JCI insight

Intestinal mucosal mitochondrial oxidative phosphorylation worsens with cirrhosis progression and is ameliorated with FMT

Jing Zeng, … , Huiping Zhou, Jasmohan S. Bajaj

JCI Insight. 2025. https://doi.org/10.1172/jci.insight.186649.

Research Letter In-Press Preview Hepatology Microbiology

Intestinal Mucosal Mitochondrial Oxidative Phosphorylation worsens with Cirrhosis Progression and is ameliorated with FMT

Jing Zeng[1, 2], Derrick Zhao[1], Grayson Way[1], Andrew Fagan[1], Michael Fuchs[1], Puneet Puri[1], Brian C Davis[1], Xuan Wang[1], Emily C Gurley[1], Phillip B. Hylemon[1, 3], Jian-Gao Fan[2], Masoumeh Sikaroodi[4], Patrick M Gillevet[1], Huiping Zhou[1, 3], and Jasmohan S Bajaj[1, 3]

[1]Virginia Commonwealth University and Richmond VA Medical Center, Richmond, Virginia, USA. [2]Department of Gastroenterology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China. [3]Stravitz-Sanyal Institute for Liver Disease & Metabolic Health, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA. [4]Microbiome Analysis Center, George Mason University, Manassas, Virginia, USA

Address correspondence to:

Jasmohan Bajaj, 1201 Broad Rock Boulevard, Richmond, Virginia 23249. Phone: 1.804.675.5802; Email: jasmohan.bajaj@vcuhealth.org

Conflict of interest: The authors have declared that no conflict of interest exists.

Cirrhosis is a critical global health concern due to its high mortality and morbidity rates and higher incidence of obesity, alcohol, and viral hepatitis (1, 2). This advanced liver disease disrupts the gut-liver axis, affecting normal physiological processes, including mitochondrial oxidative phosphorylation (OXPHOS) activity in the intestinal mucosa, which is crucial for cellular energy production. Dysfunctional OXPHOS can lead to exacerbated tissue hypoxia and energy deficits. Additionally, alterations in the gut microbiota influence metabolic and immune responses, significantly affecting liver disease outcomes (3). Furthermore, the gut-liver axis, which encompasses the bidirectional relationship between the intestinal microbiota and liver health, plays a pivotal role in the progression of cirrhosis. Alterations in gut microbiota composition have been linked to variations in metabolic and immune responses that significantly impact liver disease outcomes. In this context, fecal microbiota transplantation (FMT) emerges as a novel therapeutic approach aimed at restoring a healthy microbiota balance, potentially modulating mitochondrial function, and ameliorating cirrhosis progression (4). It is important to understand the intricate relationship between intestinal mucosal OXPHOS, changes in gut microbiota, and the impact of FMT in cirrhosis.

We conducted a cross-sectional study involving 32 age-balanced male participants divided into three groups: healthy controls, patients with compensated cirrhosis, and patients with decompensated cirrhosis. Participants underwent endoscopic procedures to obtain biopsies from the duodenum (DUOD) and ascending (ASCEND) colon. These samples were analyzed for mitochondrial OXPHOS gene expression using quantitative PCR and NanoString technologies. Additionally, a subset of patients with decompensated cirrhosis previously enrolled in a randomized clinical trial received FMT capsules from a single donor (5). Changes

in OXPHOS gene expression were measured pre- and post-FMT in the DUOD to evaluate the impact of microbiota modulation on mitochondrial function. The study also included comprehensive bioinformatics analysis to assess correlations between changes in gut microbiota composition, clinical parameters such as the Model for End-Stage Liver Disease (MELD) scores, and mitochondrial activity. Further details on methods, including patient details are in the Supplemental Materials. Sex as a biological variable was considered but we ended up including only one woman in the entire study due to the population at the Veterans hospitals. In the DUOD of patients with cirrhosis compared to healthy controls, KEGG pathway analysis of differential expressed genes (DEGs) indicated involvement in 'Oxidative phosphorylation' (Figure 1A). In patients with decompensated cirrhosis, there were more pronounced alterations (Figure 1B). Additionally, the study revealed significant upregulation of inflammation-related genes and nuclear-encoded OXPHOS genes in patients with compensated and decompensated cirrhosis compared to healthy controls ($|FC|>1.5$; $p<0.05$) (Figure 1C and 1D), correlating strongly with the gut microbiota composition changes and the severity of cirrhosis ($p<0.05$)(Figure S3). This upregulation was particularly pronounced in the decompensated cirrhosis group, indicating severe inflammation and mitochondrial dysfunction. Following FMT, there was a significant reduction in OXPHOS gene expression in the duodenum of patients ($p<0.05$), suggesting an improvement in mitochondrial function and a potential restoration of the intestinal barrier. Additionally, patients who received FMT showed enrichment in pathways associated with inhibited reactive oxygen species production and OXPHOS, which were higher at baseline ($p<0.05$, Figure 1E/F).

