Pathophysiological basis of neutrophil dysfunction in different chronic liver diseases

Summary

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Status: open
Offered by: Medical University of Graz

Description

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Background: Liver cirrhosis is the 10th most common cause of death in the western world. Patients with cirrhosis are susceptible to a variety of complications, with infections being one of the most important clinical problems. The rate of bacterial infections is as high as 34% per year in patients with advanced cirrhosis. To emphasize the vulnerability to infection, cirrhosis has been depicted as the commonest immunodeficiency syndrome worldwide, bearing a huge socioeconomic burden of disease. Severe infections are frequently fatal in liver cirrhosis. Although chronic alcoholism and hepatitis C (HCV) infection without cirrhosis also carry a high risk of infections, additionally acquired cirrhosis increases the risk to almost 5 fold (1). Impaired neutrophil function has been identified as one of the key mechanisms for this increased rate of infections (2). Neutrophils of cirrhotic patients show impairment in phagocytic capacity, oxidative burst and migration into infected tissue. Endotoxin is elevated in liver cirrhotic patients and can be linked to neutrophil dysfunction (2). The reasons for endotoxemia are increased gut permeability – either due to the underlying disease or due to cirrhosis itself - and changes in the gut microbiome composition in liver disease (3). However, so far it is not completely clear to which magnitude gut permeability and microbiome changes contribute to innate immune dysfunction in cirrhosis and if the underlying etiology cause differential effects on neutrophil function.

Hypothesis and Objectives: The aim of this project is to understand the pathophysiological mechanisms of impaired neutrophil phagocytosis in liver cirrhosis of different etiology. We hypothesize that gut barrier dysfunction, intestinal inflammation, bacterial translocation, bile acids and direct or indirect effects of viral infections are potential mechanisms of neutrophil dysfunction cirrhosis. This project specifically aims to study the influence of these factors on neutrophils in alcoholic versus HCV related versus cholestatic cirrhosis.

Methodology: The student will learn to measure neutrophil and monocyte function, including phagocytic function, oxidative burst, bacterial killing as well as receptor and cytokine expression (flow cytometry, cell culture). To understand gut permeability, a panel of gut barrier and intestinal inflammation markers (HPLC, LC-MS/MS, ELISA, bead arrays, Ussing chamber experiments) and markers of bacterial translocation (cell culture based assays, next-generation sequencing of bacterial DNA in body fluids, ELISA) will be performed by the student. Furthermore, bile acids (tandem mass spectrometry) and effects of hepatitis C infections on innate immune cells (flow cytometry, qPCR, immunofluorescence) will be studied by the PhD student. 2D gel electrophoreses and MALDI-TOF will be used to study the differential effects of liver cirrhosis etiology on serum protein composition. The student will use human samples already available at the department (serum, plasma, tissue, cells, stool, urine). To study causal relationships the student will use mouse models of alcoholic, HCV-related and cholestatic liver disease.
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