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Review

Regulation of bile acid synthesis: pathways, nuclear receptors, and mechanisms

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1. Pathways of bile acid synthesis

Cholesterol degradation to bile acids in the liver can be initiated by either cholesterol 7α-hydroxylase (CYP7A1) of the classic (neutral) pathway, or by mitochondrial sterol 27-hydroxylase (CYP27A1) of the alternative (or acidic) pathway. In the classic pathway, modification of the sterol nucleus including saturation of the double bond, epimerization of the 3β-hydroxyl group, and hydroxylation at the 7α and 12α-positions precedes oxidative cleavage of the side chain. In the alternative pathway, side-chain oxidation precedes steroid ring modification.

1.1. The classic bile acid biosynthetic (neutral) pathway

The classic bile acid synthesis pathway consists of a cascade of fourteen steps catalyzed by enzymes located in the cytoplasm, microsomes, mitochondria and peroxisomes. Fig. 1 is an abbreviated version of this complex metabolic pathway. Detailed description of the enzymes involved and reactions catalyzed can be found in a recent review [1]. In the liver, cholesterol is converted to 7α-hydroxylcholesterol by a microsomal enzyme, cholesterol 7α-hydroxylase, the rate-limiting enzyme of the pathway, which is then converted to 7α-hydroxy-4 cholesten-3-one by a microsomal 3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase/isomerase (HSD3B7). Two cytosolic enzymes, Δ^{4-3}-oxosteroid-5β-reductase (AKR1D1) and 3α-hydroxysteroid dehydrogenase (AKR1C4), reduce 7α-hydroxy-4-cholesten-3-one to 5β-cholestan-3α,7α-diol, a precursor of chenodeoxycholic acid (CDCA). For the synthesis of cholic acid (CA), 7α-hydroxy-4-cholesten-3-one is first hydroxylated at the C-12 position by a microsomal sterol 12α-hydroxylase (CYP8B1), and then reduced to 5β-cholestan-3α,7α,12α-triol by AKR1D1 and AKR1C4. Mitochondrial sterol 27-hydroxylase then oxidizes the steroid side-chain of 5β-cholestane-3α,7α-diol and 5β-cholestane-3α,7α,12α-triol (Fig. 1). This enzyme incorporates a hydroxyl group to the C_{27} position, which is subsequently oxidized to an aldehyde and then to a carboxyl group. The products, 3α,7α,12α-trihydroxy-5β-cholestanoic acid and 3α,7α-dihydroxy-5β-cholestanoic acid, respectively, are ligated

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Abbreviations: ABCA1, ATP binding cassette protein A1; AKR1D1, Δ^{4-3}-oxosteroid-5β-reductase; AKR1C4, 3α-hydroxysteroid dehydrogenase; Apo, apolipoprotein; ASBT, apical sodium-dependent bile salt transporter; BARE, bile acid response element; BACS, bile acid CoA synthase; BAT, bile acid CoA amino acid *N*-acetyltransferase; BSEP, bile salt expert pump; CA, cholic acid; CAR, constitutive androgen receptor; CBP, cAMP response element binding protein binding protein; CDCA, chenodeoxycholic acid; CETP, cholesterol ester transfer protein; COUP-TFII, chicken ovalbumin upstream transcription factor II; CREB, cAMP response element binding protein; CTX, cerebrotendinous xanthomatosis; CYP7A1, cholesterol 7α-hydroxylase; CYP8B1, sterol 12α-hydroxylase; CYP27A1, sterol 27-hydroxylase; CYP7B1, oxysterol 7α-hydroxylase; CYP39A1, 24-hydroxycholesterol 7α-hydroxylase; DBP, D-site binding protein; DHEA, dehydroepiandrosterone; DR, direct repeat; FGF19, fibroblast growth factor 19; FGFR4, FGF receptor 4; FXR, farnesoid X receptor; FTF, α-fetoprotein transcription factor; HNF4α, hepatocyte nuclear factor 4α; 3β-HSD, 3β-hydroxysteroid dehydrogenase/isomerase; HSD3B7, 3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase/isomerase; IBABP, ileum bile acid binding protein α; IL-1β, interleukin 1β; JNK, Jun N-terminus kinase; LPL, lipoprotein lipase; LXR, liver X receptor; MEKK1, MAPK kinase kinase 1; MKK4, MAPK kinase 4; MDR, multidrug resistant protein; MRP, MDR related protein; NTCP, Na^{2+}-dependent taurocholate co-transport peptide; OATP2, organic anion transport protein 2; PCN, pregnenolone 16α-carbonitrile; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, PPARγ co-activator 1α; PLTP, phospholipid transfer protein; PPAR, peroxisome proliferator activated receptor; PXR, pregnane X receptor; RAR, retinoic acid receptor; RCT, reverse cholesterol transport; SHP, small heterodimer partner; SR-B1, scavenger receptor type B1; SREBP, sterol response element binding protein; SULT, DHEA sulfate transferase; TNFα, tumor necrosis factor α; UDCA, ursodeoxycholic acid; UGT2B4, UDP-glucuronosyl transferase.

