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COMMENTARY

Unlocking the potential of the gut microbiome in liver regeneration: Benefits and mechanistic insights

KEY WORDS

Gut microbiome;
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Hydroxybutyric acid;
STAT3

Liver transplantation is oftentimes the last therapeutic resource for patients with late-stage chronic liver diseases, including cirrhosis and hepatocellular carcinoma. The liver's regenerative capacity is particularly critical following partial hepatectomy and transplantation. While extensive studies have focused on elucidating the molecular signaling pathways of liver regeneration, external factors have been relatively overlooked. Antibiotic treatment, routinely administered to prevent infections during surgery, has recently been shown to delay liver regeneration when used extensively[1]. Emerging evidence suggests that the gut microbiome, often referred to as the 'second genome' of humans, plays a vital role in maintaining liver health by supplying microbial metabolites through the gut−liver axis. For example, the production of short-chain fatty acids (SCFAs) promotes liver regeneration by enhancing hepatic membrane phospholipid biosynthesis[1]. Additionally, supplementation with *Akkermansia muciniphila* improves liver regeneration in mice with diet-induced steatohepatitis, likely through regulation of the tricarboxylic acid cycle[2]. Identifying and enriching key beneficial bacteria within the gut microbiome represents a promising therapeutic strategy to enhance recovery and regeneration after partial hepatectomy.

In a recent study published in *Acta Pharmaceutica Sinica B*, Guo and colleagues[3] investigated the role of *Parabacteroides distasonis* in promoting liver regeneration. They demonstrated that *P. distasonis* produces hydroxybutyric acid, which activates the STAT3 signaling pathway. This elegant study provides a compelling example of how beneficial bacteria can be harnessed to enhance liver regeneration.

To explore the potential role of beneficial bacteria in liver regeneration, the authors investigated the dynamic changes of the gut microbiome following partial hepatectomy, building on previous observations of dynamic changes in microbial composition during liver regeneration[4]. The authors from this study reported a positive correlation between the relative abundance of *P. distasonis* and hepatocyte proliferation kinetics, suggesting a potential role for *P. distasonis* in the process[3]. To validate this hypothesis, comprehensive experiments were conducted in which mice pretreated with an antibiotic cocktail were administered live *P. distasonis*, heat-killed *P. distasonis*, live *P. merdae*, or vehicle control (PBS) daily. Using a prevention approach, only live *P. distasonis* promoted liver regeneration after partial hepatectomy. These findings expand our understanding of the beneficial role of *P. distasonis*, building on its previously demonstrated efficacy in improving insulin resistance, nonalcoholic steatohepatitis, and liver fibrosis[5-7].

To identify metabolites associated with *P. distasonis*, the authors conducted a targeted metabolomic assay on cecal contents from mice treated with PBS or live *P. distasonis*. Rather than employing a broad exploratory approach, they utilized an integrated analysis combining correlation studies with overlapping metabolite profiles in peripheral blood serum and liver tissue[3]. Among the 34 enriched candidates, β-hydroxybutyric acid emerged as a key target, known for its metabolic benefits in treating fatty liver disease[8]. β-Hydroxybutyric acid exhibited a strong positive correlation with *P. distasonis* and demonstrated consistent increases in peripheral blood serum and liver tissue. Subsequent validation experiments confirmed that β-hydroxybutyric acid, rather than other cecum-enriched

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metabolites such as hyodeoxycholic acid and 3-hydroxyphenylacetic acid, exhibited liver regeneration-promoting effects. These findings provide new evidence that microbial associated products can benefit the host by promoting liver regeneration.

Based on prior knowledge, β-hydroxybutyric acid is primarily produced in the liver[8], which aligns with the findings of this study, where direct production of β-hydroxybutyric acid was not detected in the culture medium. To bridge the critical gap between *P. distasonis* and β-hydroxybutyric acid production, the authors conducted an integrated analysis comprising proteomic profiling, qPCR validation, and correlation analysis with hepatic β-hydroxybutyric acid concentrations. The results demonstrated that *P. distasonis* upregulated proliferation- and lipid-metabolism-related pathways, as well as genes involved in β-hydroxybutyric acid synthesis[3]. These findings suggest that *P. distasonis* promotes liver regeneration, likely by enhancing hepatic β-hydroxybutyric acid production, boosting fatty acid oxidation, and providing additional energy. Although further investigation was not conducted in this study, one possibility is that *P. distasonis* may enhance β-hydroxybutyric acid production by supplying an unknown precursor to the liver *via* the portal vein, considering the complexity of gut fermentation.

To further investigate how β-hydroxybutyric acid mediates it's effect in the liver, the authors hypothesized that transcription activator factor 3 (STAT3) might serve as a potential receptor for β-hydroxybutyric acid, given its implicated role in liver regeneration and its function as an epigenetic modifier[9,10]. This was validated through Western blot analysis, which confirmed that β-hydroxybutyric acid treatment significantly increased the levels of STAT3 pathway-related proteins in mouse liver. Additionally, the authors elegantly used the STAT3 phosphorylation inhibitor Stattic, which abolished the promoting effect of β-hydroxybutyric acid. These results collectively demonstrate that β-hydroxybutyric acid promotes liver regeneration through STAT3 signaling[3].

The findings reported by Guo et al. nicely demonstrate how the gut microbiome promotes liver regeneration, elucidating the underlying mechanism through enhanced β-hydroxybutyric acid production, which subsequently activates the STAT3 signaling pathway in the liver of mice. However, translating these mouse studies to humans presents challenges, particularly in identifying key beneficial strains. Several mysteries remain, such as whether the dynamic changes in the microbiome after partial hepatectomy are a cause or result, and how mutual benefits between the gut microbiome and the host can be achieved. Additionally, it remains to be explored how dietary nutrition may modify the gut microbiome and its associated metabolites to promote liver regeneration. Nevertheless, this study provides valuable insights into promoting liver regeneration after partial hepatectomy through precise modulation of the gut microbiome and highlights the need to limit the use of antibiotics.

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Author contributions

Wenchao Wei wrote the manuscript, Bernd Schnabl edited it.

Conflicts of interest

Bernd Schnabl has been consulting for Ferring Research Institute, HOST Therabiomics, Intercept Pharmaceuticals, Mabwell Therapeutics, Patara Pharmaceuticals, Surrozen and Takeda. Bernd Schnabl's institution UC San Diego has received research support from Axial Biotherapeutics, BiomX, ChromoLogic, CymaBay Therapeutics, Intercept Pharmaceuticals, NGM Biopharmaceuticals, Prodigy Biotech and Synlogic Operating Company. Bernd Schnabl is founder of Nterica Bio. UC San Diego has filed several patents with Bernd Schnabl as inventor.

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