Review

Nuclear bile acid receptor FXR in the hepatic regeneration ☆

Wei-Dong Chen 1, Yan-Dong Wang 1, Zhipeng Meng, Lisheng Zhang, Wendong Huang *

Division of Gene Regulation & Drug Discovery, Beckman Research Institute, City of Hope National Medical Center, 1500 E. Duarte Road, Duarte, CA 91010, USA

Abstract

The liver can fully regenerate itself by a compensatory regrowth in response to partial hepatectomy or injury. This process consists of a variety of well-orchestrated phases and is mediated by many signals. Farnesoid X receptor (FXR) is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors. Bile acids are FXR physiological ligands. As a metabolic regulator, FXR plays key roles in regulating metabolism of bile acids, lipids and glucose. Recently, bile acid/FXR signaling pathway is shown to be required for normal liver regeneration. Furthermore, FXR promotes liver repair after injury and activation of FXR is able to alleviate age-related defective liver regeneration. These novel findings suggest that FXR-mediated bile acid signaling is an integrated component of normal liver regeneration machinery, and also highlight the potential use of FXR ligands to promote liver regeneration after segmental liver transplantation or resection of liver tumors. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

© 2010 Elsevier B.V. All rights reserved.

1. Introduction

The liver is one of the few organs that can completely regenerate itself in response to partial ablation or injury. Liver regeneration has been studied intensively since the introduction of a rodent partial hepatectomy (PH) model in 1931 [1]. This process consists of a variety of well-orchestrated phases and is mediated by many signals. Farnesoid X receptor (FXR) is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors. Bile acids are FXR physiological ligands. As a metabolic regulator, FXR plays key roles in regulating metabolism of bile acids, lipids and glucose. Recently, bile acid/FXR signaling pathway is shown to be required for normal liver regeneration. Furthermore, FXR promotes liver repair after injury and activation of FXR is able to alleviate age-related defective liver regeneration. These novel findings suggest that FXR-mediated bile acid signaling is an integrated component of normal liver regeneration machinery, and also highlight the potential use of FXR ligands to promote liver regeneration after segmental liver transplantation or resection of liver tumors. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

© 2010 Elsevier B.V. All rights reserved.

2. The nuclear bile acid receptor FXR

FXR's roles in metabolic regulation and metabolic diseases have been summarized by a number of excellent reviews. Recently, several new functions of FXR beyond metabolic regulation have been identified [16–19]. FXR is the primary sensor of bile acids. In fact, both conjugated and unconjugated bile salts are able to activate FXR at physiological concentrations [17]. One of the primary bile acids, chenodeoxycholic acid (CDCA) is a potent endogenous activator of
FXR. The secondary bile acids, deoxycholic acid (DCA) and lithocholic acid (LCA), can both activate FXR but to a lesser extent than CDCA does, whereas hydrophilic ursodeoxycholic (UDCA) and muricholic acids cannot activate FXR [20]. FXR is activated by bile acid with a rank order of potency as CDCA > DCA > LCA > cholic acid (CA) [21].

By binding to FXR responsive elements (FXREs), FXR regulates many genes belonging to different metabolic pathways [22]. Over the past decade, a number of studies on FXR have established FXR as a key regulator of metabolism, which is reviewed by different groups [23–26]. FXR is well known to regulate bile acid homeostasis as well as the lipoprotein and glucose metabolism [27–37]. In summary, FXR may act as a general sensor of metabolic stresses as well as a modulator to regulate specific groups of gene expression in order to provide hepatoprotection. However, recent studies suggest that FXR also provides a second layer of hepatoprotection through promoting liver regeneration and repair.

3. FXR and liver regeneration

Liver regeneration is an adaptive response induced by specific stimuli and includes subsequently sequential changes in gene expression and morphologic reconstruction. It consists of a variety of well orchestrated phases, with rapid induction of proliferative factors that activate the quiescent hepatocytes and prime their subsequent progression through the cell cycle, followed by re-establishment of normal liver size and renewed hepatocyte quiescence [2]. The essential circuitry required for this process is defined mainly by three major networks: cytokine, growth factor and metabolic signals [38]. Although many genes and signaling pathways have been reported to be involved in liver regeneration, compared to the cytokines and growth factors, little is known about the roles of metabolic signals in liver regeneration.

