Farnesoid X Receptor

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Farnesoid X receptor (FXR) has a central role in Bile Acids (BA) homeostasis and recent publications revealed that changes in autophagy due to BA-induced reactive oxygen species and increased anti-oxidant response via nuclear factor E2-related factor 2 (NRF2), result in dysregulation of FXR signaling. Several mechanistic studies have identified new dysfunctions of the cholestatic liver at cellular and molecular level, opening new venues for developing more performant therapies.

Keywords: FXR ; liver ; cholestasis ; obeticholic acid ; rifampicin ; autophagy

1. Introduction

Cholestasis is a clinical syndrome with intra- or extra-hepatic etiology, resulting from the obstruction of bile secretion and flow from the liver into the gall bladder and duodenum [1]. Cholestasis can be caused by mutations of genes encoding for proteins with roles in bile transport from hepatocytes into cholangiocytes and bile ducts, resulting in the retention of BA in the liver. The bile flow can also be obstructed by gall stones due to metabolic dysfunctions (cholelithiasis), by tumors (hepatocellular carcinoma, cholangiocarcinoma), or by parasitic infections [1]. Other causes of cholestasis include immune-mediated conditions such as primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), and also exposure to certain medications which negatively affect the liver (non-steroidal anti-inflammatory drugs, anti-diabetic medications). Numerous cholestatic disorders are chronic and may lead to liver fibrosis and cirrhosis if left untreated.

Cholestatic liver injury is a complex disease with a multitude of dysfunctions including not only BA metabolism and transport, but also excessive cell proliferation especially of cholangiocytes and hepatic stellate cells (HSC) which become activated and initiate signaling pathways involving anti-oxidant and immune responses. Therefore, the mechanistic studies on cholestasis encompass a very large area starting with dysregulation of BA metabolism, transport, and signaling on parenchymal and non-parenchymal cells and expanding to inflammation, fibrosis, and eventually carcinogenesis.

BA have critical roles in the regulation of a multitude of physiological processes related to nutrition and digestion, mediating the transport and metabolism of lipids, influencing glucose and insulin sensitivity and modulating the overall energy expenditure in the body [2][3]. BA are signaling molecules acting on receptors that have been defined as BA sensors, and are from two different classes of receptors: (i) nuclear receptors such as farnesoid X receptor (FXR; also known as NR1H4), pregnane X receptor (PXR), constitutive androstane receptor (CAR), and vitamin D receptor (VDR), that become activated by BA and bind to specific response elements on target genes influencing the rate of their transcription; and (ii) membrane-bound G-protein coupled receptors such as Takeda G-protein receptor 5 (TGR5) or G protein-coupled BA receptor 1 (GPBAR1) and spingosine-1-phosphate receptor 2 (S1PR2).

2. FXR

The role of FXR in the regulation of hepatic triglyceride and glucose homeostasis [4][5][6] has been well described and several FXR agonist drugs have been developed for treating dyslipidemia, nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and to improve liver functions [4]. However, the beneficial effects of FXR agonists in the treatment of liver fibrosis caused by biliary cholestasis, have been controversial. In cholestasis, the activation of FXR by excessive amounts of BA accumulated in the liver, is at a maximum, and it was demonstrated that administration of CDCA or DCA in their natural form, does not improve liver fibrosis in animal models of hepatic cholestasis [4]. Semi-synthetic BA and non-steroidal agonists of FXR have been developed and tested for therapies of liver and pancreas-related diseases [4]. Thus, INT747 or obeticholic acid (OCA), a 6-α-ethyl derivative of CDCA were proposed to have hepatoprotective effects on certain types of cholestasis based on animal model experiments [7][8]. Non-steroidal agonists of FXR such as GW4064 and WAY-362450, which may modulate multiple G protein-coupled receptors besides directly activating FXR, have been proposed to be used to reduce hepatic inflammation in the context of cholestasis [9][10][11].

