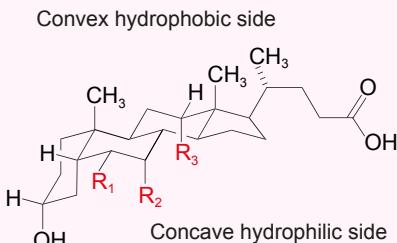
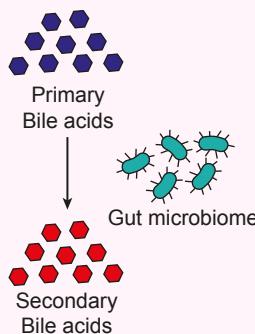


Figure 2

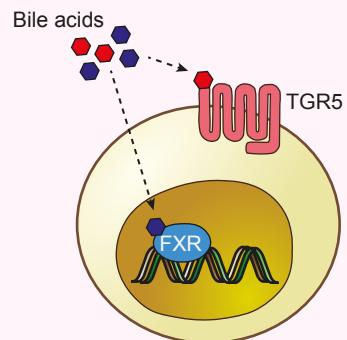
PHYSICOCHEMICAL PROPERTIES



SUBSTRATES



SIGNALING FACTORS



Intestinal lipid absorption

Shaping of microbiome

Regulation of cellular processes

Figure 3

A

BA-responsive receptors	
Nuclear	Membrane
FXR	TGR5
VDR	S1PR2
PXR/SXR	FPR
CAR	mAChR Integrins

