Curiouser and curiouiuser!

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Although Alice may have had things in mind other than bile acids, it is her fascination with the remarkable nature of her surroundings that leads to this exclamation in Lewis Carroll’s 1865 classic “Alice’s Adventures in Wonderland”. In this same frame of mind, although perhaps not as dreamily artful, we are learning more and more about the intricacies and linkages between bile acid flux, intestinal biology, and the ever-expanding roles of bile acids as signaling molecules that act directly and indirectly to orchestrate biological crosstalk between intestine and liver.

In 1999, we learned that bile acids are gene regulators, acting as strong and powerful ligands for several members of the nuclear receptor superfamily [1] including FXR, PXR, LXR, VDR, and others [2]. As potent ligands for FXR (NR1H4), bile acids regulate diverse biological pathways such as those involved in glucose, amino acid and lipid metabolism, cell cycle progression, drug detoxification, bile acid synthesis, and the adaptive response to cholestasis. In the latter capacity, bile acids, in ways that are now known to extend beyond gene regulation through FXR, act as both sensor and effector to autoregulate intracellular levels of bile acids, to reduce inherent toxicities of intracellular bile acid accumulation in hepatocytes. However, in the ensuing years, since the discovery of bile acids as gene regulators, it has become apparent that these autoregulatory pathways of bile acids in the liver were not able to fully explain the complexities of the liver’s response to bile acid retention within the same cell. There were hints that there were complexities that involved regulatory molecules and pathways that were not nuclear receptor mediated, and even involved specific intervention from its upstream neighbor—the intestine. In fact, to the consternation of hepatologists worldwide, it appears that the intestine is a great protector and regulator of liver health through fine-tuning bile acid homeostasis in ways that require intestinal FXR [3].

One of those aspects of whole body bile acid regulation that engages the intestine, and were difficult to explain with bile acids–FXR autoregulation in liver alone, is the following observation: while inhibition of apical intestinal bile acid uptake leads to induction of hepatic bile acid synthesis, blocking intestinal bile acid basolateral export (but keeping apical import) leads to suppression of hepatic bile acid synthesis. If it is just the return of bile acids to the liver that directs the expression of genes involved in hepatic bile acid synthesis, then one would presume that both intestinal processes should lead to the same hepatic outcome (i.e., reduced hepatic bile acid synthesis). However, such is not the case and hepatic bile acid synthetic responses are truly distinct when one blocks either intestinal apical import or basolateral export. A simple explanation is elusive, but may, in fact, rest on the enteroocyte’s FXR-mediated responses to retained bile acids within.

It is along these lines that Lan et al. in Dr. Paul Dawson’s laboratory directed their energies to help explain these apparently incongruous findings in a clear and important publication in this issue of the Journal of Hepatology [4]. The group focused their attention on mice where intestinal basolateral bile acid export is inhibited due to genetic disruption of the Ostα gene (Ostα–/–, whose product is a necessary component of a heterodimer responsible for basolateral bile acid export from the intestine into the portal circulation) [5,6]. Why these mice would have decreased hepatic bile acid synthesis, and if it rests with FXR-mediated pathways, formed the focus of their studies, by comparing wild type (WT) to Ostα−/− to FXR−/− to Ostα−/−FXR−/− double knockout mice (DKO).

Although there were several distinctions between the genetic subtypes, a few essential and intriguing outcomes were seen in both intestine and liver. Of note, the distal small intestine of Ostα−/− and DKO mice was remarkably thicker, blunter, with immature enterocyte morphology. There was also increased mass, cell number, and nucleic acid content along a luminal distribution, in keeping with prominent bile acid uptake in the terminal ileum. Why retention of bile acids leads to increased intestinal mass in an FXR-independent fashion remains to be determined.

For the liver, there were several notable changes, whereby the main inducer of bile acid synthesis, Cyp7a1, was markedly suppressed in Ostα−/− mice, but was substantially increased in DKO mouse livers. Thus, the similar changes in intestinal morphology did not have similar effects on liver bile acid gene regulation.

However, there was a substantial difference in an FXR-responsive gene in the ileum that is a main signaling molecule that suppresses hepatic Cyp7a1 (and other genes) after coursing through the portal circulation—FGF15. Total FGF15 protein in the hyper trophyed Ostα−/− ileal tissues was substantially higher (upwards...
Editorial

of 20×) than in WT FXR−/− and DKO mice. Intriguingly, ileal FGF15 RNA levels were not substantially increased in these same tissues, arguing for multi-layered regulation of this gene in these tissues that weaves together alterations in bile acid uptake, changed FXR functions and expression, along with bile acid regulation of other cell signaling pathways. Thus, there is both support, and new questions, that point to roles that include, and in many ways do not include, ileal FXR regulation by retained bile acids. This is an intriguing process that requires additional studies to tease apart the relevant contributors.

There are several unanswered questions uncovered by these careful studies. The lack of substantial ileal bile acid retention in Ost−/− mice suggests either a counter-regulatory process (e.g., reduced apical bile acid uptake seen in these samples) or, perhaps, new hormones or regulatory molecules as yet unnamed. The actual mechanisms leading to ileal hyperplasia and why these do not include FXR is also quite intriguing. What is clear is that bile acids, and their evolutionary roles in ileal and hepatic biology, have many secrets waiting to be discovered. Researchers like Tan et al. are likely to provide novel insights into the complexities of liver and intestinal biology to help those of us grappling with the reasons for these linked homeostatic responses [7]. In the near future, it is anticipated that our understanding of bile acid biology will be curiourser and curiourser, but also will certainly be a lot clearer.

Conflict of interest

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References