Besides its ability to control the transactivation of genes involved in BA biosynthesis and transport along the enterohepatic tract, and to contribute to liver regeneration and growth, FXR has been proved to counterbalance nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB)—mediated transcription of proinflammatory cytokines, having a role in hepatic repair in liver fibrosis [12][13][14]. Even though FXR is expressed also in HSC and cholangiocytes, it is critical in hepatocytes since BA-induced hepatocyte death activates profibrogenic factors such as transforming growth factor beta 1 (TGF-β1), platelet derived growth factor (PDGF), connective tissue growth factor (CTGF) which then act on quiescent HSC inducing their activation to proliferate and produce excessive extracellular matrix proteins and fibrosis [15][16]. Several published studies revealed that semi-synthesis and non-steroid agonist of FXR, e.g., GW4064 and WAY-362450, were able to mitigate liver inflammation and fibrosis in animal models of cholestasis [9][17][18].

Cholestatic liver diseases are characterized by chronic hepatic and systemic accumulation of total BA and especially hydrophobic bile salts due to a dramatic dysregulation of BA homeostasis [19]. Most of the cholestasis syndromes are correlated with dysfunctions of genes encoding for transporters of BA along the hepato-biliary tract, such as ATP8B1 coding for phospholipid flippase [20], and ABCB11 for bile salt export pump or BSEP [21][22]. Early studies on the role of excessive BA in liver injury, pointed out that hydrophobic BA such CDCA and GCDC are toxic and induce hepatocellular death by apoptosis [23][24].

3. Targeting FXR in Portal Hypertension Associated with Cholestasis-Induced Cirrhosis

Cirrhosis is the final stage of chronic cholestasis, in which hepatic fibrosis is very advanced so that most of the liver functions are impaired [25]. Thus, advanced hepatic inflammation, biliary and periportal fibrosis, loss of tissue homeostasis followed by abnormal remodeling are conducive to late permanent dysfunctional state of cirrhosis [26]. Portal hypertension (PHT) is commonly seen in patients with cholestatic liver cirrhosis especially in the stage of decompensation when liver injury is associated with complications such as ascites, hepatic encephalopathy, or variceal bleeding [27]. FXR has been found to be a promising target for the treatment of portal hypertension. Thus, in liver fibrosis, the blood vessels are more constricted compared to normal liver due to a significant decrease of FXR activation caused by ROS and proinflammatory cytokines, resulting in suppressed endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) [28]. Vascular FXR in general was demonstrated to be an important regulatory factor, since pharmacological and genetic activation of FXR stimulated eNOS promotor activity [28]. For the treatment of portal hypertension in particular, Mookerjee et al. studied the effect of an FXR agonist, OCA, on dimethylarginine-dimethylaminohydrolase1 (DDAH-1), a marker of portal pressure that is expressed in hepatocytes and downregulated in cirrhosis [29]. It was shown that asymmetric-dimethylarginine (ADMA), an eNOS inhibitor which is metabolized by DDAH-1 was significantly reduced upon treatment with OCA in an animal model of cholestatic cirrhosis, due to rescue of DDAH-1 expression via activation of FXR [29].

Another interesting study was performed on PX20606 (PX), a nonsteroidal agonist of FXR, in regard to its effect on portal hypertension besides liver fibrosis in experimental models of non-cirrhotic (partial portal vein ligation or PPVL) and cirrhotic (carbon tetrachloride, CCl4) models [30]. PX was able to decrease portal pressure markers in both non-cirrhotic and cirrhotic rats, confirming that FXR has critical role in the regulation of eNOS and portal pressure in the liver.