The original studies have indicated that the initiating signals of liver regeneration are in the circulation system [39]. This has been demonstrated by many studies showing that different proliferative signals in serum are upregulated after 70% PH [4,38]. Even until recently, there are still some new factors that are being identified, suggesting that more than a single signal is responsible for liver regeneration. For example, a recent finding suggests that serotonin is not only a neurotransmitter but also a hormone with various extraneuronal functions. Lesurtel et al. reported that platelet-derived serotonin is involved in the promotion of liver regeneration [40]. Matondo et al. further indicated that very low levels of serotonin in blood are sufficient for liver regeneration [41].

Although many factors are being identified, bile acids may be the neglected signals required for liver regeneration. Bile acids are end products from cholesterol catabolism and are essential for normal intestine absorption of cholesterol, lipids and fat-soluble vitamins [42]. Bile acids are synthesized in the liver and stored in the gall bladder. They are secreted into the intestine when a meal is ingested, but most bile acids (95%) are reabsorbed and transported back to the liver through the portal vein. This system is known as enterohepatic circulation. It has been known that interrupting normal enterohepatic biliary circulation inhibits liver regeneration and bile acids are able to stimulate hepatocyte proliferation [43–45]. Moreover, hepatic bile acids comprise less than 5% of the total bile acid pool and PH can increase bile flow [46,47]. These evidences suggest that bile acids may participate in liver regeneration. Indeed, supplying the mice with a low dose of bile acids promotes liver regeneration while reducing bile acid levels by a bile acid binding resin delays liver regeneration [15]. This effect of bile acids is dependent on FXR activation because in FXR null mice the observed effect disappears [15]. Therefore, it is FXR that transforms the bile acid stress into the force of promoting liver regeneration.

4. FXR promotes liver repair after injury

The nature of FXR-mediated bile acid signaling in liver regeneration is a stress response. Feeding mice with a 1% CA diet during liver regeneration is toxic and lethal, indicating that bile acids by nature are not typical mitogens and the increased levels of bile acids activate FXR to push liver regrowth in order to combat potential toxicity induced by bile acids [48]. Indeed, a sharp reduced expression of CYP7a1 was observed, the rate-limiting enzyme of bile acid production after 70% PH [48]. In addition to FXR/SHP, during the early phase of liver regeneration, MAPK and other pathways may also participate to suppress the expression of CYP7a1. These results suggest that bile acid stress is generated rapidly after 70% PH and there are multiple mechanisms to accommodate this coming stress [48]. The roles of FXR in liver regeneration were further investigated after injury by a liver toxin, carbon tetrachloride (CCL4). In this study, FXR is further confirmed to be required to promote liver regeneration. Moreover, since there is massive cell death in this model, FXR is also shown to prevent hepatocytosis from death [49]. The anti-apoptosis function of FXR has been previously demonstrated. It was shown that FXR activation specifically upregulated ERK pathways and protected liver cells from apoptosis induced by serum deprivation in vitro and fasting in vivo [19]. During liver repair after injury, this role of FXR in cell survival may be linked to the activation of STAT3, which is a key factor in cell survival [49]. Both cell proliferation and protection from apoptosis are known to be important during liver regeneration or repair. Therefore, the role of FXR in protecting hepatocytes from apoptosis is consistent with its role to promote liver regeneration or repair. However, the exact downstream events after FXR activation to prevent cell apoptosis are still unclear and needs further investigation. In summary, when liver is injured, FXR activation results in the down-regulation of CYP7a1, which help rapidly decrease hepatic bile acid levels to protect the liver from apoptosis and necrosis induced by elevated bile acid concentrations. At the same time, FXR promotes liver regeneration for proper liver repair. The ability of FXR to promote liver repair after injury is important to suppress hepatocarcinogenesis. Indeed, FXR null mice spontaneously develop liver tumors when they age [50,51]. Without the roles of FXR in promoting liver repair after injury, liver is prone to enter endless cycles of injury/repair that will keep producing inflammatory cytokines and other growth factors that are potential tumor promoters. Moreover, bile acids are known to cause DNA damage and induce cell transformation if their levels are not controlled by FXR. Therefore, FXR's role in promotion of liver repair could be an intrinsic mechanism to protect liver from carcinogenesis. We anticipate that delineation of the exact link between FXR's roles in hepatoprotection and hepatocarcinogenesis is an interesting area of future investigation.

