Editorial Commentary

New insights in the metabolic function related to gut microbiota in the process of liver regeneration

Nan Jiang^, Zhen Wang, Kefei Yuan

Division of Liver Surgery, Department of General Surgery and Laboratory of Liver Surgery, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China

Correspondence to: Kefei Yuan, PhD; Zhen Wang, MD. Division of Liver Surgery, Department of General Surgery and Laboratory of Liver Surgery, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Wuhou District, Chengdu 610041, China. Email: ykf13@163.com; wangzhen@scu.edu.cn.

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Liver disease is a prominent cause of premature mortality globally (1). Many patients with liver diseases require therapeutic liver surgery, usually through hepatectomy (2). Due to the clinical demand for such practice, the study of liver regeneration following hepatectomy holds significant value. The gut microbiota, considered as a "new organ" due to its substantial influence on various physiological functions, has gained increasing attention from the scientific community, particularly in relation to the gut-liver axis. Moreover, a large majority of physicians tend to administer antibiotics as prophylactic drugs prior to liver surgery. Hence, the development of novel tools for evaluating and predicting liver regeneration based on gut microbiota has emerged as a compelling milestone in the field.

A series of previous studies have proved that the crucial cytokines in promoting liver regeneration, including IL-6, TNF-α, IFN-γ, and TGF-β could be modulated by gut microbiota through several pathways, such as microbial extracellular vesicle migration, microbiota translocation (3,4). Despite immune regulation, thanks to the role of the liver as the largest digestive organ in the human body, the role of fermentative gut microbiota in the context of liver metabolism has been put more attention to. Carbohydrate metabolism has been demonstrated to play a leading active role in the recovery of liver function after liver surgery in quantitative proteomics. Additionally, gut microbiota, especially anaerobic bacteria, derived endogenous H_2 can regulate glucose and lipid metabolism in liver, improving a variety of liver injuries, including liver regeneration. As the major content of gut microbiota's metabolites, short-chain fatty acids (SCFAs) have shown positive effects in regulating immunity and metabolism in liver diseases and regeneration. Animal studies and limited amount of clinical research have demonstrated promising promotive effect of SCFAs towards liver regeneration. As discussed elsewhere, there are multiple underlying mechanisms through which SCFAs exert its therapeutic function, this includes regulating metabolism homeostasis and activating cell cycle-related signaling pathways. SCFAs play a pivotal role as notable extracellular agonists for specific G-protein-coupled receptors (GPCRs). Acetate and propionate have the ability to activate GPR41 and GPR43, whereas butyrate additionally activates GPR109A (5). The activation of these receptors has been recognized as a crucial component of JNK1-mediated pathways in promoting liver regeneration (6). In addition, butyrate is important in the regulation of bile secretion and facilitating liver regeneration with detail mechanism undisclosed (7). Despite the positive result,

^ ORCID: 0000-0002-4061-4723.

previous studies have focused more on the important role of gut microbiota's metabolites as regulatory molecules, but lack of knowledge provided on the role of metabolites as raw materials for metabolic synthesis. This article provides us with such a new insight based on lipogenesis.

The study conducted by Yin *et al.* emphasized the crucial influence of gut microbiota as a potential metabolic "organ" (8). The focus was on the role of gut microbiota in hepatic lipid synthesis and related mechanisms. Usage of wild-type mice, mice treated with broad-spectrum antibiotics, and gnotobiotic mice were taken as models for liver regeneration in different backgrounds in the experimental design. Yin *et al.* observed a transition from *Firmicutes* and *Bacteroidetes* to a predominance of *Proteobacteria* in their taxonomic and lipidomic analysis. This shift was accompanied by a simultaneous worsening of the survival rate after partial hepatectomy (PHx), which may indicate the origin of downstream actions caused by dysbiosis. Compared with controls, convincing evidence was collected by testing sufficient cell cycle regulators, demonstrating the significant delay of hepatocyte proliferation. The authors observed and matched by point in time the changes gut microbiota related to liver regeneration and hepatocyte proliferation cell cycle for a considerable time before and after hepatectomy, and succeeded to merge a clear picture to display the interaction between them. Most interestingly, Yin *et al.* hypothesized and managed to successfully verify that the SCFA produced by a SCFA-producing colony composed of Firmicutes and Bacteroidetes provides most of the phospholipid biosynthesis ingredients, mainly phosphatidylinositol and phosphatidylglycerol, for hepatocyte proliferation through the gut-liver axis. Additionally, in order to distinguish the gut microbiota's SCFAs from the mixed effects of different lipid metabolic materials from the whole body, they identified SCD1 as an important dependent molecule of SCFA metabolism from gut microbiota, which provides a more comprehensive view for liver regeneration lipid metabolic rewiring and therapeutic strategies and prognostic biomarkers of HCC (9). To further narrow down the range of regenerative-promoting SCFAs, acetate, the most abundant component of SCFAs, was examined using hepatic organoids and showed an exciting proliferative promoting effect. To conclude, based on the evidence presented in the text, the authors have affirmed that the gut microbiota plays a crucial role in hepatic membrane phospholipid biosynthesis and liver regeneration.

In summary, this study proposes a metabolism and nutrition-based mechanism in the interaction between gut microbiota and multiple organs of the human body. This mechanism is independent of immune-related pathways. As authors indicated in the article, further studies are needed to clarify some questions of great clinical significance, building on the findings of this study. While SCFAs have been shown to have positive effects on liver function, it is important to note that there is also a connection between high concentrations of SCFAs and the development of hepatocellular carcinoma (10). Additionally, in order to bridge the gap between experimental microorganisms colonies and clinical microorganisms transplants, it is necessary to determine whether the positive effect demonstrated in gnotobiotic animal models still holds the same significance under conditions of complex microbial competition, such as the human gut.

Taken together, the revolutionary clinical value of postoperative interventions based on gut microbiota in patients undergoing liver surgery will undoubtedly propel gut microbial interventions to become a standard of care in the future. Furthermore, the authors provide new insights into the role of changes in gut microbial composition in liver regeneration, emphasizing that individual gut microbiology-based testing and intervention will provide a range of precision therapies for a wide variety of diseases. In this rapidly evolving field, the multifaceted nature of the gut microbiome offers unlimited possibilities for research into the prediction, treatment, and intervention of many diseases.

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