BILE ACID, LIPID AND FXR CONTROL

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Bile acids, synthesized in the liver from cholesterol, play a key role in dietary lipid, cholesterol and vitamin absorption. Accumulation of high bile acids can elicit cytotoxicity, and the elevated concentrations are associated with liver injury. Hepatic bile acid levels are tightly regulated by a balance of hepatic bile acid uptake, biosynthesis and efflux. Hepatic bile acid synthesis and bile acid uptake are suppressed and biliary bile acid excretion is enhanced under conditions of hepatic bile acid accumulation. These functional changes are dependent on the hepatic levels of enzymes involved in bile acid synthesis and transporters such as CYP7A1, NTCP and BSEP. Hepatic bile acid-activated farnesoid X receptor (FXR) signaling is involved in these functional changes. FXR directly up-regulates BSEP expression and down-regulates CYP7A1 and NTCP expression through up-regulation of small heterodimer partner (SHP).

Although most studies addressing the regulation of hepatic bile acid levels have focused on liver, there is evidence that the intestine has an important role in this process. In rodents, blocking the flow of bile acids into the intestine by bile duct ligation increases CYP7A1 expression and activity in liver. Since hepatic concentrations of bile acids increase under these conditions, this unexpected result suggests a role of the intestine in feedback repression of bile acid synthesis. One possible explanation for these results is that the intestine secretes a factor that is important for feedback regulation of bile acid synthesis in liver. Fibroblast growth factor 15 (FGF15) was identified as the factor [1]. Intestinal FGF15 up-regulated by bile acid-activated FXR signaling is released into the portal circulation and carried to the liver where it signals to down-regulate CYP7A1 expression (Fig. 1). FGF15 can signal hepatocytes through its cell-surface receptor FGFR4 although hepatic FGF15 expression has not been detected. Treatment with the FXR-selective agonist GW4064 significantly repressed CYP7A1 in liver-specific Fxr-null mice but not intestine-specific Fxr-null mice, demonstrating that activation of FXR (induction of FGF15) in intestine but not liver is required for short-term repression of CYP7A1 in liver. Hepatic CYP7A1 expression is thus, coordinately modulated by FXR signaling pathways in both liver and small intestine. These facts raise a possibility that several hepatic bile acid-related genes are regulated by FGF15 derived from small intestine.

Recently, we found that administration of ampicillin or feeding of high fat diet altered ileal FGF15 mRNA levels in mice. Administration of ampicillin decreased ileal FGF15 mRNA levels in mice whereas it increased hepatic CYP7A1 mRNA levels and hepatic bile acid concentrations. On the other hand, feeding of high fat diet increased ileal FGF15 mRNA levels whereas it decreased hepatic CYP7A1 mRNA levels and hepatic bile acid concentrations. This phenomenon was observed in both wild-type and Fxr-null mice. These results suggest the existence of several FXR-independent mechanisms for the regulation of ileal FGF15 expression to modulate hepatic bile acid levels.

References