4. FXR Involvement in Autophagy during Cholestasis

Recent studies on hepatic autophagy revealed an important function of this process in maintaining the overall homeostasis of the liver. Autophagy is an evolutionary conserved mechanism of lysosome-dependent degradation of intracellular components, with multiple functions including cell energy homeostasis, organelle turnover, clearance of aggregated materials inside cells and defense against intracellular pathogens [31]. Deficiencies in autophagy result in several pathologies associated with hepatomegaly, liver inflammation and fibrosis and even carcinogenesis [31]. It was first demonstrated that in BDL mice, cholestasis was associated with hepatocyte autophagy activation [32]. In these studies, suppression of autophagy with chloroquine increased hepatocyte apoptosis, while activation of autophagy with rapamycin decreased cholestatic liver injury, and it was concluded that autophagy benefited hepatocyte survival via modulation of reactive oxygen species (ROS) [32]. Later on, it was found that the accumulation of a protein p62/SQSTM1 (sequestosome 1) disabled the ubiquitination and degradation of nuclear factor-erythroid 2-related factor 2 (NRF2), leading to liver injury [33][34][35]. Generally, NRF2 is known as a transcription factor that targets genes with role in adaptive protection against oxidative stress in cells [36]. It was also suggested that NRF2 is involved in the regulation of autophagic processes in response to oxidative stress, functioning in a negative feedback loop in opposition to AMP-activated protein kinase (AMPK), which is critical for autophagy induction via mTOR downregulation (mTOR or mammalian target of rapamycin, has role in cell growth and autophagy) [37]. Recently, it was determined that increased NRF2 due to defective autophagy, causes a larger release of high mobility group box 1 (HMGB1), a protein released during necrosis) from hepatocytes and

consequently, enhanced the ductular reaction [35]. Moreover, NRF2 is related to the dysfunction of BA synthesis, secretion and regulation, affecting the expression of FXR, the main nuclear receptor that regulates BA metabolism and transport within the liver [31]. Thus, Khambu et al. [31] demonstrated that mice deficient in autophagy due to a lack of Atg7 and Atg5 genes, exhibited hepatic cholestasis characterized by increased serum and liver BA loads, biliary hyperplasia, and suppressed BA transporters such as BSEP which are transactivated by FXR. Interestingly, deletion of Nrf2 gene in autophagy-deficient mice, rescued FXR suppression and reversed the cholestatic injuries [31]. The authors concluded that there is a regulatory loop between FXR and autophagy, in which BA can suppress autophagy, and deficiency in autophagy downregulates FXR via NRF2 expression [31]. This study suggests that several targets including AMPK, NRF2, autophagy regulators and FXR are to be considered for developing novel therapies for liver cholestatis and fibrosis. Thus, betulinic acid [38] (a natural pentacyclic triterpenoid), 5-aminoimidazole-4-carboxamide-1β-D-ribofuranoside (AICAR) [39], metformin [40][41], and GSK621 [42] are AMPK activators known for beneficial effects related to several diseases including diabetes, obesity, chronic inflammation, and cancer, and deserve to be investigated in the context of cholestasis [43]. In fact, recent studies identified the AMPK/FXR axis as having critical role in cholestatic liver injuries [44]. NRF2 transcription factor has been considered to be almost exclusively positive in promoting cell survival under detrimental conditions due to increased reactive oxygen radicals, via activation of target genes bearing antioxidant response element (ARE) in their promoters [45]. However, there are also negative effects related to NRF2, for example, excessive upregulation of NRF2 pathway can result in cell dysfunction or help cancer cell survival and chemotherapy resistance [46]. A quest for NRF2 antagonists led to the identification of brusatol, a quassinoid isolated from an evergreen shrub Brucea javanica , to decrease the level of NRF2 in a series of cancer cell lines [46][47]. The effect of such NRF2 inhibitors on models of cholestatic liver injuries, are still to be tested.

The signaling pathways initiated by BA through FXR, HNF4α, and other transcription factors and the effects of BA on various homeostatic processes such as autophagy are still to be understood (i.e., how increased BA in the liver due to biliary obstruction, influence cell energy homeostasis, autophagy and lysosome functions). Data from studies on the effect of FXR agonist on liver cholestasis, have been controversial, probably due to a poor understanding of the FXR role in autophagy.

In summary, recent studies show that increased ROS as result of BA toxicity in cholestasis, have negative effects on autophagy, and more drugs are to be designed to address the signaling pathways of FXR in connection to autophagy.

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