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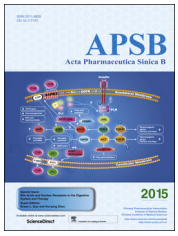

REVIEW

Farnesoid X receptor, the bile acid sensing nuclear receptor, in liver regeneration

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Abstract The liver is unique in regenerative potential, which could recover the lost mass and function after injury from ischemia and resection. The underlying molecular mechanisms of liver regeneration have been extensively studied in the past using the partial hepatectomy (PH) model in rodents, where 2/3 PH is carried out by removing two lobes. The whole process of liver regeneration is complicated, orchestrated event involving a network of connected interactions, which still remain fully elusive. Bile acids (BAs) are ligands of farnesoid X receptor (FXR), a nuclear receptor of ligand-activated transcription factor. FXR has been shown to be highly involved in liver regeneration. BAs and FXR not only interact with each other but also regulate various downstream targets independently during liver regeneration. Moreover, recent findings suggest that tissue-specific FXR also contributes to liver regeneration significantly. These novel findings suggest that FXR has much broader role than regulating BA, cholesterol, lipid and glucose metabolism. Therefore, these researches highlight FXR as an important pharmaceutical target for potential

Abbreviations: ABC, ATP-binding cassette; AMPK, AMP-activated protein kinase; BA, bile acid; CA, cholic acid; cAMP, cyclic adenosine monophosphate; CDCA, chenodeoxycholic acid; C/EBPβ, CCAAT-enhancer binding protein β; CTX, cerebrotendinous xanthomatosis; CYP7A1, cholesterol 7alpha-hydroxylase; CYP8B1, sterol 12α-hydroxylase; *Cyp*27-KO, sterol 27-hydroxylase–knockout; DDAH-1, dimethylarginineaminohydrolase-1; ERK1/2, extracellular signal-regulated kinase 1/2; FGF-15, fibroblast growth factor 15; FGFR4, FGF receptor 4; FOXM1b, forkhead boxm1b; FXR, farnesoid X receptor; *Fxr*-KO, *Fxr*-knockout; GPBAR1 or TGR5, G protein-coupled BA receptor 1; hep*Fxr*-KO, hepatocyte-specific *Fxr* knockout; HEX, hematopoietically expressed homeobox; JNK, c-Jun N-terminal kinase; KC, Kupffer cells; KO, knockout; MAPK, mitogen-activated protein kinase; MRP3, multidrug resistance associated protein 3; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor-κB; PH, partial hepatectomy; Rb, retinoblastoma; SHP, small heterodimer partner; STAT3, signal transducer and activator of transcription 3; TH, thyroid hormone; THR, TH receptor; WT, wild type

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use of FXR ligands to regulate liver regeneration in clinic. This review focuses on the roles of BAs and FXR in liver regeneration and the current underlying molecular mechanisms which contribute to liver regeneration.

1. Introduction

The liver is a central organ for homeostasis with unique capacities of regeneration following loss through trauma or surgical resection in human body. Liver regeneration has been studied intensively since the introduction of a rodent partial hepatectomy (PH) model, in which 2/3 of the liver mass is removed. Unlike anatomic true regeneration, the expanding liver does not regain its original gross anatomic structure. Following 2/3 PH, replacement of liver mass is achieved by proliferation of mature hepatocytes which each undergoes an average of 1.4 rounds of replication to re-establish normal liver weight within 5–7 days (8–15 days in humans)[1,2]. The process of liver regeneration consists of several well-orchestrated phases, with rapid induction of proliferative factors activating the quiescent hepatocytes and priming their subsequent proliferation, followed by renewed quiescence. Many details of liver regeneration have been elucidated based on the PH model in various genetically knockout mice, and several signaling pathways have been demonstrated in the progress of initiation, promotion and termination of liver regeneration over these years[2,3]. Nevertheless, the exact molecular mechanisms from the stimulation of liver regeneration to the termination of this process remain incompletely understood.