In addition to liver, FXR is also highly expressed in intestine, which is required to modulate bile acid homeostasis by suppressing CYP7a1 expression when bile acid levels are high [52]. Is intestine-FXR involved in regulation of liver regeneration in response to PH or liver injury? Activation of FXR increases the expression of FGF15 in the ileum, which travels to liver to suppress CYP7a1 gene expression. Does FGF15 contribute to liver regeneration? These questions need to be answered to determine whether this endocrine pathway of FXR is also participating in regulation of liver regeneration.

5. Nuclear receptor-mediated pathways in liver regeneration

As a member of the nuclear receptor superfamily, FXR mediates the bile acid signaling to promote liver regeneration. In addition to FXR, some other nuclear receptors have also been implicated in regulating the process of liver regeneration. In 1984, Fisher et al. first showed that estrogen and its receptor-estrogen receptor affect liver regeneration after PH [53]. Imai et al. showed that upon PH, liver regeneration is impaired in mice lacking RXRα in hepatocytes [54].
Yamamoto et al. found that the PPARγ might be one of the key negative regulators of hepatocyte proliferation and might be responsible for the inhibition of liver growth in the late phase of liver regeneration [55]. Dai et al. indicated that the xenobiotic receptor PXR is required for normal progression of liver regeneration by modulating lipid homeostasis and regulating hepatocyte proliferation [56]. Another xenobiotic receptor CAR may be also involved in regulating liver regeneration, although to a much less extent [15]. More recently, Lopez-Fontal reported that thyroid hormone receptor contributes significantly to the rapid initial round of hepatocyte proliferation following PH, and improves the survival of the regenerating liver at later stages [57]. These results indicate that the increase of different endogenous metabolites and hormones during liver regeneration may activate their individual receptor, which help liver regeneration to different extent. However, the mechanisms by which those receptors promote liver regeneration are largely unknown. Actually, direct activation of some of these receptors such as PPARα and CAR results in hepatomegaly quickly, which is distinct from the normal liver regeneration [58]. The question is whether they are all required for liver regeneration. The answer may be dependent on the levels of endogenous ligands after 70% PH or liver injury. Although all these nuclear receptors have the potential to be activated and promote liver growth, only those whose endogenous ligands are strongly increased, such as bile acids and FXR, will play major roles in contribution to normal liver regeneration. Activation of FXR by its ligand has been shown to promote liver regeneration in aged animals [6], suggesting that further understanding of the mechanism by which nuclear receptors stimulate liver regrowth may provide novel approaches to develop drugs for promotion of liver regeneration. In summary, metabolic signaling is an integrated component of normal liver regeneration. Multiple pathways are working in parallel to contribute to the overall process of liver regeneration (Fig. 1).

6. Promotion of the regeneration of aged liver by FXR activation

Although liver can fully regenerate itself, aging dramatically reduces this capacity. The mechanism for the declined proliferative capacity in aged liver is still unclear. According to the current knowledge, the delayed and reduced proliferative response has been attributed to the decreased expression of some key transcription factors such as c-Myc and Foxm1b in response to liver ablation. This may be due to the appearance of an age-specific C/EBPα–Brm–HDAC1 protein complex in aging livers, which occupies the promoters of c-Myc and Foxm1b to prevent their activation [9,10,59–61]. However, studies from Costa’s and Rando’s groups indicated that either elevated hepatocyte expression of Foxm1b [61,62] or diminished C/EBPα complex through heterochronic parabiosis between young and old mice [63] could help the aging liver proliferate after 70% PH. Foxm1b is required for the timely expression of many cell cycle regulators essential for G1/S and G2/M progression and chromosome stability and segregation [64,65]. It is a key regulator of cell replication during liver regeneration. Loss of Foxm1b function in livers of young mice results in a significant reduction in hepatocyte DNA replication and inhibition of mitosis after PH [59]. More importantly, forced expression of Foxm1b in regenerating livers of old mice is sufficient to restore hepatocyte DNA replication and expression of necessary cell cycle regulatory genes to levels as seen in young animals [61,62]. These results highlight Foxm1b as one of the key regulators in liver regeneration and indicate that activating Foxm1b may be sufficient to promote regeneration of aged liver.