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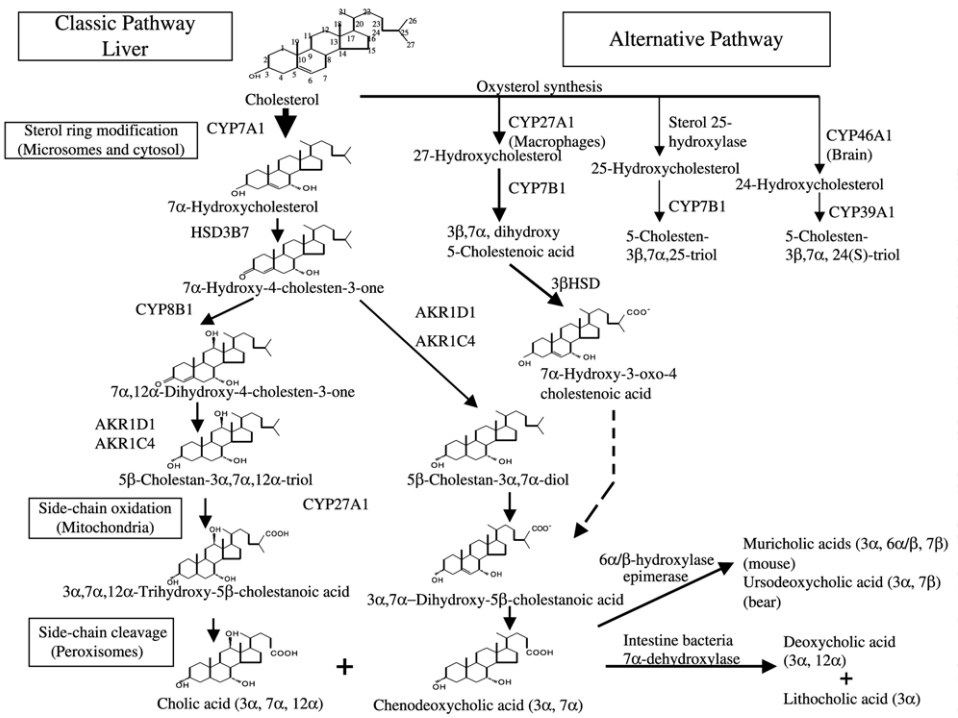

Fig. 1. Bile acid biosynthetic pathways. The classic pathway of bile acid biosynthesis is only present in hepatocytes. The alternative pathway exists in all tissues. Only major regulatory steps and enzymes are shown. The classic pathway synthesizes two primary bile acids, cholic acid and chenodeoxycholic acid. Oxysterols produced in the peripherial tissues may be transported to hepatocytes and converted to CDCA and CA. Primary bile acids are conjugated with glycine or taurine and excreted into the digestive system. Some conjugated bile acids are de-conjugated and converted to the secondary bile acids (damaged), deoxycholic acid and lithocholic acid, by 7α-dehydroxylase in intestinal bacterial flora. CDCA is converted to muricholic acids in the mouse and ursodeoxycholic acid in the bear. See text for detail description and abbreviation list for acronyms.

to coenzyme A by bile acid CoA ligase activity catalyzed by either a bile acid CoA synthetase (BACS) or very long chain acyl CoA synthetase homology 2. The cholestanoyl-CoAs are subsequently transported into peroxisomes where the side-chain is shortened by one cycle of β-oxidation to release a propionyl-CoA, and the product cholyl-CoA or chenodeoxycholyl-CoA. Four peroxisomal very long chain fatty acid β-oxidation enzymes, 2-methylacyl-CoA racemase, branched-chain acyl CoA oxidase 2, D-type bifunctional enzyme, and thiolase 2 (also known as sterol carrier protein κ) are involved in β-oxidation reactions. To increase the solubility for secretion into the bile, CoA derivatives are conjugated at C_{24} with either glycine or taurine by bile acid CoA: amino acid N-acyltransferase (BAT). Under physiological pH, bile acids form Na^{2+} salts, and are referred to as bile salts.

In the intestine, some conjugated CA and CDCA are de-conjugated and converted to the secondary bile acids, deoxycholic acid (DCA, 3α,12α) and lithocholic acid (LCA, 3α), respectively, by 7α-dehydroxylase in the intestinal bacteria flora, and are excreted into feces. Most CA and CDCA (about 95%) are quantitatively reabsorbed in the intestine and transported back to the liver via portal blood circulation.

1.2. Alternative bile acid biosynthetic (acidic or sterol 27-hydroxylas) pathway

Cholesterol is also oxidized by sterol 27-hydroxylase (CYP27A1) to 27-hydroxycholesterol and 3β-hydroxy-5-cholestenoic acid. These two compounds are converted to 7α,27-dihydroxycholesterol and 3β,7α-dihydroxy-5-cholestenoic acid, respectively, by oxysterol 7α-hydroxylase (CYP7B1). These oxidized metabolites are produced mainly in the peripheral tissues. Other enzymes involved in the alternative pathway are not well defined although many predicted intermediates of the alternative pathways have been identified in HepG2 cells and human hepatocytes. Since both CYP27A1 and CYP7B1 are expressed in various tissues and only the liver has the complete set of bile acid biosynthetic enzymes, these oxidized sterols must be transported to the liver in order to be converted to bile acids. The relative contribution of the classic and alternative pathways to overall bile acid synthesis is not clear. The classic pathway may be the main pathway that is highly regulated under physiological conditions, whereas the alternative pathway may contribute very little to overall bile acid synthesis under normal condition in humans, but may become the major bile acid biosynthetic pathway in

patients with liver diseases. In humans, CA and CDCA are synthesized in about equal amounts. In the mouse and bear, CDCA is converted to muricholic acids (3α,6α/β,7β) and ursodeoxycholic acid (3α,7β) (UDCA), respectively. Muricholic acids and UDCA are soluble and non-cytotoxic. Human livers synthesize very small amount of UDCA. UDCA is a therapeutic drug approved for treating gallstone disease and primary biliary cirrhosis [2].

1.3. Other hydroxylase pathways

Cholesterol is also oxidized to 25-hydroxycholesterol, 27-hydroxycholesterol, and 24-hydroxycholesterol, in liver, lung and brain, respectively. Oxysterols generated in the extrahepatic tissues and organs may be transported to the liver and converted to bile acids. Oxidation of cholesterol is an important mechanism for transport and disposal of biologically active oxysterols, which are potent regulators of cholesterol metabolism [3].