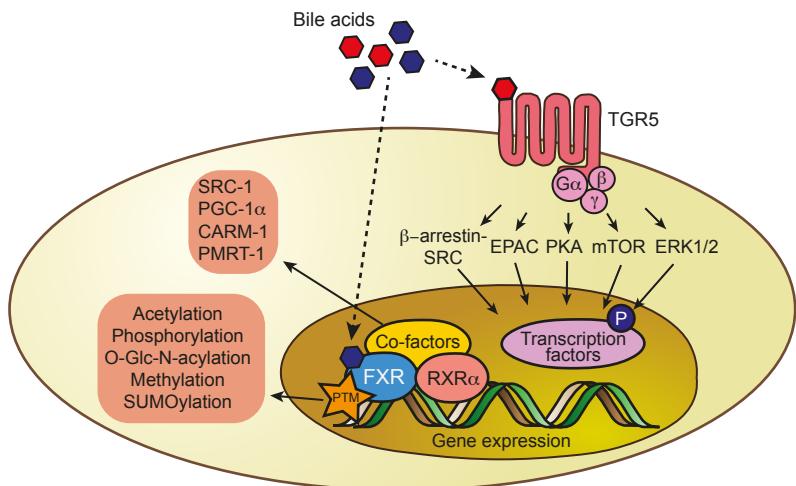
B

Figure 4

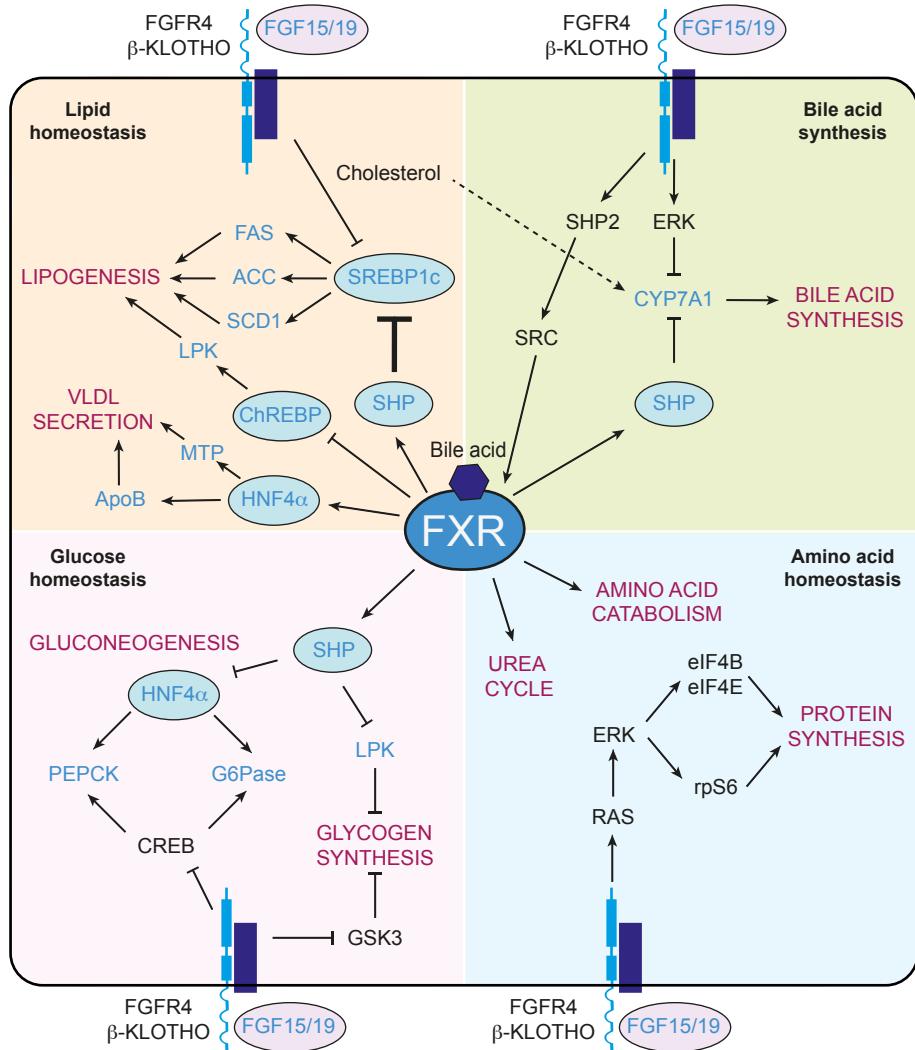


Figure 5

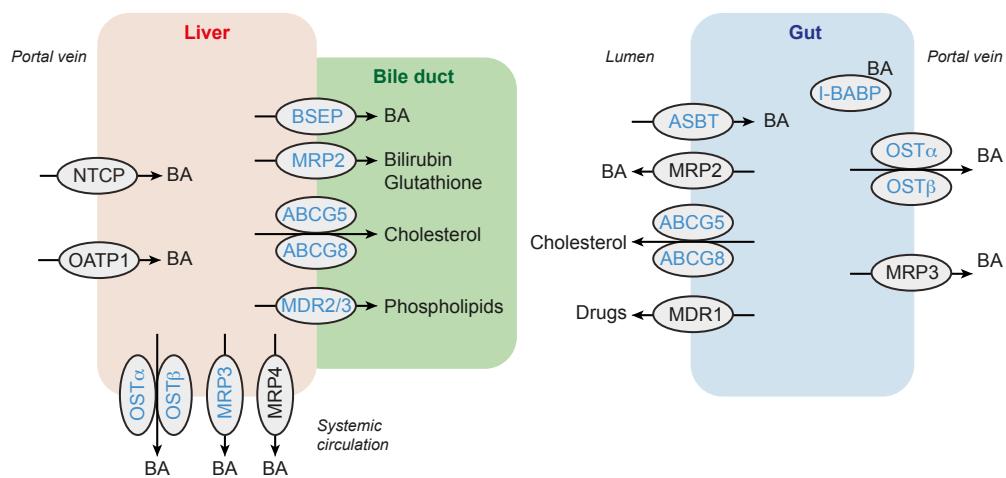


Figure 6

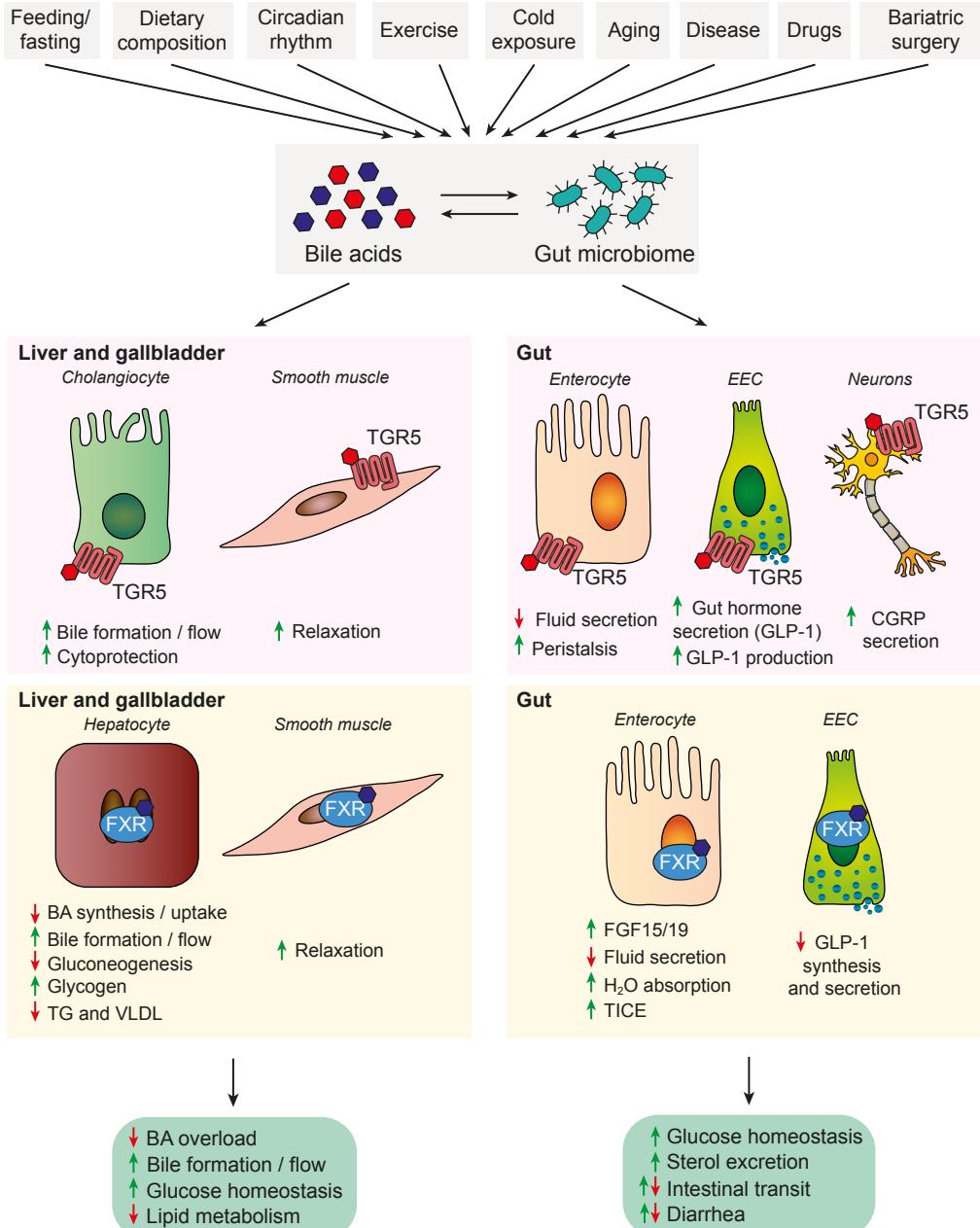


Figure 7

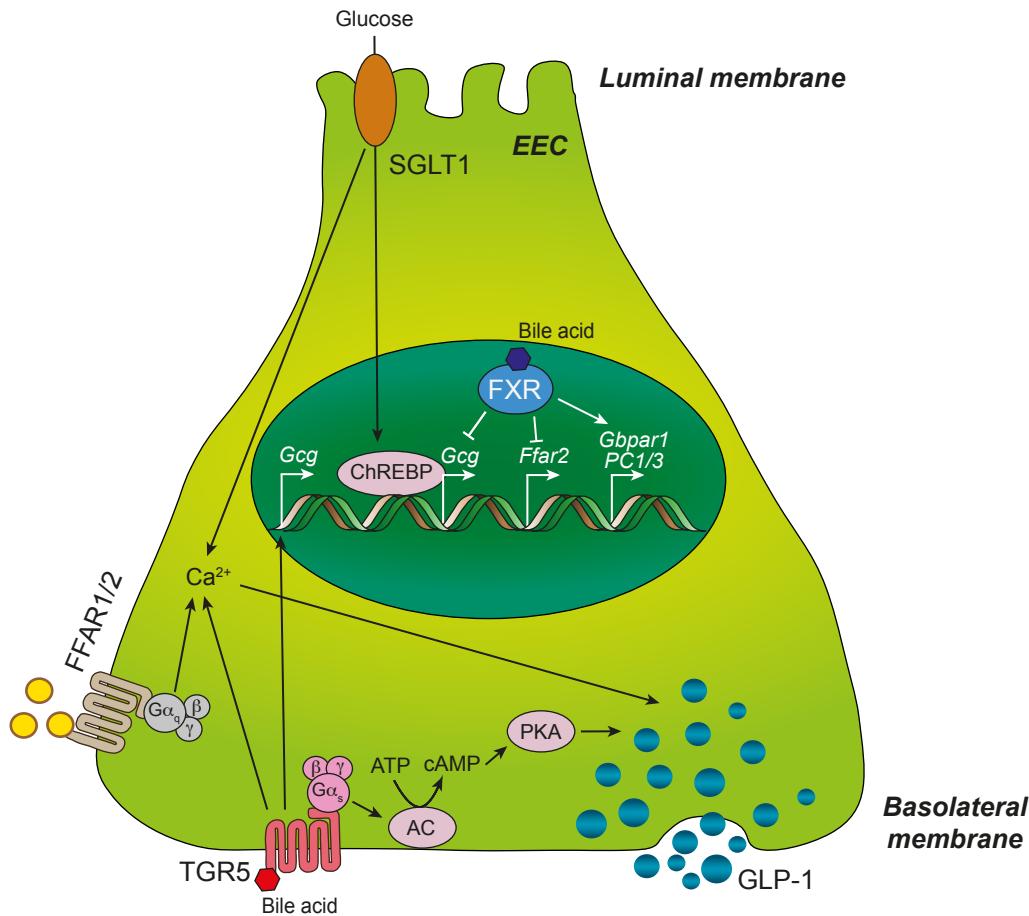


Figure 8

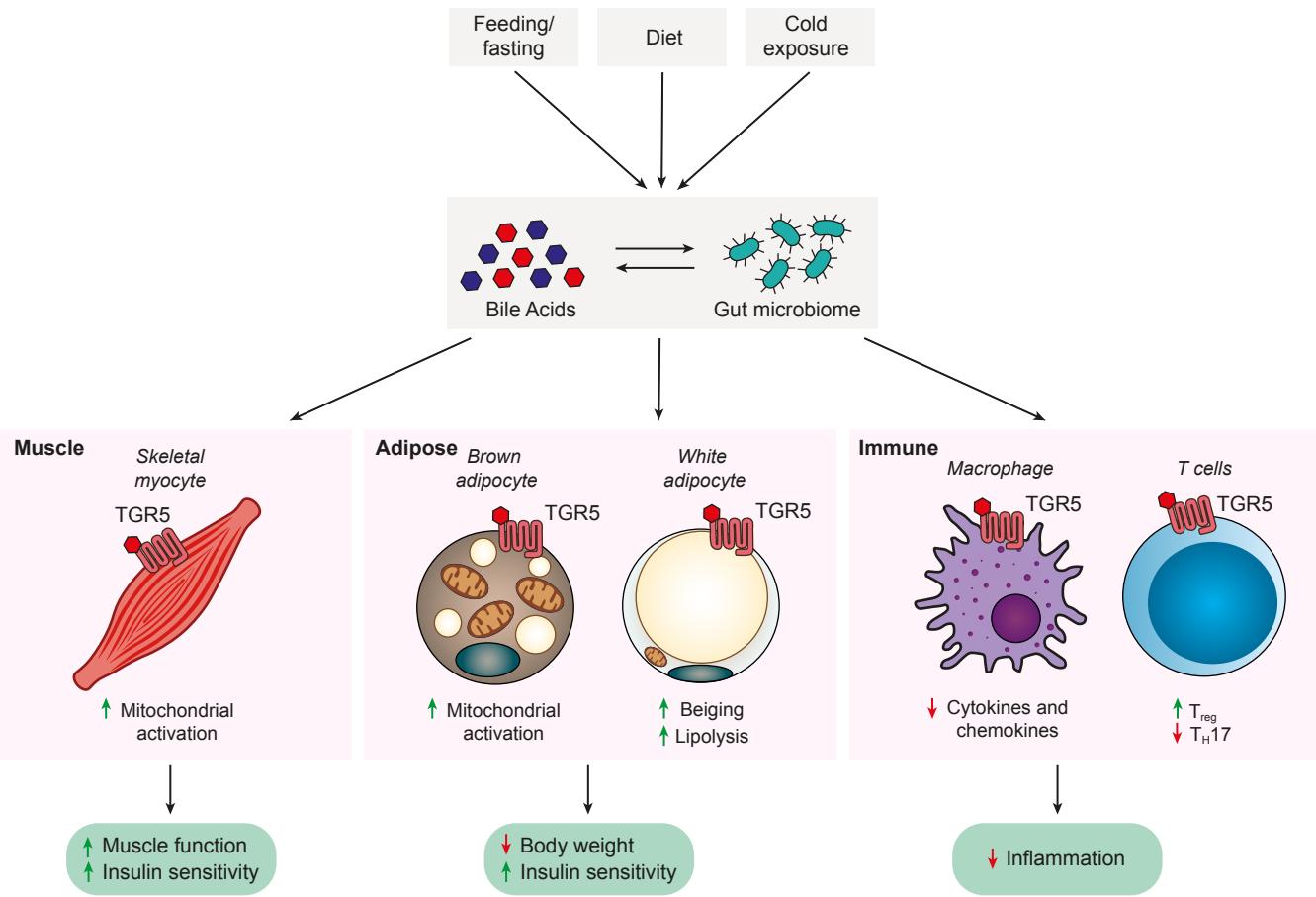


Figure 9

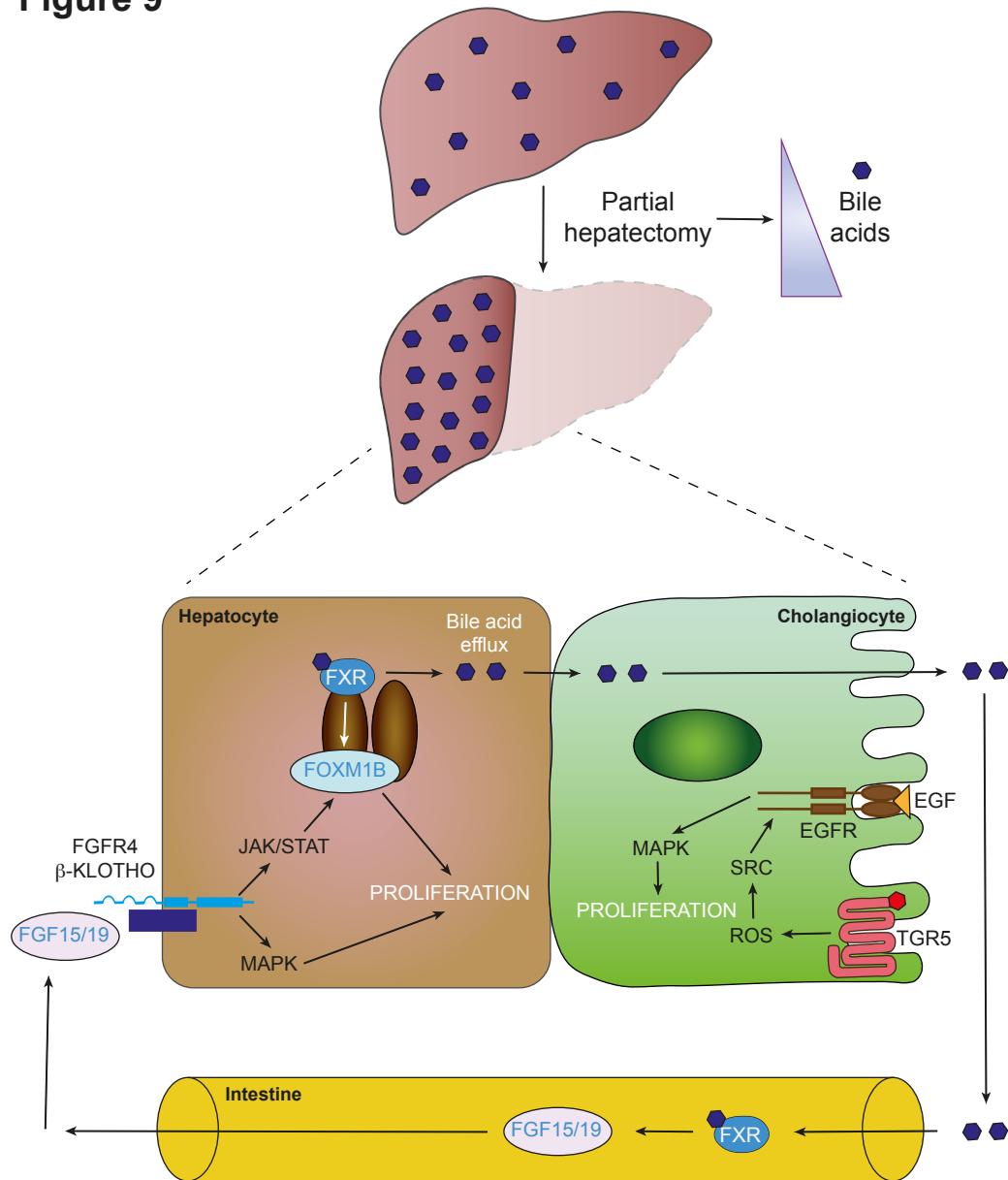