This study investigates the correlation between intestinal mucosal OXPHOS and inflammation in patients with cirrhosis, their relationship to microbiota and the progression of liver disease, as well as modulation after successful FMT. The analysis reveals changes in genes related to OXPHOS and inflammation, which are particularly pronounced in patients with decompensated cirrhosis. Moreover, the study underscores the importance of gut microbiota composition in the development of cirrhosis, with certain bacterial genera showing correlations with the expression of genes related to OXPHOS and inflammation. We hypothesized that during the development and progression of cirrhosis, intestinal inflammation, altered blood flow and resulting tissue hypoxia affect luminal oxygen availability(6) potentially disadvantaging obligately anaerobic bacteria such as *Megasphera* and *Fusicatenibacter*. In contrast, such conditions could favor facultative anaerobes like *Pasteurella*. The findings regarding changes in OXPHOS genes expression and microbiota in both the small and large intestines offer valuable insights into the potential mechanisms contributing to the progression of cirrhosis. FMT using oral capsules restored small intestinal mitochondrial OXPHOS activity in the duodenal mucosa, highlighting the potential interaction between microbial change and intestinal inflammation in cirrhosis.

Future research should seek to replicate these findings in larger and more diverse cohorts to verify the consistency of the results and assess the long-term effects of FMT on mitochondrial function and clinical outcomes in cirrhosis. Additionally, mechanistic studies are crucial for elucidating the specific pathways through which alterations in the microbiota influence mitochondrial dynamics. Identifying microbial species that impact these processes will further our understanding of their roles in liver disease progression and the potential for

targeted microbiota-based therapies. In conclusion, this study has explored the associations among intestinal mucosal OXPHOS, inflammation, and dysbiosis in patients with cirrhosis, shedding light on their interconnected roles in the progression of liver disease and underscoring the therapeutic possibilities of microbiota-based interventions. These findings highlight a complex interplay between intestinal mucosal OXPHOS function, cirrhosis, and FMT. However, it is important to recognize that these results are primarily correlational. A deeper understanding of the gut-microbiota-liver nexus and its impact on cellular energy pathways could pave the way for future research to develop therapeutic strategies that go beyond symptom management and potentially modify the disease trajectory in cirrhosis. The insights gained from this study broaden our understanding of cirrhosis pathogenesis and underscore the importance of exploring innovative treatment approaches.

References:

1. Bajaj JS, Betrapally NS, and Gillevet PM. Decompensated cirrhosis and microbiome interpretation. *Nature.* 2015;525(7569):E1-2.
2. Asrani SK, Devarbhavi H, Eaton J, and Kamath PS. Burden of liver diseases in the world. *J Hepatol.* 2019;70(1):151-71.
3. Tilg H, Adolph TE, and Trauner M. Gut-liver axis: Pathophysiological concepts and clinical implications. *Cell Metab.* 2022;34(11):1700-18.
4. Bajaj JS, Ng SC, and Schnabl B. Promises of microbiome-based therapies. *J Hepatol.* 2022;76(6):1379-91.
5. Bajaj JS, Salzman NH, Acharya C, Sterling RK, White MB, Gavis EA, et al. Fecal Microbial Transplant Capsules Are Safe in Hepatic Encephalopathy: A Phase 1, Randomized, Placebo-Controlled Trial. *Hepatology.* 2019;70(5):1690-703.
6. Albenberg L, Esipova TV, Judge CP, Bittinger K, Chen J, Laughlin A, et al. Correlation between intraluminal oxygen gradient and radial partitioning of intestinal microbiota. *Gastroenterology.* 2014;147(5):1055-63 e8.