1.3.1. Sterol 25-hydroxylases

In mouse livers, the major cytochrome P450 drug metabolizing enzyme, CYP3A11 is able to catalyze 25-hydroxylation of 5β-cholestan-3α,7α,12α-triol to 5β-cholestan-3α,7α,12α,25-tetrol, which is then converted to cholic acid [4]. Another enzyme, microsomal cholesterol 25-hydroxylase is a none-heme iron protein that hydroxylates cholesterol to 25-hydroxycholesterol in different tissues [5]. 25-Hydroxycholesterol is converted to 5β-cholesten-3α,7α,25-triol by CYP7B1 and subsequently converted to bile acids in the liver. However, the 25-hydroxylase pathway may not contribute significantly to bile acid synthesis in humans [6].

1.3.2. Sterol 24 hydroxylase

Microsomal sterol 24-hydroxylase (CYP46A1) converts cholesterol to 24(*S*)-hydroxycholesterol, a cerebrosterol found in the brain and spinal cord [7]. CYP46A1 is expressed at 100-fold higher levels in the brain than in the liver. Mice lacking the Cyp46a1 gene have normal bile acid synthesis, but markedly reduced cholesterol synthesis and 24-hydroxycholesterol levels in the brain [8]. This enzyme may play a role in cholesterol turnover in the brain. An oxysterol 7α-hydroxylase (CYP39A1) specific for hydroxylation of 24-hydroxycholesterol has been identified [9]. The 24-hydroxylase pathway contributes very little to overall bile acid synthesis.

2. Nuclear receptor regulation of bile acid synthesis

The enterohepatic circulation of bile acids is an important physiological process that generates bile flow and feedback controls bile acid synthesis. The rate of bile acid synthesis, bile acid composition, and bile acid pool size vary significantly depending on the species, sexes, genetics, pathophysiological conditions, and environmental factors such as diets and drugs [10,11]. Many nuclear receptors have been found to play pivotal roles in regulating transcription of the genes involved in bile acid synthesis [12,13]. In general, hydrophobic bile acids (CA, CDCA, DCA and LCA) are potent inhibitors of bile acid biosynthesis, whereas hydrophilic bile acids, such as 7β-bile acids, e.g. ursodeoxycholic acid and β-muricholic acids are not. Chiang and coworkers proposed that bile acids might bind to a bile acid receptor that interacts with a bile acid responsive protein and inhibits its trans-activation of the CYP7A1 gene [14,15]. This nuclear receptor-mediated mechanism is supported by recent identification of several nuclear receptors as bile acid receptors [12,13,16].

2.1. Nuclear receptors

Nuclear receptors are ligand-activated transcription factors that regulate many genes involved in cell growth, differentiation, and metabolism [17–19]. There are 48 nuclear receptor genes in the human genome. Nuclear receptors that have no identifiable ligand are referred to as orphan receptors (Class II receptors) [18,20,21]. Potential ligands of several orphan receptors identified are small lipid metabolites. These 'adopted' receptors, including farnesoid X receptor (FXR), liver orphan receptor (LXR), and peroxisome proliferators-activated receptors (PPARs), form heterodimers with retinoid X receptor (RXR) and bind to direct repeats of AGGTCA-like sequences [19]. The nuclear receptor has a modular structure that consists of an N-terminal variable activation function 1 domain, a conserved Zn^{2+} finger DNA-binding domain, a hinge domain, a highly conserved ligand-binding domain, and a C-terminal activation function 2 domain. In general, a nuclear receptor binds to co-repressor in the absence of a ligand. Upon binding of a ligand, a nuclear receptor undergoes conformational changes and releases a co-repressor and recruits a co-activator to the AF2 domain and activates gene transcription [22,23].

Three nuclear receptors have recently been identified as the bile acid-activated receptors. FXR regulates bile acid synthesis, transport and absorption, as well as reverse cholesterol transport (RCT) [24–26]. Pregnane X receptor (PXR), or its human ortholog, steroid and xenobiotic receptor (SXR) regulates lithocholic acid and drug metabolisms. [27,28]. Vitamin D receptor (VDR) regulates calcium and phosphate homeostasis [29]. Bile acid metabolites also activate LXRα, which is an oxysterol receptor that plays a central role in lipid metabolism [30–33]. Hepatocyte nuclear factor 4α (HNF4α) binds fatty acids and plays important roles in lipoprotein metabolism [34,35]. Chicken ovalbumin upstream promoter transcription factor II (COUP-TFII) (or apolipoprotein A1 regulatory protein-1) is an orphan receptor that regulates lipoprotein metabolism [36,37]. Peroxisome proliferator-activated receptors (PPARα, γ, δ) are activated by fatty acids and fibrates and

induce genes involved in fatty acid transport and oxidation, and energy metabolism in liver, muscle and adipocytes [38,39]. These nuclear receptors regulate key bile acid biosynthetic genes [13], and have been referred to as the 'metabolic receptors' that coordinately regulates a network of genes involved in integrated control of energy metabolism, bile acid metabolism, lipoprotein metabolism, and triglyceride metabolism [40].

