

Intestinal nuclear bile acid receptor FXR and cholestasis

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Article commented:

Salvatore Modica, Michele Petruzzelli, Elena Bellafante, Stefania Murzilli, Lorena Salvatore¹, Nicola Celli, Giuseppe Di Tullio, Giuseppe Palasciano, Tarek Moustafa, Emina Halilbasic, Michael Trauner, Antonio Moschetta. Selective Activation of Nuclear Bile Acid Receptor FXR in the Intestine Protects Mice Against Cholestasis. *Gastroenterology* 2011; Doi:10.1053/j.gastro.2011.10.028.

Original abstract

Background & aims. Cholestasis is a liver disorder characterized by impaired bile flow, reduction of bile acids (BA) in the intestine, and retention of BAs in the liver. The farnesoid X receptor (FXR) is the transcriptional regulator of BA homeostasis. Activation of FXR by BAs reduces circulating BA levels in a feedback mechanism, repressing hepatic cholesterol 7 α -hydroxylase, the rate-limiting enzyme for the conversion of cholesterol to BA. This mechanism involves the hepatic nuclear receptor small heterodimer partner and the intestinal fibroblast growth factor (FGF) 19 and 15. We investigated the role of activation of intestine-specific FXR in reducing hepatic levels of BA and protecting the liver from cholestasis in mice. **Methods.** We generated transgenic mice that express a constitutively active FXR in the intestine. Using FXR gain- and loss-of-function models, we studied the roles of intestinal FXR in mice with intrahepatic and extrahepatic cholestasis. **Results.** Selective activation of intestinal FXR induced FGF15 and repressed hepatic Cyp7a1, reducing the pool size of BA and changing the BA

pool composition. Activation of intestinal FXR protected mice from obstructive extrahepatic cholestasis following bile-duct ligation or administration of a-naphthylisothiocyanate. In Mdr2^{-/-} mice, transgenic expression of activated FXR in the intestine protected against liver damage, whereas absence of FXR promoted progression of liver disease. **Conclusions.** Activation of FXR transcription in the intestine protects the liver from cholestasis in mice by inducing FGF15 expression and reducing the hepatic pool of BA; this approach might be developed to reverse cholestasis in patients.

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Comment

Bile secretion involves complex mechanisms, from the formation of bile in the liver, its modification in the ductules and bile ducts, to discharge into the intestine.^{1,2} The best defined nuclear receptor for bile acids, farnesoid X receptor (FXR, NR1H4), is critically involved in the regulation of Na⁺-dependent (NTCP) and Na⁺-independent hepatocellular bile acid uptake (OATP1B1 and OATP1B3),^{3,4} canalicular excretion of monovalent (BSEP)⁵ and divalent bile acids (MRP2), excretion of phospholipids (MDR3), and conjugated bilirubin (MRP2); it also regulates the limiting step of bile acid production (Cyp7a1).^{6,7}

Collectively, activation of FXR reduces hepatocellular bile acid concentration and bile acid-induced toxicity and therefore represents a key molecular target when dealing with cholestasis.¹⁵ The reduction of hepatic BA overload and of the hydrophobic index of the BA pool are both recognized therapeutic goals for the management of cholestasis.

In the physiopathology of cholestatic diseases FXR plays a pivotal role in maintaining BA homeostasis by regulating every aspect of BA metabolism, including synthesis, transport, and refilling of the gall bladder.^{8,9} FXR senses elevated hepatic bile acid levels and inhibits hepatic bile acid biosynthesis from cholesterol by induction of the metabolic repressor Small

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Heterodimer Partner (SHP). SHP inhibits expression of cholesterol 7 α hydroxylase (Cyp7a1), a rate limiting enzyme in the BA biosynthetic pathway, by blocking transactivation of hepatic activators, LRH-1 and HNF-4, at the promoter.¹⁰⁻¹²

Modica, *et al.*, in the present publication, generated a transgenic mouse model expressing a constitutively active form of FXR in the gut (iVP16FXR) and they tried it with three different conditions of cholestasis. They present evidence that selective activation of intestinal FXR improves cholestatic diseases.

First, they used a severe condition of obstructive extrahepatic cholestasis (BDL mouse model) where BA accumulate in the liver when the drainage of bile from the liver to the duodenum is interrupted. Then they used an intrahepatic cholestasis model, (the ANIT model). In this model of chemically induced intrahepatic cholestasis, ANIT damages the cholangiocytes in the bile duct. Finally, they mated iVP16FXR mice with Mdr2^{-/-} mice, a model of genetically-induced intrahepatic cholestasis.

In the first model of cholestasis, histological analysis of the liver showed large areas of necrosis with inflammatory cell infiltration in BDL iVP16 mice, while BDL iVP16FXR mice were protected, exhibiting fewer and smaller necrotic lesions.

In the ANIT model, Modica, *et al.* demonstrated that a selective activation of intestinal FXR protects from chemically-induced intrahepatic cholestasis. They arrived at this conclusion when iVP16FXR mice treated with ANIT exhibited fewer and smaller necrotic areas, while liver damage in iVP16 mice was shown by the yellowish color saturation of serum.

In the genetically-induced intrahepatic cholestasis model, the suppression of Cyp7a1 by activation of intestinal FXR was observed in the reduced amount and reduced hydrophobic index of the biliary BA pool in iVP16FXR/Mdr2^{-/-} mice. Histological analysis of the liver showed fewer and smaller areas of necrosis with less severe inflammatory cell infiltration with respect to iVP16/Mdr2^{-/-} mice.

In all three models of cholestasis the selective activation of intestinal FXR yielded significant reduction in serum transaminase activities with a significant improvement in the hepatic function.

The fine work of Modica, *et al.* clearly shows the protective effects of selective activation of intestinal FXR against cholestasis due to the reduced BA pool total size.

The importance of this work lies in a better understanding of the various mechanisms involved in the physiopathology of cholestasis where FXR is involved.

FXR protects the liver from high BA by regulating the expression levels of BA transporters. The events triggered by FXR in the gut liver axis probably represent a therapeutic option through the decrease in the excess of bile acids in the liver. However, this mechanism is ruled out in extrahepatic cholestasis. On the other hand, activation of the FXR-Fgf15 pathway in the intestine could orchestrate the primary mode of action to improve cholestatic disease.

In fact Fgf15 senses bile acid concentrations in the intestine in an FXR-dependent manner; it is in turn secreted from enterocytes and signals to the liver, where it binds to Fgf receptor and represses Cyp7a1 through a mechanism involving a c-Jun N-terminal kinase-dependent pathway. In humans FGF19 could be involved in repression of Cyp7a1, and could also be the major molecular mechanism for understanding the protection in cholestasis by intestinal FXR activation.¹³⁻¹⁵

It would be important to start studying molecular interactions between intestinal FXR and FGF15 because such interactions showed favorable biochemical, histological and genetic results in a biological model of cholestasis. Circulating FGF15 levels could not be measured due to the absence of a validated protocol; more research is needed about FGF15 for it might be considered as the prototype for a new therapeutic target involving activation of intestinal FXR and repression of hepatic cholesterol 7 α -hydroxylase. Finally, we encourage the study of BSEP and MDR2 (mouse)/MDR3 (human) transporters for cholestasis, as once a reduction of the pool size of bile acids is achieved using intestinal FXR / FGF15 the following step is to help to the proper secretion of bile acids and phospholipids, both of which occur concomitantly.

This could be greatly helpful in better understanding the physiopathology of cholestasis, which could allow us to efficiently confront a whole range of diseases arising from the interruption of bile flow.

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