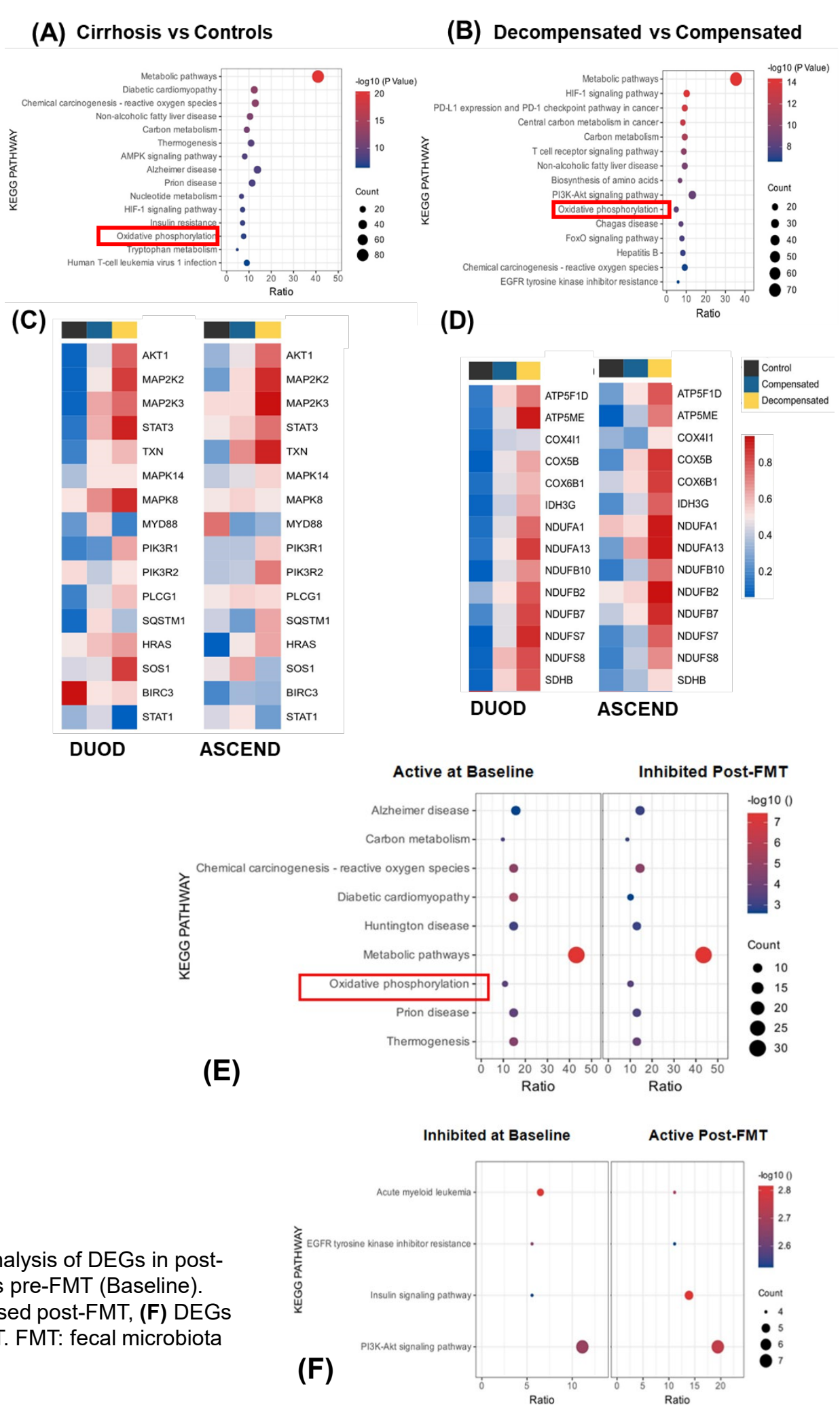

Figure 1. Intestinal Mucosal Changes in Cirrhosis using Cross-sectional and post-FMT approaches. Functional Gene Analysis in the DUOD: KEGG pathway analyses differentiate between healthy controls and patients with cirrhosis **(A)**, as well as between compensated and decompensated stages of cirrhosis **(B)**. Gene Expression Profiles in Cirrhosis: Hierarchical clustering heatmaps display changes in inflammation-related **(C)** and OXPHOS-related gene expressions **(D)** in the duodenum (DUOD) and ascending colon (ASCEND) of patients across different stages of cirrhosis compared to healthy controls, utilizing NanoString nCounter metabolic, inflammation, and fibrosis mRNA panels. KEGG Pathway Analysis of DEGs in post-FMT DUOD versus pre-FMT (Baseline). **(E)** DEGs suppressed post-FMT, **(F)** DEGs activated post-FMT. FMT: fecal microbiota transplant.