2.2. Regulation of key genes

2.2.1. CYP7A1

Promoter mapping and analysis have identified two potential transcription factor-binding regions in the CYP7A1 promoter [14]. These two highly conserved sequences (named bile acid response elements, BARE-I and BARE-II) are essential for basal transcription and also conferring bile acid inhibition [14,41]. The BARE-I contains a direct repeat separated by four bases (DR4), which binds COUP-TFII and markedly stimulates CYP7A1 gene transcription [41]. The DR4 in mouse BARE-I also binds LXRα, which induces CYP7A1 to convert excess cholesterol to bile acids in wild-type mice [42] but not in Lxrα null mice, which accumulates cholesteryl esters in the liver [43]. In contrast, the human CYP7A1 gene lacks an LXRα binding site and is not regulated by cholesterol [44,45]. The BARE-II contains overlapping DR1 and DR5 motifs that bind HNF4α and retinoic acid receptor α (RARα), respectively. Conditional knockout of Hnf4α gene in mouse liver reduced serum cholesterol and triglyceride levels and Cyp7a1 mRNA expression, suggesting that HNF4α plays a critical role in bile acid metabolism and lipid homeostasis [35]. The factor that binds to the BARE-II (HNF4α) interacts with the factor that binds to the BARE-I (COUP-TFII) and synergistically stimulates CYP7A1 gene transcription [46,47]. The BARE-II also contains a binding site for the NR5A2 family of monomeric orphan receptors including rat and human α-fetoprotein transcription factor (FTF) [48], mouse liver related homologue (LRH) [49,50], and human cholesterol 7α-hydroxylase promoter factor [51]. FTF is a weak transcription factor that has been referred to as a competent factor for LXRα regulation of the CYP7A1 gene [52].

Bile acid-activated FXR inhibits CYP7A1 gene transcription and the negative FXR response element has been mapped to the BARE-II. However, FXR does not bind to the BARE-II and apparently inhibits the CYP7A1 gene by an indirect mechanism (Section 3) [48]. Chiang and coworkers reported that pregnenolone 16α-carbonitrile (PCN) or dexamethasone strongly inhibited CYP7A1 activity, mRNA and protein expression in rat livers [53,54]. Recent studies show that CYP7A1 gene expression is not inhibited by PCN in Pxr null mice, suggesting that PXR may mediate PCN inhibition of CYP7A1 gene expression [27,28]. However, the mechanism by which PXR inhibits the CYP7A1 gene transcription is not known.

CYP7A1 activity and mRNA expression shows strong diurnal expression patterns. The expression is the highest at midnight and decreases during the day [53,55]. The circadian rhythm of CYP7A1 gene expression coincides with diurnal expression pattern of the PAR family of basic leucine zipper (bZIP) transcription factors, albumin D-site binding protein (DBP). DBP binds to the CYP7A1gene and stimulates CYP7A1gene transcription [56,57]. Parenteral nutrition and restricted feeding can uncouple liver clocks from synchronization by the central pacemaker in the suprachiasmatic nucleus (SCN) and alter CYP7A1 gene expression [58–61]. CYP7A1 gene expression is increased in fasted livers, and is linked to the induction of PPARγ coactivator-1α (PGC-1α) and cAMP in fasting response [62]. PGC-1α is a versatile coactivator that regulates energy metabolism in response to cold, fasting and other stresses [63]. PGC-1α interacts with several nuclear receptors, including PPARγ, glucocorticoid receptor, HNF4α, LXRα, and RXRα [63]. HNF4α is believed to be the main target of PGC-1α in induction of the phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase genes involved in gluconeogenesis [64,65]. Similarly, PGC-1α enhances HNF4α induction of the CYP7A1 gene [62]. Insulin is known to inhibit bile acid synthesis by inhibiting CYP7A1-gene transcription [66,67], likely by a phosphoinosital-3-kinase/AKT (protein kinase B) mechanism that inhibits the forkhead transcription factor, FOXO1, and PGC-1α [68]. PPARα and its agonists, fibrates, inhibit the CYP7A1 gene by inhibiting HNF4α activation of CYP7A1 gene transcription [69]. The CYP7A1gene is a negative acute phase gene that is repressed by lipopolysaccharide (LPS) and inflammatory cytokines (TNFα and IL-1β) [70]. During acute phase response, HMG-CoA reductase and LDL receptor are induced and bile acid synthesis is repressed and leads to an increase of cholesterol synthesis and hypercholesterolemia [71].

Genetic ablation of the Cyp7a1 gene in mice causes marked decrease of bile acid synthesis, malnutrition phenotypes, and postnatal lethality in mice [72]. A mutation of the CYP7A1 gene has recently been identified in a family of patients with hypercholesterolemia, premature gallstone disease and premature atherosclerosis [73]. This supports the hypothesis that CYP7A1 plays a critical role in maintaining bile acid and cholesterol homeostasis, and that a deficiency of CYP7A1 would lead to cardiovascular and gallstone diseases in humans. However, residual CYP7A1 activity remained in the liver may be sufficient for the survival of these patients.

2.2.2. CYP8B1

CYP8B1 is required for synthesis of cholic acid and determines the ratio of CA to CDCA, which may affect intestinal cholesterol absorption. Similar to CYP7A1, CYP8B1 gene transcription is strongly inhibited by bile acids. In contrast to their stimulatory effects on CYP7A1, cholesterol and thyroid hormones decrease CYP8B1

expression in the rat [74]. Insulin markedly inhibits CYP8B1 activity and mRNA levels [75]. Fasting of rats and mice leads to a several-fold increase in both CYP8B1 enzyme activity and mRNA levels. The CYP8B1 activity and mRNA exhibit a marked circadian rhythm. The rhymicity of CYP8B1 and CYP7A1 activity may alter the CA/CDCA ratio that regulates bile acid synthesis. Glucagon and cAMP stimulate CYP8B1 mRNA expression and antagonize insulin suppression. Peroxisome proliferators have been shown to stimulate CYP8B1 activity and mRNA levels in rat livers and might mediate fasting-induced stimulation of CYP8B1 gene transcription [76]. The FTF and HNF4α bind to the CYP8B1 promoter and stimulate CYP8B1 gene transcription [77–79]. These two nuclear receptors may compete for binding to overlapping sequences and differentially regulate CYP8B1 gene transcription.

Genetic knockout of the Cyp8b1 gene in mice eliminates CA synthesis, but induces Cyp7a1 gene expression [80]. The induction of Cyp7a1 may be due to de-repression of the Cyp7a1 gene since most bile acids in Cyp8b1 − /− mice are muricholic acids, which are not FXR ligands. Cholic acid is more efficient in facilitating absorption of cholesterol in the intestine. Lack of cholic acid reduces intestinal cholesterol absorption and increases hepatic cholesterol synthesis in Cyp8b1 null mice. No human CYP8B1 gene mutation has been reported.

