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Review

Bile acid signaling and liver regeneration ☆

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ABSTRACT

The liver is able to regenerate itself in response to partial hepatectomy or liver injury. This is accomplished by a complex network of different cell types and signals both inside and outside the liver. Bile acids (BAs) are recently identified as liver-specific metabolic signals and promote liver regeneration by activating their receptors: Farnesoid X Receptor (FXR) and G-protein-coupled BA receptor 1 (GPBAR1, or TGR5). FXR is a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors. FXR promotes liver regeneration after 70% partial hepatectomy (PHx) or liver injury. Moreover, activation of FXR is able to alleviate age-related liver regeneration defects. Both liver- and intestine-FXR are activated by BAs after liver resection or injury and promote liver regeneration through distinct mechanism. TGR5 is a membrane-bound BA receptor and it is also activated during liver regeneration. TGR5 regulates BA hydrophobicity and stimulates BA excretion in urine during liver regeneration. BA signaling thus represents a novel metabolic pathway during liver regeneration. This article is part of a Special Issue entitled: Nuclear receptors in animal development.

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1. Introduction

Liver is one of the few organs that can powerfully regenerate itself in response to partial ablation or liver injury. Liver regeneration has been widely studied as a paradigm for regenerative organ regrowth since the introduction of a rodent partial hepatectomy (PHx) model in 1931 [1]. Unlike a typically anatomic regeneration, regeneration of the liver is a compensatory hyperplasia of the remaining tissues and is driven by the functional deficit of the organism. Liver regeneration consists of several well orchestrated phases, with rapid induction of proliferating factors activating the quiescent hepatocytes and priming their subsequent progression through the cell cycle, followed by re-establishment of normal liver size and renewed quiescence [2–4]. Growth factors and cytokines are the important early signals to induce the expression of downstream target genes via activation of several key transcription factors [5]. In addition to growth factors and cytokines, metabolic signals are considered as the third major signals during liver regeneration, which is however relatively less studied [6]. Recently, BAs were identified as key metabolic signals during liver regeneration and their roles in promoting liver regeneration have received more and more attention [7,8]. In this review, the recent advance of BA signaling in liver regeneration will be summarized and discussed.

2. Metabolic signals and liver regeneration

Liver regeneration is an adaptive regrowth response induced by specific stimuli and the subsequently sequential changes in gene expression and morphologic reconstruction. It is generally accepted that the remaining hepatocytes are the major cell types that replicate to regenerate liver in the models of 70% PHx or liver injury. Only in some special injury models, activation and replication of liver progenitors are observed when the hepatocytes fail to replicate normally. In addition to hepatocytes, other cell types are also actively involved in liver regeneration or repair. Recently, several excellent reviews also highlight the roles of liver stellate cells, liver sinusoidal endothelial cells and liver stem/progenitor cells in liver regeneration and repair [9–12].

Liver regeneration includes a highly complex network of signal transductions. The essential circuitry required for this process is defined mainly by three major networks: cytokine, growth factor and metabolic signaling [13]. These three networks subsequently activate specific genes and signaling pathways that are essential for liver regeneration. Compared to the cytokine and growth factor networks, little is known about the roles of metabolic signals in liver regeneration. The identification of several nuclear receptors as receptors for liver metabolites provides a novel insight into the roles of metabolic signals in liver regeneration. Among them, the Farnesoid X Receptor (FXR, NR1H4) is identified as a primary BA receptor [14,15]. FXR belongs to a sub-cluster of metabolic nuclear receptors that also includes Vitamin D Receptor (VDR, NR1I1), Constitutive Androstane Receptor (CAR, NR1I3), Pregnane X Receptor (PXR, NR1I2) and Liver X Receptor alpha and beta (LXRα, NR1H3; LXRβ, NR1H2). Peroxisome proliferator-activated

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receptors (PPARs) are also important metabolic nuclear receptors. All these receptors bind to DNA either as a monomer or as a heterodimer with a common partner for nuclear receptors, Retinoid X Receptor (RXR, NR2B1) to regulate the expression of various genes involved in BA, lipid, glucose, and drug metabolism [16]. Interestingly, their roles in liver regeneration are also under active investigation. For example, upon PHx, liver regeneration is impaired in mice lacking RXRα in hepatocytes [17]. LXR may suppress liver regeneration after PHx through regulating the cholesterol levels in the liver [18]. CAR activation strongly induces hepatomegaly and may contribute to normal liver regeneration after 70% PHx [7,19]. Dai et al. indicated that PXR is required for normal progression of liver regeneration by modulating lipid homeostasis and regulating hepatocyte proliferation [20]. In contrast, PPARγ acts as a negative regulator of hepatocyte proliferation and may be responsible for the inhibition of liver growth in the late phase of liver regeneration [21]. There is a detailed summary on nuclear receptors in liver regeneration recently [22].

Liver is a major organ for metabolism. Therefore, there is an immense metabolic demand during liver regeneration. The requirement of metabolic signals for liver regeneration has been known for a long time. However, their direct effect on liver regeneration is still unclear. Among different metabolic signals, BAs are attractive signals for liver regeneration because the levels of BAs are tightly regulated. BAs are intrinsically toxic and cause liver injury if the levels are not controlled properly. As such, liver resection or injury will generate a BA overload in the liver, which is a potential driving force for liver regeneration [7,8].