Table 1. Main BA biotransformation reactions catalyzed by intestinal bacteria.

Reaction	Enzymes/Bacteria	Substrates*	Products*
Deconjugation	Bile salt hydrolase (BSH)	TCDCA	CDCA
		TCA	CA
		GCDCA	CDCA
		GCA	CA
Hydroxyl group oxidation	Hydroxysteroid dehydrogenase (3 α , 7 α , 12 α -HSDH)	CA	3-oxo-CA, 7-oxo-DCA
		CDCA	3-oxo-CDCA 7-oxo-LCA
7-dehydroxylation	Bile acid oxidoreductase and bile acid dehydratase (among others)	CA	DCA
		CDCA	LCA
		α MCA/ β MCA	MDCA
		ω MCA/HCA	HDCA
6 α -epimerization	Unknown	β MCA	ω MCA
		α MCA	HCA
7 β -epimerization	7 β -hydroxysteroid dehydrogenase (7 β -HSDH)	CDCA	UDCA
		α MCA	β MCA
3 β -epimerization	3 β -hydroxysteroid dehydrogenase (3 β -HSDH)	CA	Iso-CA
		CDCA	Iso-CDCA

*List is non-exhaustive

TCDCA, taurodeoxycholic acid; TCA, taurocholic acid; GCDCA, glycochenodeoxycholic acid; GCA, glycocholic acid; CDCA, chenodeoxycholic acid; CA, cholic acid; 3-oxo-CA, 3-oxo-cholic acid; 7-oxo-DCA, 7-oxo-deoxycholic acid; 3-oxo-CDCA, 3-oxo-chenodeoxycholic acid; 7-oxo-LCA, 7-oxo-lithocholic acid; α MCA, alpha-muricholic acid; β MCA, beta-muricholic acid; ω MCA, omega-muricholic acid; HCA, hyocholic acid; DCA, deoxycholic acid; LCA, lithocholic acid; MDCA, murideoxycholic acid; HDCA, hyodeoxycholic acid; UDCA, ursodeoxycholic acid; Iso-CA, iso-cholic acid; Iso-CDCA, iso-chenodeoxycholic acid.

Table 2. FXR and TGR5 agonists and antagonists.