2.2.3. CYP27A1

CYP27A1 has broad substrate specificity and is expressed in many tissues including the vascular endothelium [81], atherosclerotic plaque [82,83], macrophages [84], and fibroblasts [85]. Mutations of the CYP27A1 gene have been found in patients with cerebrotendinous xanthomatosis (CTX), a rare autosomal recessive defect of cholesterol metabolism manifested by tendon xanthomatosis, progressive neurologic dysfunction, accumulation of cholesterol in the tissues, premature atherosclerosis, osteoporosis, and cholesterol gallstones [86–89]. A defect in CYP27A1 leads to excessive accumulation of 7α-hydroxycholesterol, 7α-hydroxy-4-cholesten 3-one, 5β-cholestane-3α,7α,12α-triol, cholesterol, and cholestanol. The synthesis of bile acids, particularly CDCA, is reduced and CYP7A1 activity is up regulated leading to the accumulation of both 7α-hydroxycholesterol and 7α-hydroxy-4-cholesten-3-one, the latter is converted to cholestanol. Despite the normal circulating cholesterol levels, CTX patients develop xanthoma and premature atherosclerosis. This may be due to the reduced elimination of cholesterol from macrophages by CYP27A1. Despite the link of the CYP27A1 mutations to CTX, the etiology of this disease is still not known. Disruption of the Cyp27a1 in mice markedly reduced bile acid synthesis and fecal bile acid excretion, but Cyp27a1 − /− mice do not accumulate cholestanol and do not exhibit the progressive neurological defects observed in CTX patients [90]. Recent reports suggest that 5β-cholestan-3α,7α,12α-triol is an endogenous ligand of PXR, which induces Cyp3a11 in mouse livers to convert the triol to 5β-cholestan-3α,7α,12α,25-tetrol [91,92]. This alternative bile acid synthesis pathway for cholic acid synthesis is absent in human livers because the triol is a weaker ligand of PXR in humans [91,92]. However, the cause of progressive neurological dysfunction in CTX remains unknown. The Cyp27a1 − /− mice have enlarged livers and kidneys, and have increased triglyceride levels, SREBP expression, fatty acid synthesis, cholesterol absorption, and cholesterol synthesis [93]. These phenotypes suggest that CYP27A1 may play a major role in cholesterol and triglyceride metabolism. Transcription of the CYP27A1 gene is suppressed by bile acids in rats [94]. Insulin suppresses CYP27A1 gene transcription to reduce bile acid synthesis and pool size [66]. Feeding of a high-cholesterol diet to rabbits stimulates CYP27A1 activity and increases bile acid pool size [95]. The CYP27A1 gene is a negative acute phase gene repressed by lipopolysaccharide and cytokines [96].

2.2.4. CYP7B1

CYP7B1 has broad substrate specificity and is widely distributed in most organs. CYP7B1 catalyzes 7α-hydroxylation of 27- and 25-hydroxycholesterol, dehydroepiandrosterone (DHEA) and pregnenolone [97]. Disruption of the cyp7b1 gene in mice does not show the severe phenotypes as seen in cyp7a1 − /− mice [98]. Cholesterol contents and bile acid synthesis are normal in these mice. In Cyp7b1 − /− mice, DHEA hydroxylation is abolished in the brain, prostate, and other tissues [99]. Interestingly, Cyp7b1 mRNA and activity are widely expressed during ontogeny, but shows more restricted expression in the hippocampus in newborn mice [100]. CYP7B1 is highly active in hydroxylation of DHEA to 7α-hydroxyDHEA. DHEA is a neuroactive steroid in the brain astrocytes (glial cells) and neurons, and is converted to androgens, estrogens, or other metabolites. CYP7B1 metabolizes 5α-androstene-3β,17β-diol, a selective endogenous ligand of estrogen receptor β (ERβ). CYP7B1 also metabolizes 17β-estradiol, a ligand of both ERα and ERβ. Therefore, CYP7B1 regulates the availability of the endogenous ER ligands in the steroidogenic tissues. ERβ null mice have proliferation in ventral prostate [101]. It has been suggested that CYP7B1 may regulate ERβ function by regulating its ligand [102]. It seems that in addition to bile acid synthesis, CYP7B1 also plays important roles in steroid metabolism in the steroidogenic tissues, in detoxification of oxysterols, and in regulation of lipid metabolism.

A mutation of the CYP7B1 gene has been identified in a child with a severe defect of bile acid synthesis, neonatal cholestasis, and cirrhosis [103]. Extremely highly levels of 24-, 25- and 27-hydroxycholesterol accumulate in the serum, and 3β-hydroxy-5-cholestenoic and 3β-hydroxy-5-cholenoic acids in the urine. These oxysterols and monohydroxylated bile acids are highly toxic and may cause

severe liver injury in this patient. This finding supports that a major function of CYP7B1 may be to detoxify oxysterols. The severe phenotypes in this infant patient are very different from those of Cyp7b1 null mouse. It is possible that CYP7B1 is expressed very early in life, when CYP7A1 has not expressed yet, to produce bile acids via the alternative pathways. This is in contrast to the late expression of Cyp7b1 in mice [72].

3. Bile acid regulation of lipid metabolism

Bile acids not only regulate bile acid synthesis, but also regulate other pathways in the enterohepatic system including bile acid transport and absorption, RCT, lipoprotein metabolism, triglyceride metabolism, and drug metabolism. Ablation of the Fxr gene in mice increases serum bile acid, cholesterol and triglycerides, and results in a proatherogenic serum lipoprotein profile, consistent with the roles of FXR in bile acid synthesis, excretion and lipid metabolism [104]. Fig. 2 shows FXR, LXR, PXR and PPAR target genes involved in bile acid metabolism, RCT, triglyceride metabolism, lipoprotein metabolism and drug metabolism.