Farnesoid X receptor (FXR, gene symbol *NR1H4*/*Nr1h4*) is a ligand-activated transcription factor and a member of the nuclear receptor superfamily, which was initially cloned in 1995[4,5]. FXR is highly expressed in the liver, intestine, kidney and adrenals. As a transcription factor, FXR induces the small heterodimer partner (SHP, gene symbol *NR0B2*/*Nr0b2*) in liver that downregulates the expression of cholesterol 7α-hydroxylase (*CYP7A1*/*Cyp7a1*) and sterol 12α-hydroxylase (*CYP8B1*/*Cyp8b1*) genes encoding enzymes that synthesize bile acids from cholesterol. Thus, FXR is known to critically regulate nascent bile formation and bile acid (BA) enterohepatic circulation. Great progress has been made in the understanding of the physiological roles of FXR during the last two decades. Up to now, FXR has been shown to have crucial roles in controlling BA homeostasis, lipoprotein and glucose metabolism, hepatic regeneration, carcinogenesis, intestinal bacterial growth and the response to hepatotoxins[6–8]. Recent evidence suggests that the BAs-FXR interaction is highly involved in the pathophysiology of hepatic regeneration[9].

In the current review, we will discuss the current knowledge of BAs-FXR interactions in the pathology as well as physiology of the hepatic regeneration and the proposed underlying mechanisms.

2. The role of FXR in liver regeneration

2.1. BA regulates liver regeneration mainly through FXR

BAs are synthesized from cholesterol in hepatocytes, conjugated to either glycine or taurine and actively secreted *via* ATP-binding cassette (ABC) transporters on the canalicular membrane into the bile. BA synthesis represents a major output pathway of cholesterol from the body. BAs are detergent molecules and form mixed micelles with cholesterol and phospholipids, which help to keep cholesterol in solution in the gall bladder. Eating stimulates the gall bladder to contract, emptying its contents into the small intestines. BAs undergo enterohepatic circulation several times each day, which helps 95% BAs to be reabsorbed from the ileum and transported back to the liver through the portal vein.

BAs are involved in nascent bile formation, biliary cholesterol solubilization and intestinal absorption of lipids and lipid-soluble molecules. Various transport proteins for BAs and the other major bile lipids (phosphatidylcholine and cholesterol) have been identified in the liver, which are tightly regulated by nuclear receptors, such as FXR. Currently, BAs are also increasingly recognized as signaling molecules in a wide range of fields, such as energy homeostasis and metabolism of glucose and lipids. BA-mediated activation of FXR is a major underlying pathway for these effects[10,11]. Moreover, G protein-coupled BA receptor 1 (GPBAR1 or TGR5) has also been identified recently as liver-specific metabolic signals and promotes liver regeneration through BAs[12]. It has been demonstrated that, in the hepatobiliary system, TGR5 is detected in Kupffer cells (KC), biliary epithelium and sinusoidal endothelial cells, which constitute a permeable barrier between hepatocytes and blood[13]. A recent study indicates that TGR5 is crucial for liver protection against BA overload after PH, primarily through the control of bile hydrophobicity and cytokine secretion in the genetic deletion of *Tgr5* mouse models. Further research found that after PH, bile-duct ligation, or upon BA-enriched feeding, intrahepatic stasis of abnormally hydrophobic bile may be one of the primary factors involved in liver injury observed in *Tgr5*-KO mice[12].

BAs are potentially toxic, and substantial increase in hepatic BA levels will induce hepatocyte death. However, previous studies indicate that BAs promote normal liver regeneration and repair after injury. Normal physiological levels of BAs are required for liver repair[10,14]. During the early phase after PH, under physiological conditions, serum and hepatic BA concentrations tend to increase, thus leading to the activation of FXR and of other pathways crucial for hepatocyte protection from BA toxicity. This would increase the capacity of the liver to manage BA overload and promote liver regrowth. Huang and co-workers[15] showed that liver regeneration was accelerated in mice in which BA pools were increased by feeding with a 0.2% cholic acid (CA) diet. In contrast, decreasing BA pool by feeding with a diet supplemented with the BA-sequestering resin, cholestyramine, strongly decreased the rate of liver regeneration. The effects of both CA and cholestyramine feeding on liver regeneration were absent in *Fxr*-knockout (*Fxr*-KO) mice, suggesting that *Fxr* is the mediator of the effect of BA signaling on liver regeneration. Further studies demonstrate that *Fxr*-KO mice are unable to handle BA overload that may elicit detrimental effects including cell death, DNA