Compound	Chemical Class or Synonym	Nature	Reference
FXR AGONISTS			
Chenodeoxycholic acid (CDCA)	3 α ,7 α -dihydroxy-5 β -cholanoic acid	Natural bile acid	(274, 320, 434)
Obeticholic acid (OCA)	INT-747; 6 α -ethyl-chenodeoxycholic acid (6-ECDCA)	Semi-synthetic bile acid (Intercept Pharmaceuticals)	(328)
GW4064	Isoxazole	Small molecule	(275)
Tropifexor	LJN452	Small molecule	(417)
Nidufexor	LMB763	Small molecule	(66)
Cilofexor	GS-9674	Small molecule	(415)
EDP305		Small molecule	(103)
PX20606	Px-102	Small molecule	(148)
FXR-450	WAY-362450 XL335, Turofexorate	Small molecule	(111)
Fexaramine	Benzopyran	Small molecule	(93)
FexD	Deuterated Fexaramine analogue	Small molecule	(121)
FXR ANTAGONISTS			
Tauro- β -muricholic acid (T β MCA)		Natural bile acid	(250)
Glycoursodeoxycholic acid (GUDCA)		Natural bile acid	(404)
Gly-MCA (Intestine-selective)	Glycine- β -muricholic acid	Modified bile acid	(194)
Guggulsterone	Z-guggulsterone 4,17(20)-pregnadiene-3,16-dione	Natural sterol (guggul tree)	(421, 453)
TGR5 AGONISTS			
Lithocholic acid (LCA)	3 α -hydroxy-5 β -cholanoic acid	Natural bile acid	(203)
Deoxycholic acid (DCA)	3 α ,12 α -dihydroxy-5 β -cholanoic acid	Natural bile acid	(203)
INT-777	6 α -ethyl-23(S)-methylcholic acid (S-EMCA)	Semi-synthetic bile acid	(329, 410)
BAR501	6 β -ethyl-3 α ,7 β -dihydroxy-5 β -cholan-24-ol	Semi-synthetic bile acid	(354)
SB-756050	1,4-bis{[3,4-bis(methyloxy)phenyl]sulfonyl}hexahydro-1H-1,4-diazepine	Small molecule	(168)
Oleanolic acid		Triterpene	(368)
DUAL FXR AND TGR5 AGONISTS			
INT-767	6 α -ethyl-3 α ,7 α ,23-trihydroxy-24-nor-5 β -cholan-23-sulfate	Semi-synthetic bile acid	(358)

Table 3. FXR agonists in clinical trials.

Drug	NCT Number	Acronym	Disease	Phase, Status	Outcome	(n)	Ref.
OCA, placebo	00501592		T2DM, NAFLD	II, Completed	Improved insulin sensitivity and reduced hepatic inflammation and fibrosis.	64	(305)
OCA, placebo	01265498	FLINT	NAFLD, NASH	II, Completed	Improved liver histology and serum biochemistry, weight loss, increased VLDL and LDL, decreased HDL, pruritus.	283	(58, 149, 311, 384)
OCA, placebo	01473524	POISE	PBC	III, Completed	Decreased serum ALP and bilirubin, improvement or stabilization of disease features, pruritus, fatigue.	217	(39, 312, 416)
OCA	01585025	OBADIAH1	Primary and Secondary BA Malabsorption, Chronic Diarrhea	II, Completed	Increase in FGF19 levels, reduced BA synthesis, reduced TGs, clinical improvements, increase in total and LDL cholesterol.	35	(431)
OCA, placebo	01625026	OCABSGS	Obesity, Gallstones	II, Completed	Increased biliary FGF19, decreased biliary BAs, higher cholesterol saturation index, increased risk of gallstone formation.	40	(3)
OCA	01904539		Liver Cirrhosis	I, Completed	Hepatic impairment increases by 2-fold the exposure of the liver to the drug.	32	(101)
OCA, placebo	02177136	AESOP	PSC	II, Active not recruiting	Sustained reduction of serum ALP, pruritus.	77	(228)
OCA, placebo	02548351	REGENER-ATE	NASH	III, Active, not recruiting	Improvement of liver fibrosis (interim analysis) while the NASH resolution endpoint was not met.	2480	(351, 466)
Cilofexor, placebo	02854605		NASH	II, Completed	Reduction of hepatic fat and serum BAs, improvement in hepatic biochemistry, pruritus.	140	(323)
Cilofexor, placebo	02943460	PBC-Phase 2	PSC	II, Active, not recruiting	Significant improvement of plasma and liver biochemistry, as well as in cholestasis markers. Treatment well tolerated.	52	(415)

OCA, obeticholic acid; T2DM, type 2 diabetes mellitus; NAFLD, nonalcoholic fatty liver disease; FLINT, The farnesoid X receptor ligand obeticholic acid in NASH treatment trial; NASH, nonalcoholic steatohepatitis; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; POISE, phase 3 study of obeticholic acid in patients with primary biliary cirrhosis; PBC, primary biliary cholangitis; ALP, alkaline phosphatase; OBADIAH1, obeticholic acid in bile acid diarrhea; FGF19, fibroblast growth factor 19; BA, bile acid; TGs, triglycerides; OCABSGS, obeticholic acid in bariatric and gallstone disease; AESOP, obeticholic acid in primary sclerosing cholangitis; PSC, primary sclerosing cholangitis; REGENERATE, randomized global phase III study to evaluate the impact on NASH with fibrosis of obeticholic acid treatment.

