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LETTER TO THE EDITOR

Intestinal virome: An important research direction for alcoholic and nonalcoholic liver diseases

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Abstract

In recent years, the interaction between the gut microflora and liver diseases has attracted much attention. The intestinal microflora is composed of bacteria, archaea, fungi and viruses. There are few studies on the intestinal virome, and whether it has a causal relationship with bacterial changes in the gut is still unclear. However, it is undeniable that the intestinal virome is also a very important portion of the blueprint for the development of liver diseases and the diagnosis and therapeutic modalities in the future.

Key Words: Alcoholic fatty liver disease; Nonalcoholic fatty liver disease; Fatty liver disease; Gut microbiome; Intestinal virome

Core Tip: As of the study of the gut microflora expands, the interaction between the intestinal virome and liver diseases has been gradually revealed. In this letter to the editor, we discuss the changes in the intestinal virome in patients with alcoholic liver disease and nonalcoholic liver disease, and provide suggestions for developing future diagnosis and treatment methods.

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TO THE EDITOR

We have carefully studied the reviews recently written by Sharma *et al*[1], titled "Significance of gut microbiota in alcoholic and nonalcoholic fatty liver diseases". The authors elaborated the intestinal microecological changes in both alcoholic and nonalcoholic liver diseases, and the important effects of intestinal microorganisms on the development of fatty liver diseases. These findings could provide new ideas for the future diagnosis and treatment of fatty liver disease.

In addition to bacteria, archaea and a small amount of fungi, viruses are also an indispensable part of the intestinal microflora in human[2] . In 2020, a multicenter observational study on the enteroviruses from 89 patients with alcoholic hepatitis, 36 patients with alcohol use disorder and 17 patients without alcohol use disorder was concluded[3]. The results showed that in stool samples from patients with alcoholic liver disease, bacterial and fungal diversity decreased and virus diversity increased, which mainly manifested as a large increase in the number of *Myoviridae*, *Lactobacillus* phages, *Streptococcus* phages, *Podoviridae*, *Geobacillus* phages, *Escherichia* phages, and *Herpesviridae*[3]. This trend was positively correlated with the severity of the disease. The changes in the intestinal microecology of people with alcohol use disorder are mainly characterized by an increase in *Parvoviridae* and *Lactococcus* phages[3]. Another study of the intestinal virome in patients with nonalcoholic fatty liver disease (NAFLD) showed that the average relative abundance and viral diversity of phages in patients with NAFLD and severe hepatic fibrosis were significantly lower than those in patients with NAFLD and no or mild hepatic fibrosis[4]. Hence viruses also have positive implications in the diagnosis, severity classification, treatment and prognosis of alcoholic and nonalcoholic liver diseases. However, as an easily neglected part of gut microecology, the impact of viruses was not mentioned in Sharma *et al*[1]'s article.

Bacteria and fungi in the gut microflora have large individual variability and are susceptible to various factors such as age, drugs[5], environment[6], and diet[7]. Likewise, the same is true for viruses. A shotgun metagenome sequencing analysis of DNA viruses in fecal samples from cynomolgus monkeys of different ages showed that the abundance of DNA viruses was inversely proportional to age; that is, the DNA virus group in fecal samples of elderly individuals decreased significantly[8]. However, Lang *et al*[4] found that after the use of proton pump inhibitors, enteroviruses in the feces of patients with nonalcoholic liver disease were also changed. In addition, in high-fat diet-fed mice, the structural composition and β-diversity of enteroviruses were changed. There was a significant decrease in the expression of *Siphoviridae* and a significant increase in the expression of the eukaryotic viruses *Phycodnaviridae* and *Mimivirdae*, and these changes were accompanied by changes in intestinal bacteria [9]. Therefore, considering the original proposal that gut microorganisms should be included in future liver disease diagnosis and treatment, we suggest that in addition to performing a horizontal comparison and finding representative biological markers, it is indispensable to have a methodological design and vertical comparison. However, the effects of confounding factors should also be considered, and individualized diagnosis and treatment plans should be developed for different patients.

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