oxidative damage, inflammation, nuclear factor-κB (NF-κB) activation, aberrations of the mitotic machinery and cell hyperproliferation[16]. Delayed liver regeneration during the early stage after PH, and decreased expression of FXR and c-Jun, but induction of *Cyp7a1* mRNA levels were also found in rat models with the reduction in BA pool size[17]. Thus, a delicate regulation of *Cyp7a1*/*CYP7A1* gene expression maybe very important for a stringent control of BA levels during liver regeneration. During liver regeneration, hepatic BA levels need to be suppressed rapidly to prevent the toxic effect of increased BAs in liver, as shown by a dramatic down-regulation of *Cyp7a1* mRNA levels[18]. Activation of FXR by either 0.2% cholic acid feeding or oral infusion of an FXR agonist greatly promoted liver regeneration in sterol 27-hydroxylase-knockout (*Cyp27*-KO) mice, which are genetic animal models with low BA levels[19]. Patients with BA sequestrant medications or cerebrotendinous xanthomatosis (CTX) disease due to *Cyp27* gene mutations may have an increased risk of liver failure, and treatment with FXR ligands can promote liver regeneration of patients with low BA levels[20]. These results suggest that individuals with low BA levels have a higher risk of liver injury due to their insufficiency of liver repair. Thus, FXR plays a key role in mediating effects of BAs on promoting liver regeneration.

Besides FXR, the BA membrane transporter, multidrug resistance associated protein 3 (MRP3, gene symbol *ABCC3*/*Abcc3*), has also been investigated in the hepatic growth response elicited by BA and in liver regeneration after PH. Liver regeneration after PH was significantly delayed in *Mrp3*-deficient mice. Moreover, *Mrp3*-deficient mice showed decreased portal serum levels of BA and reduced FXR activation in the liver after BA administration[21]. These data suggest that MRP3 plays an important role in the regulation of BA flux during liver regeneration. TGR5 is a G protein-coupled receptor, from which activation by BA induces cyclic adenosine monophosphate (cAMP) synthesis[22]. It is considered as a crucial regulator of energy homeostasis, as well as a potential target for the treatment of metabolic syndrome and its complications, including nonalcoholic steatohepatitis (NASH), in the context of diabetes and obesity. After PH, severe hepatocyte necrosis, prolonged cholestasis, exacerbated inflammatory response, and delayed regeneration were observed in *Tgr5*-KO mice. The lack of *Tgr5* led to more hydrophobic bile and excessive hepatic inflammation after PH, which were associated with deficient adaptation of bile composition and flow, and insufficient BA efflux in urine. All these factors contributed to excessive BA overload, which induced liver injury and delayed regeneration. Further research showed that in the absence of *Tgr5*, early post-PH liver injury was not affected by KC depletion. Thus, inflammation appears more as a worsening, rather than a triggering, factor in the *Tgr5*-KO mice after PH[12].

In conclusion, a relative high level of BAs is important for the initiation of hepatic regeneration. Moreover, the BA-mediated siginaling pathways are parts of the molecular mechanisms affecting liver regeneration, which need to be further investigated.

