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EDITORIAL

Bile Acids: Connecting Link Between Autophagy and Gut Microbiome

Bile acids are amphiphilic molecules earlier known only for their role in digestion but more recently found to be critically involved in intraorgan and interorgan signaling.[1] Their role in establishing communication between organs, such as liver, gut, heart, and brain, has been well documented.[2,3] Increases in bile acid levels are generally injurious to health. Particularly, chronic bile acid elevation leads to liver injury and hepatocellular carcinoma.[4] However, at normal levels, bile acids play a major role in maintaining gut health and regulating liver regeneration.[5] Autophagy is a cellular recycling process that can reuse cellular macromolecules.[6] Maintaining autophagic flux is critical for cellular function and dysregulation of autophagy is involved in pathogenesis of several diseases that share inflammation and tissue injury as common features.[7] In the liver, autophagy plays a role in liver injury, regeneration, prevention of metabolic diseases, and its dysregulation leads to liver cancer.[8] However, the role of autophagy in interorgan signaling, such as the gut-liver axis, which is a critical feature of physiology and pathology, is not known.

In this issue of the *Cellular and Molecular Gastroenterology and Hepatology*, Yan et al[9] demonstrate that bile acids are the connecting link between hepatic autophagy and gut microbiota. In these studies conducted using Atg5 null mice ($Atg5^{-/-}$), the authors demonstrate that disruption of autophagy in the hepatocytes results in changes in bile acid levels and composition, which in turn affect the gut microbiome. Alterations in the gut microbiome result in hyperactivation of bile acid–induced FXR signaling in ilial epithelial cells causing significantly higher FGF15 levels. Yan et al[9] further showed that antibiotics-mediated decrease in gut microbiome or reduction of bile acids using bile acid sequestrant cholestyramine resulted in decreased FGF15 levels. Reduction in FGF-15 levels cause an increased injury in the $Atg5^{-/-}$ mice, highlighting the protective role of FGF15 in autophagy-deficient mice. The interesting part is that the $Atg5^{-/-}$ mice exhibited specific change in bile acids composition favoring growth of gut microbes that in turn affected secondary metabolism of bile acids by reducing levels of conjugated bile acids and increase in unconjugated bile acids. Increased unconjugated bile acids drive ilial FXR activation to induce FGF15 production, which is hepatoprotective because studies using antibiotic treatment or bile acid sequestration in the $Atg5^{-/-}$ mice reduce FGF15 and increase liver injury.

Overall, these studies have identified an interesting adaptive mechanism in autophagy-deficient $Atg5^{-/-}$ mice that protects them from ongoing liver injury. These findings raise further questions, both mechanistic and those related to clinical application. It is not clear, for instance, why lack of autophagy results in a specific change in bile acid composition. Furthermore, how different bile acids actually dictate gut microbiome composition was also not addressed. However, the data indicate that loss of hepatic autophagy tries to self-correct the damage by using bile acids as signals to change the gut microbiome and induce FGF15, which are hepatoprotective. This publication contributes to the mechanistic understanding of the role autophagy in chronic liver diseases, such as primary sclerosing cholangitis and primary biliary cirrhosis, where a significant change in the gut microbiome is observed. Observations by Yan et al[9] argue that changes in the gut microbiome could be a protective adaptive mechanism brought about by alerted bile acid levels and composition. The notion that dysregulation in autophagy could be responsible for such change is interesting and innovative.

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Conflicts of interest
The authors disclose no conflicts.


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