Medical University of Graz

Drug-microbiome interaction in liver cirrhosis

Summary

Vanessa Stadlbauer-Köllner, Department of Gastroenterology and Hepatology

Supervisor:	Prof. Dr. Vanessa Stadlbauer-Köllner
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 10, 2020 00:00 and March 30, 2020 23:59 (Europe/Zurich)

Description

Background: Patients with end-stage liver disease, also known as cirrhosis, are highly susceptible to a number of severe and even lethal complications, resulting in a markedly reduced life expectancy. (1) This makes cirrhosis the 10th most common cause of death in the western world. The gut microbiome is severely altered in liver cirrhosis (2) and we have recently shown that, besides disease severity and etiology, drug intake and inflammation are important influencing factors of microbiome composition in cirrhosis. (3, 4) On the one hand, altered gut microbiome composition has been linked to progression of liver disease and the development of complications via increased gut permeability, bacterial translocation and inflammation. (2, 5-7) We could identify proton pump inhibitor induced dysbiosis in liver cirrhosis as a major culprit in the development of complications and death. (4) On the other hand, modulation of the gut microbiome with probiotics can result in improvement of liver function (7) but conditions for response need to be defined and optimized. This leads to the notion that understanding changes in gut microbiome composition and function, especially in reaction to drugs, leads to a better understanding of the pathophysiology of the disease and that the gut microbiome serves as a novel therapeutic target in liver cirrhosis.

Hypothesis and Objectives:

We hypothesize that the interplay between drugs and the gut microbiome in liver cirrhosis is the key to understand pathophysiology of complications and to the development of novel therapeutic concepts.

The hypothesis will be tested by two approaches:

1. *In-silico* part: To study, whether the clinical benefit of drugs, such as probiotics, can be predicted, multi-omics datasets will be analysed with advanced bioinformatics methods including artificial intelligence. To achieve this aim, the PhD candidate will do multi-omics analyses on exsisting large datasets of patients with liver cirrhosis who were treated with probiotics or placebo by combining gut microbiome data with metabolomics data from urine and a large number of serum and fecal biomarkers. The results of this project part will lead to the identification of a panel of biomarker that predict response to probiotics.
2. *In-vitro* part: The pathophysiological basis of beneficial or detrimental effects of different drugs on the microbiome in cirrhosis will be studied in gut microbiome and gut barrier *in-vitro* models. The PhD candidate will test probiotic bacteria and target bacteria of dysbiosis that are identified in the *in-silico* part of the project in anaerobic bacterial cocultures and in a microbiome bioreactor model, to understand how drugs modulate the composition of the micrbiome. The PhD candidate will further study the effect of bacterial metabolites on gut barrier function and inflammation in cell culture experiments.

Methodology:

The PhD student will use advanced biostatistical and bioinformatics methods to analyze microbiome sequencing data, metabolomics data and biomarkers of inflammation and gut barrier dysfunction (e.g. principal component analysis, redundancy analysis, ANCOM, LEfSe, random forrest, LASSO regression XGBoost and many more). Knowledge on some of these methods and basics in R will be necessary for this project part. Additionally, the PhD candidate will use different bacterial culture techniques under anaerobic conditions, cell culture models of the gut barrier and inflammatory cells and methods to study gut barrier integrity (TEER, Ussing chamber), as well as standard molecular biology techniques (qPCR, Western blot, ELISA, immunofluorescence etc.), to understand the interplay between probiotics and the host microbiome.

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References:

1. Bosetti C, Levi F, Lucchini F, Zatonski WA, Negri E, La Vecchia C. Worldwide mortality from cirrhosis: an update to 2002. J Hepatol. 2007;46(5):827-39.

2. Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, Guo J, Le Chatelier E, Yao J, Wu L, Zhou J, Ni S, Liu L, Pons N, Batto JM, Kennedy SP, Leonard P, Yuan C, Ding W, Chen Y, Hu X, Zheng B, Qian G, Xu W, Ehrlich SD, Zheng S, Li L. Alterations of the human gut microbiome in liver cirrhosis. Nature. 2014;513(7516):59-64.

3. Stadlbauer V, Komarova I, Klymiuk I, Durdevic M, Reisinger A, Blesl A, Rainer F, Horvath A. Disease severity and proton pump inhibitor use impact strongest on faecal microbiome composition in liver cirrhosis. Liver Int. 2020.

4. Horvath A, Rainer F, Bashir M, Leber B, Schmerboeck B, Klymiuk I, Groselj-Strele A, Durdevic M, Freedberg DE, Abrams JA, Fickert P, Stiegler P, Stadlbauer V. Biomarkers for oralization during long-term proton pump inhibitor therapy predict survival in cirrhosis. Sci Rep. 2019;9(1):12000.

5. Bajaj JS, Heuman DM, Hylemon PB, Sanyal AJ, White MB, Monteith P, Noble NA, Unser AB, Daita K, Fisher AR, Sikaroodi M, Gillevet PM. Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol. 2014;60(5):940-7.

6. Schnabl B. Linking intestinal homeostasis and liver disease. Current opinion in gastroenterology. 2013;29(3):264-70.

7. Horvath A, Leber B, Schmerboeck B, Tawdrous M, Zettel G, Hartl A, Madl T, Stryeck S, Fuchs D, Lemesch S, Douschan P, Krones E, Spindelboeck W, Durchschein F, Rainer F, Zollner G, Stauber RE, Fickert P, Stiegler P, Stadlbauer V. Randomised clinical trial: the effects of a multispecies probiotic vs. placebo on innate immune function, bacterial translocation and gut permeability in patients with cirrhosis. Aliment Pharmacol Ther. 2016;44(9):926-35.

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