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EDITORIAL

Interplay of Gut Microbes and Aryl Hydrocarbon Receptor in Alcohol-Associated Liver Disease

Alcohol-associated liver disease (ALD) is a major public health concern, causing 0.9% of all deaths in 2010.[1] In some cases, ALD can progress to alcoholic hepatitis, which presents as acute-on-chronic liver failure and has limited treatment options.[2] Reports of changes in alcohol consumption and increases in severe ALD during the COVID-19 pandemic reinforce the urgent need to provide therapeutic targets and develop new treatments for ALD.[3]

The importance of intestinal microbiota has been demonstrated in the initiation, progression, and severity of ALD.[4] An elegant study using mice transplanted with intestinal microbiota from patients with alcoholic hepatitis suggest that intestinal microbiota is a causal factor for ALD.[5] In addition, Wrzosek et al[6] recently reported that treatment with pectin, a prebiotic fiber that alters intestinal microbiota composition,[7] improved ALD in mice transplanted with humanized intestinal microbiota by increasing gut microbial production of tryptophan metabolites, many of which activate aryl hydrocarbon receptor (AHR), a widely expressed and conserved ligand-activated nuclear receptor. Studies using whole-body *Ahr*-knockout mice demonstrated that the efficacy of pectin treatment in a mouse ALD model was partially dependent on AHR, whereas ligand activation of AHR imitated the effect of pectin.[6] Importantly, serum levels of tryptophan and its metabolites that act as AHR agonists are reduced in patients with severe alcoholic hepatitis compared with those with mild or moderate alcoholic hepatitis, and negatively correlate with disease severity, suggesting that restoration of AHR activation may be a therapeutic strategy for ALD.[6] However, it is not clear which cell types contribute to AHR-mediated protection against ALD because AHR is widely expressed.

In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, by using intestinal epithelial cell (IEC)-specific *Ahr* knockout mice ($Ahr^{\Delta IEC}$), Qian et al[8] demonstrated that AHR signaling in IEC plays an important role in ameliorating ALD. They found that ethanol consumption in mice and humans reduced intestinal expression of AHR. Ethanol feeding in $Ahr^{\Delta IEC}$ mice increased liver injury and induced gut dysbiosis characterized by increases in *Helicobacter ganmani* and *Helicobacter hepaticus* content and translocation to the mesenteric lymph nodes and liver compared with $Ahr^{f/f}$ mice. Moreover, the authors also found that compared with wild-type mice, ethanol-fed $Ahr^{\Delta IEC}$ mice had alternation of many metabolites in the gut, with notable elevation of short-chain fatty acid isobutyric acid (IBA). Administration of IBA exacerbated ethanol-induced liver injury and steatosis in mice, which is partly mediated via the upregulation of hepatic elongation of long-chain fatty acids 7 (*Elovl7*) expression. Importantly, oral administration of AHR agonists ameliorated ALD in mice with upregulation of AHR-target genes in the intestine but not in the liver, providing intestinal AHR as a potential therapeutic target for ALD.

The importance of the work by Qian et al[8] goes beyond intestinal AHR; understanding how ethanol disrupts the vital crosstalk between the gut microbiota, intestine, and liver is essential to discover druggable therapeutic targets for ALD. Previous studies have demonstrated that the alteration of intestinal microbiota by fecal microbiota transplantation, pectin supplementation, or bacteriophage targeting of cytolytic *Enterococcus faecalis* show preclinical (and potentially clinical) promise in ALD.[6,9] The identification of *H hepaticus* and, to a lesser extent, *H ganmani*, as potential mediators of ALD severity and dysbiosis is significant, and future clinical studies should evaluate the role of these bacteria in ALD to determine whether their alteration would improve liver injury markers.

There are several important findings in the study by Qian et al[8] that need further investigation to determine their significance in ALD. Although intraperitoneal administration of IBA alone induced liver injury, it is not clear whether intestinal IBA can reach the liver. Future studies should evaluate whether IBA administration via gavage induces liver injury in vivo and evaluate the impact of IBA generation on ALD. In addition, *Elovl7* seems to be a promising target to limit ethanol-induced steatosis and deserves further study. In fact, hepatic *ELOVL7* expression is upregulated in patients with alcoholic hepatitis compared with that in healthy control subjects, making ELOVL7 an even more intriguing target for further study.[10]

In our opinion, intestinal AHR activation provides a novel approach to limit liver injury in ALD and perhaps limit progression to alcoholic hepatitis. It is important to note that mouse and human AHR may differ in their transcriptional regulation, and because AHR is widely expressed throughout the body, systemic activation may induce unwanted side effects.[11] Alteration of intestinal microbiota in ALD provides another therapeutic avenue to increase intestinal AHR activation via microbial tryptophan metabolites and to

reduce metabolites that may exacerbate ALD. Well-designed clinical trials using fecal microbiota transplantation or AHR agonists in ALD are warranted because limited treatment options exist.

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