2.2. *FXR regulates pathways independent of BAs in the process of liver regeneration*

As mentioned, FXR promotes liver regeneration after PH or liver injury. The FXR transcriptional activity in control of BA levels and other signaling pathways is crucial for hepatocyte protection and cell proliferation during heptic regeneration. Monte and colleagues[23] studied the changes in the expression patterns of genes involved in BA synthesis during rat liver regeneration after 2/3 PH. The *Fxr* mRNA levels were first reduced (day 1–2) and then (day 3) increased. However, the *Shp* mRNA levels were also transiently enhanced at an earlier time point than those of *Fxr* (day 2). As a pleiotropic regulator, SHP modulates the expression of multiple target genes involved in diverse biological processes, including regulation of metabolic pathways, stress and inflammatory response, detoxification, cellular adhesion and differentiation, and cell cycle control[24]. Thus, activation of SHP may regulate the downstream apoptosis pathways in hepatocytes after PH.

The thyroid hormone (TH) plays a significant role in diverse processes related to growth, development, differentiation, and metabolism. At the cellular level, the TH exerts its effects after concerted mechanisms to facilitate binding to the TH receptor (THR)[25]. Although THs and their receptors are not required for liver regeneration, mice lacking *Thrα1*/*Thrβ* or *Thrβ* alone showed delayed commitment to the initial round of hepatocyte proliferation[26]. Moreover, the remaining hepatocytes in the mouse livers were found transient but intense apoptosis at 48 h after PH, which may be due to the induction of FXR to upregulate the activity of dimethylargininеaminohydrolase-1 (DDAH-1) in the regenerating liver[26].

FXR is the primary sensor of BAs, and both conjugated and unconjugated BAs can activate FXR at physiological concentrations. One of the primary BAs, chenodeoxycholic acid (CDCA) is a potent endogenous activator of FXR. Diets enriched with CDCA increase the liver/body weight ratios by 50% due to hepatocellular hypertrophy in wild type (WT) but not *Fxr*-KO mice. Further research demonstrated that hematopoietically expressed homeobox (HEX), a central transcription factor in vertebrate embryogenesis and liver development, is the BA-induced FXR target gene during adaptation of hepatocytes to chronic BA exposure[27]. CCAAT-enhancer binding protein (C/EBPβ) is a key transcription factor which is necessary for the expression of genes involved in maintaining normal liver physiology. Recent study demonstrated that CDCA induces antioxidant and xenobiotic-metabolizing enzymes by activating C/EBPβ through phosphorylation. Further research revealed that CDCA treatment activated AMP-activated protein kinase (AMPK), which led to extracellular signal-regulated kinase 1/2 (ERK1/2) activation, through the activation of FXR. Moreover, enforced expression of FXR promoted the phosphorylation of AMPKα, ERK1/2, and C/EBPβ, verifying that C/EBPβ phosphorylation elicited by CDCA results from the activation of AMPK and ERK1/2 by FXR. Thus, the mechanism of C/EBPβ activation by CDCA is regulated by FXR through the AMPK-ERK1/2 pathway. Therefore, activation of C/EBPβ by CDCA may be necessary for the induction of detoxifying enzymes during liver injury[28]. To study the mechanism that terminate liver regeneration, Timchenko's group[29] generated C/EBPα-S193A knockin mice, which have decreased the phosphorylation of S193A in formation of complexes of C/EBP family proteins. They found that, livers of C/EBPα-S193A mice fail to stop liver regeneration after surgery when livers reach the original pre-resection size. Further research showed C/EBPβ-HDAC1 complexes repress *Sirt1*, *Pgc1α*, *Fxr*, *p53* and *Tert* gene expression in livers of S193A mice, which may be responsible for the failure of terminating liver regeneration. These results showed that activation of FXR may be one of the termination pathways in the late stage of hepatic regeneration.

Forkhead box m1b (FOXM1b) is a proliferation-specific member of the forkhead box family of transcription factors that is ubiquitously expressed in embryonic tissues and cultured cells.

