Role of oxysterols and the oxysterol receptor EBI2 in the pathogenesis of inflammatory bowel diseases and non-alcoholic steatohepatitis

Summary / Zusammenfassung
Oxysterols are known signaling molecules in metabolism and the immune system. 7α, 25 dihydroxyoxysterol (7α, 25 OHC) is a newly discovered ligand for Epstein Barr virus induced gene 2 (EBI2) and regulator of B cell differentiation. Even though a much broader role in immunity is likely, EBI2 and 7α, 25 OHC have not been directly implicated in human diseases.

EBI2 is a risk gene for inflammatory bowel diseases (IBD) and various lines of evidence suggest an involvement of oxysterols in the pathogenesis of non-alcoholic steatohepatitis (NASH). In line with these observations, our preliminary data suggest an involvement of the EBI2 - 7α, 25 OHC system in experimental models of IBD and NASH.

In our experiments we will first test activity of 7α, 25 OHC synthesis enzymes and the receptor EBI2 as well as oxysterols levels in samples of human patients from an IBD and NASH cohort using rt-PCR, Western blot and mass spectroscopy. We will determine localization and cell type of activation and correlate these data with markers of the acquired and adaptive immune system.

Next we will study the EBI2 7α, 25 OHC system in experimental models for IBD and NASH. In addition to the experiments described above we will specifically inhibit the activity of the 7α, 25 OHC system using knockouts of EBI2 or 7α, 25 OHC synthesizing enzymes as well as pharmacological inhibitors and study any influence on the disease process. We will for the therapeutic effect of synthetic oxysterols.

Our results will lead to a better understanding of the emerging role of oxysterols in immunity and the pathogenesis of IBD and NASH and might finally open new therapeutic options.

Project Leadership and Contacts / Projektleitung und Kontakte
PD Dr. med. Benjamin Misselwitz (Project Leader)  benjamin.misselwitz@usz.ch

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In Collaboration with / In Zusammenarbeit mit
Prof. Dr. Dr. med. Gerhard Rogler  Switzerland
Klinik für Gastroenterologie und Hepatologie
Universitätsspital Zürich
gerhard.rogler@usz.ch

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