3.1. FXR regulation of bile acid synthesis, transport and absorption

FXR plays a central role in regulation of bile acid synthesis and transport. FXR inhibits the CYP7A1 and CYP8B1 genes involved in bile acid synthesis. On the other hand, FXR stimulates bile acid conjugation by inducing BCAS and bile acid CoA:amino acid *N*-acetyltransferase (BAT). FXR markedly induces bile salt export pump (BSEP, ABCB11) [105], which is the principle bile acid transporter for excretion of bile acid conjugates. FXR also induces multidrug resistance associated protein 2 (MRP2, ABCC2) for transport of sulfate, glutathione or glucuronide conjugated anionic compounds including bile acids [106]. Bile acids facilitate the biliary excretion of phosphatidylcholine by inducing multi-drug resistant protein 2 (MDR2), and cholesterol by inducing ABCG5 and G8 half transporters [107]. Bile acids are quantitatively reabsorbed in the intestine, mostly in the ileum by an active transport process involving the apical sodium-dependent bile salt transporter (ASBT) [108]. FXR induces ileum bile acid binding protein (IBABP) [109], which binds bile acids and protects enterocytes for cytotoxic effect of bile acids. Bile acids are excreted into portal circulation, transported back to the liver, and reabsorbed into hepatocytes by sinusoidal Na^{2+}-dependent taurocholate cotransport peptide (NTCP). FXR inhibits NTCP and may protect hepatocytes from accumulating high levels of toxic bile acids during inflammation [110]. FXR also induces organic anion transport protein 2 (OATP2), which takes up bile acids from the sinusoid. FXR induces DHEA-sulfate transferase (SULT2A1), which transfers a sulfate group to the secondary bile acids for rapid excretion into bile via MRP2. Guggulsterone, a FXR antagonist, has been used as a lipid-lowering drug in humans [111]. Guggulsterone inhibits IBABP gene in the intestine [112], and BSEP and CYP7A1 gene expression in the liver [113–115]. Selective FXR modulators may be useful for lipid-lowering [116].

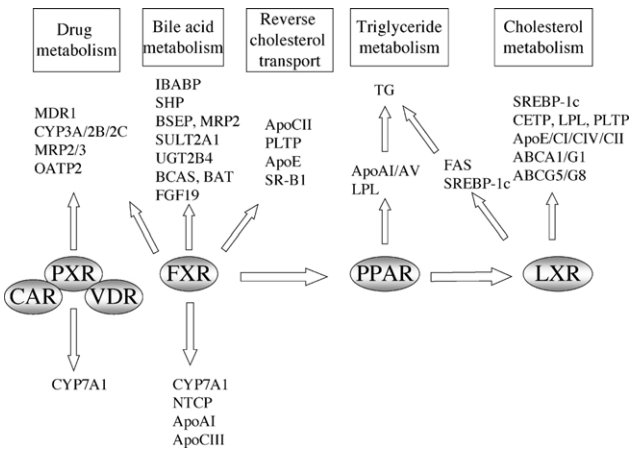

Fig. 2. Nuclear receptor regulation of the genes involved in bile acid metabolism, reverse cholesterol transport, cholesterol metabolism, triglyceride metabolism and drug metabolism. Target genes that are regulated by nuclear receptors, CAR/PXR/VDR, FXR, PPAR and LXR are grouped according to their roles in drug metabolism, bile acid metabolism, reverse cholesterol transport, triglyceride metabolism and cholesterol metabolism. Upward arrows indicate induction and downward arrows indicate suppression of the target genes by each nuclear receptor. See text for detail description and abbreviation list for acronyms.

3.2. FXR and LXRα regulation of lipoprotein metabolism

Both FXR and LXRα play important roles in regulation of lipoprotein metabolism, RCT, and triglyceride metabolism. The target genes of FXR and LXR overlap indicating that these two receptors may coordinately regulate lipid metabolism. Both FXR and LXRα induce phospholipids transfer protein (PLTP) [117,118], ApoCII [119] and ApoE [120–122]. In addition, LXRα induces lipoprotein lipase (LPL) [123] and cholesteryl ester transfer protein (CETP) [124]. These genes are involved in RCT from peripheral tissues to the liver for conversion to bile acids. Ablation of the Fxr gene in mice increases plasma cholesterol and triglyceride, very low density lipoprotein (VLDL), and intestinal cholesterol absorption, but decreases expression of hepatic genes involved in RCT including hepatic lipase, cholesterol ester hydrolase, lecithin cholesteryl acyl transferase (LCAT), PLTP, and scavenger receptor type BI (SR-BI), a high density lipoprotein (HDL) receptor [125]. It has been reported that FXR inhibits ApoAI gene expression by direct binding to a negative element [126].

Oxysterols are derived from cholesterol and bile acid

synthesis pathways and are potent regulators of cholesterol synthesis and lipid metabolism. Oxysterols produced in macrophages and extrahepatic tissues are excreted into circulation and may be transported to the liver to be converted to bile acids. This is analogous to RCT and may be a defense against atherosclerosis. LXRα induces ABCA1 and ABCG1 [127], which effluxes cholesterol and phospholipids from macrophages and the peripheral tissues for synthesis of HDL [128]. HDL plays a central role in lipoprotein metabolism by providing apoCII and ApoE to VLDL and chylomicron (CM). Mutations of the ABCA1 gene have been identified in the Tangier disease patients who have severe defects in lipoprotein metabolism and atherosclerosis [128]. LXRα induces expression of the entire ApoE/C-I/C-IV/C-II gene cluster in mouse and human macrophages [129]. PPARγ has been implicated in the induction of LXRα [130]. In the intestine, LXRα and RXRα agonists induce ABCA1 [131], but the evidence against the role of LXR in the regulation of ABCA1 and cholesterol efflux has been reported [132]. Over expression of ABCG5/ABCG8 induces biliary cholesterol excretion, reduces fractional cholesterol absorption, and increases fecal bile acid excretion in mice [107]. LXRα induces ABCG5/G8 gene expression to excrete sitosterol (plant sterol) and may be also cholesterol, thus reducing intestinal absorption of dietary cholesterol [107]. Mutations of the ABCG5 and ABCG8 genes have been identified in sitosterolemia patients [133,134]. LXRα plays a major role in protecting against atherosclerosis and cardiovascular diseases [135].

