Acta Pharmaceutica Sinica B 2015;5(2):93–98

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Acta Pharmaceutica Sinica B

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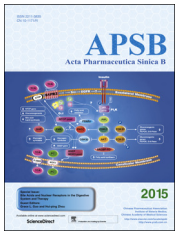

REVIEW

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

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Received 2 December 2014; received in revised form 2 January 2015; accepted 5 January 2015

KEY WORDS

Farnesoid X receptor;
Liver regeneration;
Bile acids;
Fibroblast growth factor 15;
Liver-intestine cross talk;
Transmembrane G protein coupled receptor 5

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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Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2015.01.005

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