Editorial Commentary

Microbial influence on liver regeneration: understanding gut microbiota and hepatic recovery post partial hepatectomy

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The liver is a unique solid organ with a regenerative capacity that is an important factor in the outcome of partial hepatectomy (PHx) performed to treat life-threating liver diseases (1-3). Multiple intrahepatic and extrahepatic signaling pathways synergistically regulate liver regeneration to restore typical liver functionality and thereby promote maximal life expectancy (2,4). Among the extrahepatic factors, gut metabolites are pivotal signaling molecules that affect the regulation of liver regeneration (5,6). Interestingly, dysbiosis of the gut microbiota due to disease or treatment strategies can influence liver regeneration negatively and delay recovery (7-9). In this empirical study, Yin *et al.* report the substantial role of acetate, a microbial metabolite, in liver regeneration; specifically, acetate was found to increase the activity of lipid synthesis pathways regulated by the *FASN* and *SCD1* genes, which help to produce higher numbers of membrane phospholipids and boost liver regeneration following PHx.

Notably, antibiotic treatment altered the composition of gut bacteria and significantly impeded liver regeneration in mice by affecting the hepatic lipid metabolism required for effective regeneration. Even short-term antibiotic treatment led to delayed proliferation of hepatocytes, which was directly associated with a reduction in short-chain fatty acids (SCFAs), crucial components in liver lipid synthesis (7). However, this study revealed a potential remedy: the restoration of specific microbial taxa capable of producing SCFAs, particularly acetate, effectively rescued liver regeneration in mice. This finding indicates potential implications for humans undergoing liver resection procedures, namely, that gut dysbiosis could adversely affect the regeneration process and subsequent patient survival (10,11).

This study emphasizes the vital role of the gut microbiota and its metabolites in influencing liver regeneration and provides insights into the relationship between bacterial composition, metabolites, and hepatic lipid metabolism. It uncovers specific shifts in the composition of gut bacteria, particularly an increase in Proteobacteria and a decrease in *Firmicutes* and *Bacteroidetes*, mirroring findings in patients with nonalcoholic fatty liver disease. The induction of dysbiosis in mice through antibiotic treatment provides a valuable model for studying the impacts of alterations in the composition of gut microbes on liver regeneration, promoting the design of controlled experiments. This study correlates specific changes in the gut microbiota composition with delayed liver regeneration and compromised hepatocyte proliferation, establishing a link between gut dysbiosis and impaired liver function.

Additionally, the adaptive potential of the gut microbiota is highlighted in this study; in particular, it was found that

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some fermentation-competent bacteria increased in late stages after antibiotic treatment, potentially impacting hepatocyte proliferation positively. SCFAs, primarily acetate, were identified as crucial for liver regeneration and lipid metabolism, providing insight into their role as building blocks of membrane lipid biosynthesis in the liver. This study corroborates findings in mice with human liver biopsies, demonstrating increased expression of lipogenic enzymes associated with liver proliferation and regeneration in patients undergoing hepatic resection.

Moreover, the reintroduction of a defined set of microbes capable of SCFA production into germ-free mice rescued impaired liver regeneration, demonstrating the importance of specific microbial taxa in this process. This study demonstrates a significant association between acetate levels in the gut, host lipogenesis, and liver regeneration, validating the importance of acetate as a critical factor in liver growth. Additionally, the findings of this study suggest potential implications for preoperative screening by analyzing the microbial composition in patients undergoing hepatic resection, offering new avenues for understanding the role of the gut microbiota in liver regeneration. This study provides valuable insights into the interplay between the gut microbiota, microbial metabolites, and liver regeneration and reveals potential targets for therapeutic interventions and further research in understanding liver diseases and recovery after hepatic surgeries.

Despite these promising findings, caution is advised when considering the manipulation of the gut microbiota for therapeutic purposes due to potential side effects. This study emphasizes the indispensable role of the gut microbiota in liver regeneration post-PHx, highlighting the complex connections between the microbial composition, SCFAs, liver lipid metabolism, and the regenerative process. Nevertheless, to gain a more comprehensive understanding, further research is necessary to unravel the intricacies of this relationship, including establishing causality in the setting of antibiotic-induced dysbiosis, and comprehensively delineate the microbiome's involvement in liver health and diseases such as hepatocellular carcinoma.

We emphasize the limitations of this preclinical trial to underscore the complexities and challenges in directly translating findings from animal models to human patients; notably, careful consideration and additional research are necessary to validate these findings and before applying these insights in clinical practice. Existing studies heavily rely on mouse models, and the findings might not necessarily translate directly to human physiology due to inherent differences in the gut microbiotas and immune systems between mice and humans (12,13). The profound gut dysbiosis induced by the administration of antibiotics in this preclinical trial might not precisely mirror the effects of long-term antibiotic exposure in humans, especially considering the differences in dosage, duration, and bacterial resistance mechanisms. While the current study demonstrates significant alterations in the gut microbial composition and the effects on liver regeneration, the human gut microbiome is highly diverse and can vary significantly among individuals, impacting the generalizability of these findings.

Responses of microbial populations to dysbiosis and subsequent adaptation observed in mice may differ substantially in humans due to varying factors such as diet, lifestyle, and overall health status. The specific shifts in bacterial taxa observed in mice after antibiotic treatment might not be precisely replicated in the human gut microbiota under similar conditions, limiting direct correlations to human scenarios (14). While the current study suggests a clear association between gut dysbiosis and impaired liver regeneration in mice, establishing a direct causative relationship between alterations in the gut microbiota and liver function in humans is complex and challenging. Colonization of germ-free mice with a minimal set of specific bacteria might not recapitulate the full complexity and variability of the human gut microbiota, raising questions about the applicability of these findings to human interventions. Therefore, the role and impact of SCFAs on liver regeneration and lipid metabolism might not directly mirror human responses, as their effects can be influenced by various other factors and conditions specific to human physiology. The study's experimental design and observations, particularly in terms of antibiotic treatment and microbial shifts, might not fully represent the complexities and diversity of dysbiosis observed in human populations. While this study provides insights into potential connections between the gut microbiota, SCFAs, and liver regeneration, the direct clinical applicability and translation of these findings to human therapeutic interventions require further comprehensive validation and extensive clinical studies.

The current preclinical study delves deep into how the gut microbiota and its metabolic byproducts influence liver regenerative capabilities and its functionalities, which can be very helpful in establishing further innovative clinical trials of targeted microbial byproducts, specifically, the application of acetate in regenerative medicine. Additionally, these findings are a reminder to clinicians to be more cautious about

administering antibiotics, particularly to patients undergoing PHx, as the use of antibiotics can delay liver regeneration by disrupting the microbial ecology of the gut.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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