3.3. FXR, LXRα, and PPAR regulation of triglyceride metabolism

Bile acid sequestrants and bile diversion are known to induce bile acid synthesis but increase serum triglyceride levels. CDCA and a FXR agonist, GW4064, reduce serum triglycerides in mice [136]. The FXR agonist reduces serum triglyceride levels by inducing ApoCII, a cofactor of LPL that hydrolyzes triglycerides carried by VLDL and CM in the epithelium of blood vessels in muscles and adipocytes [117], and inhibiting the ApoCIII gene [137]. PPAR agonists stimulate fatty acid oxidation and reduce serum triglyceride levels by inducing ApoAI, ApoAV and LPL. ApoAV is a newly identified lipoprotein that has been shown to reduce serum triglycerides [138]. PPARα and FXR induce ApoAV expression in the liver [139]. Interestingly, FXR induces human, but not mouse liver PPARα. It appears that FXR and PPARα may coordinately regulate triglyceride metabolism.

The LXRα agonists cause hypertriglyceridemia by inducing sterol response element binding protein 1c (SREBP-1c), which stimulates the genes involved in cholesterol and triglyceride synthesis [140]. Despite their adverse effects on hypertriglyceridemia, LXR agonists are potential therapeutic agents for dyslipidemia and atherosclerosis [141].

3.4. Bile acid regulation of drug metabolism

It has been known for a long time that PCN affects microsomal metabolism of steroids and bile acids in rodents [142,143]. PCN and dexamethasone markedly reduce CYP7A1 gene expression in rat livers [53,54]. Recent studies of Pxr null mice have uncovered a link between bile acids and drug metabolism [27,28]. PXR is activated by a large number of endogenous and exogenous compounds including steroids, drugs, and secondary bile acids (LCA and CDCA). PXR induces CYP3A family of enzymes involved in the metabolism of a wide variety of drugs and xenobiotics in the liver and intestine [16,91,92]. PXR, CAR (constitutive androgen receptor) and VDR induce CYP3A4 to convert CDCA to hyocholic acid and LCA to hyodeoxycholic acid in the liver and intestine. These soluble, nontoxic bile acids are conjugated by UDP-glucuronosyl transferase (UGT2B4) and excreted into bile or urine. PXR also induces drug transporters, MDR1, MRP3 and OATP2. Thus PXR coordinately regulate genes involved in bile acid synthesis, transport, and detoxification, thus protecting the liver and intestine from accumulating toxic bile acids. CYP3A4 is the most abundant P450 isozyme in human liver and intestine and metabolizes about 60% of prescription drugs, many of them are known to activate PXR. A potent PXR agonist, rifampicin has been used to treat pruritis in patients with intrahepatic cholestasis and primary biliary cirrhosis [144,145]. Selective PXR agonists with low hepatotoxicity may be developed for treating cholestatic pruritis.

3.5. Bile acid regulation of glucose metabolism

De Fabiani et al. recently reports that bile acids inhibit PEPCK gene transcription and may regulate gluconeogenesis during fasting-fed cycle [62]. In response to fasting, glucagons and cAMP are increased to activate CREB, which induces PGC-1α expression and gluconeogenesis [64]. It appears that the same mechanism also regulate CYP7A1 gene transcription in fasted state. HNF4α and PGC-1α may coordinately regulate bile acid synthesis and gluconeogenesis. It is intriguing that bile acids are able to inhibit HNF4α interaction with CBP or PGC-1α. However, the mechanism of bile acid disruption of HNF4α interaction with these co-activators is unknown. Nevertheless, this finding suggests that bile acids may regulate glucose and energy metabolism in response to fasting. In Type I diabetes, the increase of bile acid synthesis may facilitate intestinal cholesterol absorption, which contributes to hypercholesterolemia, whereas the induction of gluconeogenesis contributes to hyperglycemia. In Type II diabetes with insulin resistance, CYP7A1 gene expression may be reduced and cholesterol accumulation may contribute to

hypercholesterolemia. It has been reported that the control of lipid and glucose metabolism is tightly linked and activation of LXRα improve glucose tolerance through coordinate regulation of glucose metabolism in liver and adipose tissue [146]. All these point to coordinate regulation of bile acid synthesis and glucose metabolism, at least during post-absorptive state and starvation.

4. Mechanisms of bile acid feedback inhibition of gene transcription

It has been very difficult to decipher the mechanism of bile acid inhibition of CYP7A1 gene transcription. Many lines of evidence suggest that multiple mechanisms are involved in bile acid feedback inhibition of CYP7A1 gene transcription. These multifaceted regulatory mechanisms may be separated to SHP-dependent and SHP-independent mechanisms illustrated in Fig. 3.