3. BA signaling and liver regeneration

BAs are liver-specific metabolites. They are end products from cholesterol catabolism and are important for nutrition absorption in the intestine, which include cholesterol, lipids and fat-soluble vitamins. BAs are synthesized in the liver and stored in the gall bladder. They are secreted into the intestine when a meal is ingested, but 95% BAs are reabsorbed and transported back to the liver through the portal vein. This system is known as enterohepatic circulation. Hepatic BAs comprise less than 5% of the total BA pool and PHx increases bile influx, which rapidly generates a BA overload in the liver. Consistently with this, there is a sharp repression of Cyp7a1 gene expression after 70% PHx or liver injury [23]. Cyp7a1 is the rate-limiting enzyme required for the BA production from cholesterol catabolism. The importance for a stringent control of BA levels is illustrated by a delicate regulation of Cyp7a1 expression. There are many factors and pathways that can regulate the expression of Cyp7a1 gene. A negative feedback loop is identified to regulate BA levels, in which high levels of BA activate FXR to increase the mRNA levels of SHP, which is a negative regulator of Cyp7a1 gene expression. Moreover, additional regulators of Cyp7a1 expression are identified, including cytokines, growth factors and nuclear receptors [24–30]. During liver regeneration, in addition to FXR-SHP axis, hepatocyte growth factor and JNK pathways are also involved in suppressing Cyp7a1 expression during the acute phases of liver regeneration [23].

The strong suppression of BA synthesis during liver regeneration indicates a BA overload stress in the liver. This also suggests that BAs may participate in the liver regeneration. Indeed, interruption of normal enterohepatic biliary circulation has been previously known to inhibit liver regeneration [31,32]. Moreover, there is also some direct evidence that BAs are able to stimulate hepatocyte proliferation [33–35]. In a study of 70% PHx mouse model, supplementation with a low dose of BAs promotes liver regeneration, while reduction of BA levels by a BA-binding resin delays liver regeneration [7]. Defective BA signaling that causes delayed liver regeneration is also demonstrated in other animal models. In the absence of MRP3, a BA transporter, liver regeneration is delayed in mice due to lower BA concentration in the portal blood [36]. Similarly, deletion of Cyp27, an enzyme required for normal BA production and metabolism, results in lower BA pool and defective liver regeneration in mice [37]. In FXR −/− mice, the effect of BAs on promoting liver regeneration is lost [7]. Similarly, in MRP3 −/− and Cyp27 −/− mice, the delayed liver regeneration is due to impaired FXR activation, suggesting that FXR is the key player to mediate BA effect on liver regeneration. In conclusion, the identification of a novel role of FXR in liver regeneration is a key to understand the molecular mechanism by which BAs affect liver regeneration.

4. FXR and liver regeneration

FXR is highly expressed in the liver, intestine, and kidney where the levels of BAs are relatively high [38]. FXR is the primary sensor of BAs and both conjugated and unconjugated bile salts are able to activate FXR at physiological concentrations [39,40]. FXR regulates BA homeostasis by regulating genes involved in BA synthesis, secretion, transportation, absorption, conjugation, and detoxification [41–45]. As expected, FXR is also the BA receptor to mediate BA's effect on liver regeneration [7]. FXR is shown to promote liver regeneration after 70% PHx and stimulate liver repair after CCl_4-induced liver injury [46]. Interestingly, different from 70% PHx, there is massive cell death in liver injury model. FXR is shown to have a dual role in promoting liver regeneration by both stimulating hepatocyte proliferation and protecting the hepatocyte from death [46,47].

In addition to metabolic genes, Foxm1b is identified as a FXR direct target gene during liver regeneration [7,48]. Foxm1b is a key cell cycle regulator essential for G1/S and G2/M progression [49,50]. Animal studies indicate that Foxm1b is a key transcription factor in liver regeneration. Although liver can fully regenerate itself, aging dramatically reduces this capacity of the liver. The delayed and reduced proliferative response has been attributed to the decreased expression of some key transcription factors, such as c-Myc and Foxm1b and to the failure of aging-liver to diminish the age-specific C/EBPα–Brm–HDAC1 complex after PHx [51–53]. The complex suppressed Foxm1b induction after PHx through binding to Foxm1b promoter, which results in age-related proliferation defects upon PHx or liver injury [54]. These studies highlight Foxm1b as one of the key regulators in aging-liver regeneration. Defective activation of FXR occurs in aged regenerating livers [48], which may account for the insufficient Foxm1b induction. Compared with young mice, aging mice did not have altered protein levels of FXR and RXR. Therefore, aging may affect the levels of endogenous FXR ligands such as BAs, which could result in defective activation of FXR during liver regeneration. Interestingly, in pregnant mice, the loss of FXR results in reduced liver growth, indicating a similar function of FXR in mediating the liver growth during pregnancy [55].

Sirtuin1 (SIRT1) that can modulate FXR activities also has an effect on liver regeneration through modulating FXR activities during liver regeneration [56]. The transgenic mice that overexpress SIRT1 showed increased mortality, enhanced liver injury and impaired hepatocyte proliferation after PHx. SIRT1 reduces FXR activities through persistent deacetylation and lower FXR expression. In summary, FXR is a key receptor and transcription factor that specifically mediates the effect of BA signaling to promote liver regeneration.

5. Intestine FXR and liver regeneration

FXR is highly expressed in both the liver and intestine. Both hepatic- and intestine-FXR are involved in the regulation of BA homeostasis [57]. One critical FXR target gene in the intestine is FGF15. Indeed, several reports suggest that FGF15 secreted from the ileum has profound effects on the suppression of Cyp7a1 gene expression and liver metabolism through FGF receptor-mediated signaling pathways in the liver [58–60]. Suppression of Cyp7a1 expression and decreased bile acid synthesis are known to be beneficial for liver regeneration. Therefore, FGF15 induction after liver damage may also contribute to the normal liver regeneration. Indeed, there is a significantly delayed liver regeneration and increased liver injury in intestine-specific FXR

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