This protein, which regulates chromosome segregation and hepatocyte proliferation by regulating the expression of cell cycle genes that stimulate cyclin-dependent kinase 2 and cyclin-dependent kinase 1 activity, is essential for hepatocyte entry into mitosis during liver development, regeneration, and carcinogenesis[30–32]. FOXM1b transcription factor is required for normal liver regeneration. The rate of liver growth was much slower in the early stages of liver regeneration in *Fxr*-KO mice. Activation of FXR by BAs increased the expression of FOXM1b, which was shown to regulate cell cycle progression during liver regeneration[33]. Huang's group[34] further found that *Foxm1b* is a direct FXR target gene involved in cell cycle regulation. They also demonstrated that defective activation of FXR, which results in inhibition of *Foxm1b*, is an intrinsic defect in aging regenerating livers. Moreover, activation of FXR is able to alleviate age-related liver regeneration defects[14,15,35]. These findings highlight FXR as a potential target of drug design for promoting liver regeneration in older subjects. Other studies in rodents suggest that FXR agonists may improve liver metabolic functions, prevent cell death and promote hepatocyte proliferation thus highlighting the potential use of FXR agonists in conditions such as pathological suppression of liver regrowth, liver failure, or after hepatectomy/liver transplantation. In summary, FXR plays an important role in the whole process of liver regeneration through regulation of various signaling pathways.

2.3. *Intestinal FXR in the regulation of liver regeneration*

The BA enterohepatic circulation and the process of bile formation are tightly regulated, depending on modulating dietary and hormonal signals. The importance of BA-mediated, FXR-dependent pathways for liver regeneration emerged from the observation that external biliary drainage and biliary obstruction, which interrupt BA enterohepatic circulation and delay liver regeneration[36]. Whole body deletion of *Fxr* results in significant inhibition of liver regeneration after PH. Since *FXR* gene is highly expressed in the liver and intestine, both hepatic- and intestine-FXR are involved in the regulation of BA homeostasis[14]. Moreover, recent reports indicate that FXR regulates a distinct set of genes in a tissue-specific manner[37,38]. Recent studies using tissue-specific *Fxr*-KO mice showed that both liver- and intestine-specific *Fxr*-KO mice exhibit impaired regeneration in response to resection- and toxin-induced regenerative stimuli[38,39].

Liver regeneration after PH in hepatocyte-specific *Fxr*-KO (hep*Fxr*-KO) mice was studied over a time course of 0–14 days. Although the overall kinetics of liver regrowth in hep*Fxr*-KO mice was not affected, a delay in peak hepatocyte proliferation from day 2 to day 3 after PH was observed in hep*Fxr*-KO mice compared with the control mice[39]. Further studies revealed decreased Cyclin D1 gene expression and decreased association of cyclin D1 with CDK4 in hep*Fxr*-KO mice after PH were correlated with decreased phosphorylation of the retinoblastoma (Rb) protein and delayed cell proliferation in the hep*Fxr*-KO livers. Moreover, a significant delay in hepatocyte growth factor-initiated signaling, including the AKT, c-Myc and ERK1/2 pathways, was observed in hep*Fxr*-KO mice[39]. These data indicate that regulation of liver regeneration after PH by FXR is likely dependent on the gut-liver FXR signaling axis and not on the hepatic FXR alone. These studies highlight the complex multipathway signaling involved in regulation of liver regeneration after PH, and suggest a strong role for metabolic signals in the initiation and termination of liver regeneration.

