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EDITORIAL

OSTα-OSTβ Guards the Ileal Enterocyte From the Accumulation of Toxic Levels of Bile Acids

OSTα-OSTβ (*SLC51A* and *SLC51B*) is a heteromeric organic solute transporter that was first isolated from the liver of a marine skate, *Leukoraja erinacia*, by Ballatori's lab in a quest for a sodium-independent transporter of hepatic bile acid uptake.[1] Subsequent studies identified SLC51A and B orthologues from mice and humans. These 2 gene products are the only known members of this SLC family. The transporter is unique in requiring 2 subunits for function. Human *SLC51A* encodes for a 340–amino acid protein with 7 membrane-spanning domains whereas *SLC51B* encodes for a 128–amino acid single-membrane-spanning domain protein. Functional solute transport requires heterodimerization of both gene products for stability and delivery to the basolateral plasma membrane. OSTα-OSTβ is expressed in many tissues, but primarily the distal intestine, renal proximal tubule, and bile duct, where it is known to transport bile acids across the basolateral membrane of the ileal enterocyte, renal proximal tubule, and the cholangiocyte. The mechanism of transport is by facilitated diffusion, either efflux or uptake, depending on the electrochemical gradient. OSTα-OSTβ also transports steroids, particularly in the ovary, testes, and adrenal gland, as well as eicosanoids and possibly other sterols.

Bile acid absorption from the intestinal lumen is performed by the apical sodium-dependent bile acid transporter (ASBT) in the ileal enterocyte. Bile acids then are transported by OSTα-OSTβ across the basolateral membrane and out of the cell, back to the liver via the portal circulation. Together, ASBT and OSTα-OSTβ are key regulators that maintain homeostasis of the bile acid pool and guard against tissue bile acid accumulation and toxicity via Farnesoid X Receptor (FXR)–fibroblast growth factor 15/19-fibroblast growth factor receptor 4 regulatory mechanisms.[2]

Deletion of *Ostα* in mice produces a paradoxical phenotype compared with *Asbt* deletion: it reduces the bile acid pool size by approximately 50%, down-regulates rather than increases hepatic Cyp7A1 activity, decreases the absorption of intestinal lipids, and protects these animals from cholestatic injury induced by bile duct ligation or cholic acid feeding.[3] *Ostα-/-* mice also have an interesting intestinal phenotype manifested at birth by an increase in intestinal length, a marked decrease in villous height with accumulation of goblet cells on the apical mucosal surface, and an increase in epithelial proliferation. These observations raised the inevitable question as to whether these intestinal changes are the result of accumulation of toxic bile acids in the enterocyte.

This is the subject of the article by Ferrebe et al in this month's issue of *Cellular and Molecular Gastroenterology and Hepatology*.[4] They focused on neonatal *Ostα-/-* mice and showed that the bile acid transporter, Asbt, is expressed earlier in the knockout mice, thus potentially allowing increased uptake of bile acids into the intestine in the absence of efflux. Although the authors were unable to measure intracellular levels of bile acids in the enterocyte of the young mice, they showed a significant increase in bile acid–activated FXR target genes, suggesting that the enterocyte intracellular bile acid concentration is increased. Furthermore, they were able to completely restore the intestinal histologic abnormalities to normal by introducing an Asbt deletion in *Ostα-/-* mice, thus preventing bile acids from entering the ileal enterocytes. Evidence also is put forward that the gene expression of major anti-oxidants (nuclear factor-like 2 and reduced nicotinamide adenine dinucleotide phosphate oxidase-1) in the enterocyte of neonatal *Ostα-/-* mice is increased and that the expression of these genes also reverts to normal in the double *Asbt/Ostα* knockout mice. In a parallel study, the authors deleted nuclear factor-like 2 in the intestine of Drosophila, resulting in increased sensitivity to bile acid toxicity, providing supporting evidence for a role of antioxidant defense mechanisms in protecting against bile acid tissue toxicity. Thus, the main conclusion of this study was that in addition to its role in maintaining bile acid homeostasis, OSTα-OSTβ also serves to protect the ileal enterocyte from accumulating toxic levels of bile acids. *Ostα* null mice mature to adults and have a normal life span, suggesting that the anti-oxidant response, although not reducing the pathologic phenotype, manages to keep it from progressing to irreversible tissue damage.

One limitation of this study was the technical inability to directly measure ileal tissue levels of bile acids. Thus, it remains possible that other substrates also might play a role in producing this intestinal pathology. Nevertheless, the significant increases in expression of FXR-regulated genes in the ileum such as the ileal bile acid–binding protein, lbabp, supports the presumption that tissue levels of bile acids are increased in the ileum of the *Ostα-/-* mice. Bile acid accumulation in the ileum also is thought to play a role in the pathogenesis of necrotizing enterocolitis, where diminished expression of OSTα-*OSTβ* could be contributing factors.

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Conflicts of interest
The author discloses no conflicts.

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