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EDITORIAL

Protein Kinase Cβ: Linking Intestine Fibroblast Growth Factor 15 to Hepatic Extracellular Signal Regulated Kinase 1/2 Signaling in Bile Acid and Cholesterol Homeostasis

Cholesterol homeostasis is maintained by balancing cholesterol input from diet and de novo synthesis and output via conversion to bile acids in the liver and sterol hormones in steroidogenic tissues. About 50% of cholesterol is converted to bile acids, which facilitates biliary secretion of another 40% of cholesterol. Thus, bile acid synthesis and metabolism is critical for maintaining whole-body cholesterol homeostasis. Most bile acids (~95%) in the gastrointestinal system are reabsorbed in the ileum and transported back to the liver to inhibit the transcription of cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme in bile acid synthesis. The enterohepatic recirculation of bile acids is an important physiologic process that plays a critical role not only in feedback regulation of bile acid synthesis but also in nutrient absorption and metabolic homeostasis in the entire body. Imbalance of cholesterol and bile acid homeostasis contributes to cholesterol gallstone disease.

The lithogenic diet is a high-fat diet supplemented with 0.5% cholic acid and 1% cholesterol. Addition of cholic acid facilitates cholesterol absorption in the intestine. This diet is widely used to induce cholesterol gallstones and hypercholesterolemia in rodents. In this issue of *Cellular and Molecular Gastroenterology and Hepatology,* Huang and Mehta[1] reported that a lithogenic diet strongly induced PKCβ and PKCδ mRNA and protein in hepatocytes; deficiency of protein kinase C β (PKCβ) but not PKCδ promoted lithogenic diet-induced gallstone formation. Furthermore, induction of PKCβ via lithogenic diet was reduced in Apoe$^{-/-}$ mice but enhanced in liver orphan receptor α–deficient (Lxrα$^{-/-}$) mice. LXRα is an oxysterol sensor that induces CYP7A1 and bile acid synthesis but increases serum triglycerides in mice. In PKCβ$^{-/-}$ mice, CYP7A1 mRNA expression was reduced; low-density lipoprotein receptor, involved in uptake of serum cholesterol to the liver, and steroid response element–binding protein 2, involved in haptic de novo cholesterol synthesis, were increased.

These data suggest that induction of PKCβ via a lithogenic diet may coordinately regulate hepatic cholesterol and bile acid synthesis. Interestingly, this study showed that the lithogenic diet enhanced the induction of fibroblast growth factor 15 (FGF15) in the intestine of PKCβ$^{-/-}$ mice. This study uncovered an interplay between the ileum PKCβ/FGF15/FGF receptor 4 (FGFR4)/extracellular signal regulated kinase (ERK) axis and the hepatic PKCβ/proto-oncogene serine/threonine-protein kinase (Raf-1)/mitogen-activated protein (MAP) kinase kinase (MEK)/ERK axis to modulate hepatic cholesterol and bile acid homeostasis via lithogenic diet. In PKCβ$^{-/-}$ mice, this intestine to liver signaling crosstalk is impaired to exacerbate the lithogenic diet-induced cholesterol gallstone formation.

This study has added to our increasing appreciation of the critical role of the gut-to-liver axis in gastrointestinal diseases, diabetes, and obesity. The gut microbiota are involved in the deconjugation of conjugated bile acids for subsequent dehydroxylation of cholic acid and chenodeoxycholic acid (primary bile acids) to deoxycholic acid and lithocholic acid (secondary bile acids), respectively. The secondary bile acids have antibacteria activity that controls bacteria overgrowth and inflammation in the intestine. It is somewhat surprising that CYP7A1 expression is reduced in PKCβ$^{-/-}$ mice. Previous studies showed that bile acids activated classic PKCα and novel PKCδ in hepatocytes to activate cJun and (ERK1/2), which inhibited bile acid synthesis.[2–4] It is possible that different PKC isoforms expressed in hepatocytes may have different effects on bile acid synthesis.

It is also quite intriguing that the lithogenic diet induced PKCβ in wild-type mice, but also induced FGF15 expression in both wild-type and PKCβ$^{-/-}$ mice. This is in contrast to the induction of FGF15 by bile acid–activated farnesoid X receptor in the intestine. It has been reported that intestine-produced FGF15 may be secreted to the portal circulation to the hepatocytes to activate FGFR4/β-Klotho/cJun and ERK1/2 signaling, which inhibits *CYP7A1* gene transcription.

Further study is needed to resolve the paradoxical effect of bile acid–induced PKCβ signaling in inhibiting FGF15 production in the intestine and to understand the underlying molecular mechanism. As suggested by these investigators, elucidating the impact and the underlying mechanism of PKCβ in diet-induced gallstone formation may identify therapeutic targets for treating this common gastrointestinal disease.

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Conflicts of interest
The author discloses no conflicts.

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