Intestinal FXR affects BA homeostasis in mice by inducing intestinal epithelial expression of fibroblast growth factor 15 (FGF15) in mice and FGF19 in humans, which is transported *via* portal circulation to the liver, where it suppresses BA synthesis[40]. Consistently, several reports also suggest that FGF15 secreted from ileum has profound effects on liver metabolism as well as regeneration[41,42]. Interestingly, *Fgf15*-KO mice were recently reported to exhibit both impaired resection-induced hepatic regeneration and reduce enteral BA-stimulated hepatomegaly[43]. Therefore, FGF15 induction after liver damage may also contribute to the normal liver regeneration. Previously studies showed that the suppression of CYP7A1 expression and decreased BA synthesis was beneficial for liver regeneration[15]. Huang's group also found that, during liver regeneration/repair, activation of FXR induces the expression of FGF15 in the intestine to suppress *Cyp7a1* transcription. Thus, induction of FGF15 after liver damage may also contribute to normal liver regeneration through enterohepatic circulation. Recently, we found that *Fgf15*-KO mice following 2/3 PH displayed extensive liver necrosis, and marked elevation of serum BAs and bilirubin compared with WT mice. Furthermore, hepatocyte proliferation was reduced in the *Fgf15*-KO mice due to impaired cell cycle progression which is important for liver regeneration. Less activation of signal transducer and activator of transcription 3 (STAT3), NF-κB, and mitogen-activated protein kinase (MAPK) is also shown in the *Fgf15*-KO mice compared with WT mice after 2/3 PH. Meanwhile, a reduction with/without delayed induction of immediate-early response genes, including growth-control transcription factors, was found at early time points after PH in livers of the *Fgf15*-KO mice[44]. Therefore, activation of FXR in the intestine can induce FGF15 protein, which could repress *Cyp7a1* gene transcription by the activation of c-Jun N-terminal kinase (JNK)/ERK pathways in the liver through its receptor FGF receptor 4 (FGFR4). Lack of FGF15 feedback suppression by *Fgf15* deletion leads to increased BA biosynthesis. The accumulation of BAs would further cause toxicity and damage to hepatocytes. In addition to feedback regulation of *Cyp7a1* transcription, reduced JNK/ERK activation could deactivate STAT3/NF-κB signaling pathways, which are crucial for the priming phase of liver regeneration. In conclusion, FGF15 is necessary to maintain BA homeostasis and prevent liver injury during liver regeneration. Moreover, FGF15 is an essential mediator of the liver growth-promoting effects of BAs. Preoperative administration of this enterokine to patients undergoing liver resection might be useful to reduce damage and foster regeneration.

In summary, intestine FXR can activate FGF15 expression in the intestine to promote liver regeneration. Therefore, in addition to the cell-autonomous and hepatic regenerative effects of hepatic FXR, the endocrine FGF15 pathway induced by intestine FXR also participates in the promotion of liver regeneration. Thus, hepatic and intestine FXR, FGF15, and enterohepatic circulation of bile acids are the fundamental frames in the metabolic regulation of liver regeneration system.

3. Conclusions and perspectives

Normal liver regeneration is important for restoring the liver mass following liver injury. The function of FXR has been expanded from regulating BA homeostasis to mediating lipid and glucose

metabolism, hepatic regeneration even carcinogenesis. Activation of FXR by elevated BA levels accelerates liver regeneration, whereas decreased BA levels and absence of *FXR*/*Fxr* inhibit liver growth. Of note is that although the absence of *FXR*/*Fxr* inhibits liver growth, *Fxr*-KO mice spontaneously develop liver tumors as they age, asserting that BA-induced DNA damage in *Fxr*-KO mice may be critical in liver tumor development even if *FXR*/*Fxr* absence limits liver regeneration[45]. The novel roles of FXR in promoting liver regeneration and protecting against hepatocarcinogenesis, however, are consistent with its previously defined functions in regulating BA metabolism and defending against BA toxicity. TGR5, which is one of the new BA receptors, is needed to be further studied to understand the underlying mechanism of liver regeneration. Moreover, further work should be done to reveal the role of FGF15, the key regulator of BA enterohepatic circulation, in the process of heptic regeneration. Therefore, increased understanding of the hepatic regenerative process will be significant benefit in the treatment of liver failure. Furthermore, understanding of liver regeneration may shed light on the development of hepatocellular cancer. In addition, given the rapidly increasing demand of liver transplantation, targeting FXR pharmacologically may provide a novel approach to accelerate liver regeneration after liver transplantation or surgery.

In summary, elucidating the molecular mechanisms of liver regeneration by FXR and BAs could lead to life-saving therapy for a large number of patients, especially elderly patients, after segmental liver transplantation or resection of liver tumors.

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