The ability of an aged liver to regenerate can be restored by exposing to growth hormone [62] or serum from young animals [63], suggesting that aged liver cells retain their regenerative potency and can be rejuvenated in response to the serum of young animals. It was shown that there was a defective activation of FXR and diminished binding of Fxr to a FXR in Foxm1b gene in aged regenerating livers [6]. This suggests that untimely activation of FXR, resulting in defective liver regeneration, could be an intrinsic defect in aged regenerating livers. However, compared with young mice, aged mice did not have altered protein levels of FXR and RXR. Therefore, aging may reduce the levels of endogenous Fxr ligands such as bile acids, oxysterols, and other unknown factors [17], which could result in defective activation of FXR in regeneration of aged liver. This is confirmed by the facts that treatments with synthetic FXR ligands are sufficient to induce Foxm1b gene expression and promote liver regeneration in old mice [6]. Whether FXR activation is able to remove (HDAC1)–C/EBPα–E2F–Rb complex from Foxm1b promoter is worthy of future investigation. However, it is still possible that FXR activates a pathway independent of (HDAC1)–C/EBPα–E2F–Rb complex to induce Foxm1b expression in aged livers.

7. Conclusions and perspective

The function of FXR is expanded rapidly from initial roles in controlling metabolism to regulating cell growth and malignancy. However, the novel roles of FXR in promoting liver regeneration are consistent with its previously defined functions in regulating bile acid metabolism and defending against liver toxicity. We hypothesize that either resection or injury of liver will rapidly generate a bile acid stress that may cause liver failure. The activation of FXR leads to a decrease of bile acid levels in the liver, activates Foxm1b and other genes involved in cell cycle progression, and promotes liver regrowth, which helps accommodate and release the increased metabolic stresses. Therefore, further understanding of the roles of FXR in hepatic regeneration will provide novel insights into the complex mechanism of this process.

The function of FXR to promote liver repair is also essential to prevent hepatocarcinogenesis and other liver pathogenesis such as fibrosis. The prompt liver repair process will help liver to resume

---

![Fig. 1. Multiple pathways are engaged in promoting liver regeneration. In addition to cytokines and growth factors, metabolic signals are also generated during liver regeneration, which activate their receptors to modulate the expression of a specific group of genes involved in liver regeneration and repair.](image1)

![Fig. 2. Multiple beneficial effects of FXR ligands on liver regeneration.](image2)
homeostasis. Failure to achieve this will force liver to enter cycles of chronic injury and regeneration, which leads to chronic inflammation and creates a liver environment to develop fibrosis and cancer.

No effective therapies are currently available to promote liver regeneration. Our studies indicate that FXR agonist ligands may offer potential approaches to promote liver regeneration after segmental liver transplantation or after resection of liver tumors. Using FXR ligands to promote liver regeneration can have several advantages: 1) FXR activation will improve liver metabolic functions; 2) prevent cell death; and 3) directly promote liver regrowth (Fig. 2). We expect that the development of more potent and safe FXR ligands will go into clinical trials in the near future for those patients who need accelerated liver regeneration after surgery.

Acknowledgements

We apologize to colleagues whose work could not be cited due to space limitations. We would like to thank Dr. David Moore at Baylor College of Medicine and Dr. Barry Forman at City of Hope for their support of FXR projects. This work is supported partially by Dr. Ibrahim Training Grant.

References


