commentary

Resolving the mechanism of bile acid negative-feedback regulation, a *Journal of Lipid Research* tradition[1]

The December 2007 issue of the *Journal of Lipid Research* contains a paper deserving of recognition both for its scientific importance and for addressing a topic that has been central to the interests of this journal. The paper by Kim et al. (1) addresses the controversial role of bile acids in the regulation of cholesterol-7α-hydroxylase (CYP7A1), the enzyme responsible for regulating the conversion of cholesterol into bile acids. The cholesterol-to-bile acids pathway is important as a means to maintain cholesterol homeostasis and to produce bile acids, which are essential for the absorption of essential fat-soluble nutrients. In 1970, Erwin Mosbach, an editor of the *Journal of Lipid Research*, and his coworkers showed that bile acids attenuate their own synthesis by reducing the activity of CYP7A1 (2). Because bile acids are potentially potent toxins (they are powerful detergents used experimentally to disrupt membranes), bile acid negative-feedback regulation of CYP7A1 was proposed as an important means to limit the size of the bile acid pool. Although these results led to the common belief that bile acids were the immediate factors that attenuated CYP7A1, the discovery that isolated liver cells in culture failed to display bile acid negative feedback (3, 4) initiated a controversy that appears now to be reconciled in the paper by Kim et al. (1).

The discovery that bile acids were the specific ligands necessary for activating the bile acid nuclear receptor FXR (5–7) provided an essential but circuitous lead toward elucidating a mechanism linking bile acids to the control of hepatic gene expression. The discovery that gene-targeted deletion of FXR blocked bile acid repression of CYP7A1 in mice provided solid evidence that FXR played a key role (8). Subsequent findings showing that the FXR-inducible factor SHP-1 repressed the expression of CYP7A1 (9) focused attention on this enigmatic non-DNA transcription factor. The unexpected finding that CYP7A1 expression in mice lacking SHP-1 was repressed normally following administration of bile acids, but was unaffected by the FXR-specific agonist GW4064, led to the proposal that there were both SHP-1-dependent and SHP-1-independent mechanisms by which FXR regulated CYP7A1 (10, 11).

Two SHP-1-independent mechanisms mediating bile acid-mediated repression of CYP7A1 have been proposed. One involves the ability of unconjugated bile acids to activate Kupffer cell secretion of inflammatory cytokines, which subsequently act on hepatocytes, causing an SHP-1-independent repression of CYP7A1 (12). The other SHP-1-independent mechanism involves activation of the tyrosine kinase associated with fibroblast growth factor receptor 4 (FGFR4) (13). The FGFR4 ligands responsible for initiating repression of CYP7A1 are FGF15 (mouse) and FGF19 (human), which are both produced by intestinal ileal cells (14–16). The discovery that intestinal expression of FGF19 (17) and FGF15 (18) is induced by activation of FXR explains why bile acid negative-feedback regulation of CYP7A1 could not be reproduced in cell culture systems consisting only of hepatic parenchymal cells (19).

Using tissue-specific gene deletion of FXR, Kim et al. (1) show that deletion of FXR in intestinal epithelial cells blocks the ability of the FXR agonist GW4064 to repress CYP7A1, owing to the inability of intestinal cells to express FGF15. In marked contrast, deletion of FXR selectively in liver parenchymal cells did not interfere with the ability of GW4064 to repress CYP7A1 via a mechanism that was independent of increasing hepatic SHP-1 expression. This mechanism required induction of intestinal FXR-dependent FGF15, which subsequently acted on hepatic FGFR4 to elicit transcriptional repression of CYP7A1. Because bile acids apparently do not require SHP-1 expression to repress CYP7A1 expression, whereas GW4064 does (10, 11), it would have been interesting to know how selective deletion of intestinal and liver FXR affected the ability of bile acids to repress CYP7A1.

The *Journal of Lipid Research* should take pride in having played such an important role in bringing the issue of bile acid negative-feedback regulation to the attention of the scientific community. One might expect that Erwin Mosbach, Sarah Shefer, and their coworkers (2, 20), who pioneered the first attempts to elucidate the mechanism responsible for bile acid negative-feedback regulation, would appreciate the complexity of the answer provided by Kim et al. (1). Bile acid negative-feedback regulation is a clear example of how biological systems tend to follow circuitous paths that can initially confound logical understanding. However, with respect for the capricious vagaries of biology, complex mechanisms can be elucidated with clever, systematic study.

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