4.1. SHP-dependent mechanism

It is thought that bile acid-activated FXR induces an atypical, negative nuclear receptor, SHP, which subsequently interacts with FTF and inhibits CYP7A1 gene transcription [49,50]. This cascade mechanism is supported by the lack of inhibition of CYP7A1 and induction of SHP mRNA expression by bile acid feeding in Fxr null mice [104]. Shp null mice fail to repress CYP7A1 in response to the FXR agonist, GW4064 as expected. Surprisingly, Shp null mice remain responsive to inhibition of CYP7A1 mRNA by bile acid feeding [147,148]. These mice have no severe phenotype and have only mild defects in bile acid synthesis. It is suggested that redundant pathways for bile acid inhibition of CYP7A1 may exist in Shp null mice, and the FXR agonist inhibits CYP7A1 via a SHP-dependent pathway [147]. However, the SHP-dependent mechanism suffers from the lack of specificity, because SHP is known to interact with most, if not all nuclear receptors. Being a negative regulator, SHP must be under a stringent control in vivo in order to prevent bile acids from inhibiting nuclear receptor-regulated genes involved in liver development, differentiation and metabolism. This gene induction mechanism may be a response to massive accumulation of cytotoxic bile acids by bile acid feeding in rodents. It is not certain that this mechanism is a physiological mechanism for bile acid feedback inhibition of bile acid synthesis in humans.

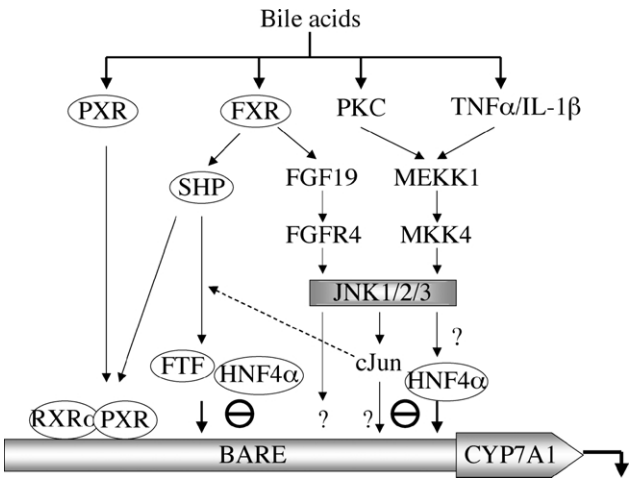

Fig. 3. Bile acid signaling pathways in bile acid feedback inhibition of CYP7A1 gene transcription. In SHP-dependent pathway, FXR induces SHP, which then inhibits FTF, HNF4α, or PXR trans-activation of the CYP7A1 gene. In SHP independent pathways, bile acids activate protein kinase C (PKC) and inflammatory cytokines (TNFα, and IL-1β), and initiates MAP kinase/JNK pathway. The downstream targets (cJun, HNF4α) of JNK1/2/3 is not certain. FXR also induces FGF19, which binds FGFR4 and activates a signaling pathway led to phosphorylation of JNK. LCA-activated PXR may bind to the BARE and directly inhibit the CYP7A1 gene. See text for detail description and abbreviation list for acronyms.

4.2. SHP-independent mechanisms

Bile acids are signaling molecules that have been shown to induce protein kinase C (PKC) and inhibit CYP7A1 gene expression via the cJun N-terminus kinase (JNK) pathway [149,150]. Bile acids are known to induce inflammatory cytokines, TNFα and IL-1β, in hepatic macrophages (Kupffer cells). These cytokines may cross the sinusoid and inhibit CYP7A1 gene expression in hepatocytes [151]. The JNK pathway may regulate CYP7A1 gene expression in Shp null mice [148]. The downstream target of the JNK pathways in bile acid inhibition of CYP7A1 gene expression is not certain. The JNK pathway may lead to inactivation of HNF4α and inhibition of CYP7A1 gene transcription [152]. It is possible that HNF4α is a primary target of JNK phosphorylation. It is known that HNF4α is phosphorylated by PKC, PKA, AMP kinase (AMPK), and tyrosine kinase to lower its DNA binding affinity and trans-activating activity. On the other hand, HNF4α is acetylated by histone acetyltransferase and is involved in pre-initiation complex assembly and chromatin remodeling [153,154]. Furthermore, FXR induces a fibroblast growth factor 19 (FGF19), which activates a surface fibroblast growth factor receptor 4 (FGFR4) signaling pathway leading to the inhibition of CYP7A1 via the JNK pathway [155]. It should be noted that SHP is not involved in this FXR-dependent pathway. Preliminary results from this laboratory suggest that LCA-activated PXR binds to the BARE-I of the CYP7A1 promoter and inhibits CYP7A1 gene transcription by both SHP-dependent and -independent pathways. SHP interacts strongly with PXR in the presence of a PXR ligand and inhibits CYP7A1 gene transcription. PXR strongly interacts with HNF4α in a ligand-dependent manner. Interestingly PXR strongly interacts with PGC-1α in the absence of a PXR ligand. LCA specifically disrupted PXR and PGC-1α interaction and resulted in inhibition of the CYP7A1 gene.

5. Conclusion and future perspectives

Cloning and genetic knockout of the CYP7A1 and other genes involved in bile acid synthesis and identification of human patients with mutations in these genes have greatly advanced our understanding of the regulatory mechanism of bile acid synthesis. A recent discovery that bile acids and oxysterols are the endogenous ligands of several nuclear receptors has generated a plethora of interest in bile acid research. These exciting advances have greatly improved our knowledge on hepatic lipid metabolism and homeostasis. However, most studies on bile acid synthesis and lipid metabolism are carried out using intact and genetic knock out mouse models. The phenotypes of Cyp7a1, Cyp7b1 and Cyp27a1 knockout mice are different from those observed in the human patients with respective mutations. Humans are very different from mice in bile acid synthesis and lipoprotein metabolism. Further study of bile acid synthesis in humans and identification of more human patients with defects in bile acid metabolism would help us to understand the molecular mechanisms of liver and cardiovascular diseases, such as atherosclerosis, hyperlipidemia, diabetes, cholestatic liver diseases, gallstone disease, and for developing new drug therapies targeted to nuclear receptors for lowering serum lipids and treating these diseases.

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